THE MEDICAL MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA: A PROGRESS REPORT

JEAN D. WILSON

INTERNAL MEDICINE GRAND ROUNDS
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

FEBRUARY 5, 2004

Dr. Wilson was a member of the Merck Institute Scientific Advisory Board from 1984-1992. He will not discuss off-label use of drugs.

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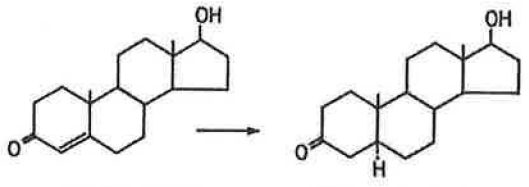
INTRODUCTION

Benign prostatic hyperplasia is a common affliction of aging in men. Although not a major contributor to mortality, the disorder has a significant impact on the quality of life and on 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 impractical or contraindicated. I began working on prostate physiology and pathophysiology in the early 1960s and have given three previous medical grand rounds on benign prostatic hyperplasia (1969, 1978, 1990). In the early years of my interest in the subject research was largely limited to experimental animals. However, as a result of advances in imaging techniques and in the methods for dynamic assessment of blood flow, and as the result of the development of medical therapies and a host of new surgical therapies, prostatic hyperplasia is now the subject of intense interest to the extent that Ovid lists nearly 12,000 citations, most in the past 10 years. The purpose of today's talk (which it is safe to assume will be my last grand rounds on the subject) is to provide a progress report on the quest for medical therapy. This is an appropriate time for such an undertaking because of the publication last month of the results of the long-awaited MTOPS study, a six year trial of finasteride and doxazosin, alone and in combination (1). I was actively involved in this field through the animal studies and the testing of 5α-reductase inhibitors through the phase 2 studies but have not been involved in the efficacy studies in men. Two UT Southwestern faculty members in the Department of Urology—John McConnell and Claus Roehrborn—have been largely responsible for the design and conduct of the prospective studies. Although I will be quoting their work extensively, today's talk is my interpretation of the field and not necessarily theirs. I should make clear at the onset some of the topics that I will not be covering; namely, alternative medical therapies (except to note in passing that the sales of saw palmetto in this country topped $3 billion last year) or the new approaches to prostatic surgery [including laser prostatectomy, transurethral and transrectal microwave thermotherapy, transurethral needle ablation utilizing radiofrequency energy, high intensity focused ultrasound, and the vaportrode, which vaporizes the prostate (1)].

ENDOCRINE CONTROL OF PROSTATE DEVELOPMENT AND GROWTH

My interest in prostatic hyperplasia arose as a by-product of studies designed to explore the mechanism of hormone action. We decided in 1960 to study the male hormone testosterone and after trying other experimental systems turned to the ventral prostate of the rat as a paradigm. The rat prostate is predominately composed of one cell type; 95% of the tissue consists of follicles of columnar epithelial cells loosely tied together by a stromal network. We had shown that testosterone action takes place in the cell nucleus, and Nick Bruchovsky, a post-doctoral fellow in the lab, discovered that testosterone in the prostate is converted to dihydrotestosterone, so that within a few minutes after injecting radioactive testosterone, most radioactivity that is bound to the nuclear macromolecules is in the form of dihydrotestosterone (3,4).



Testosterone **Dihydrotestosterone**

There are in fact two steroid 5α-reductase enzymes that perform this reaction (5). The encoding genes are located on different chromosomes, but structural homology of the two enzymes indicates that the two genes arose from gene duplication. The two isoenzymes are expressed in

different tissues. In the male urogenital tract, including the prostates if all species, including man, the predominant enzyme is isoenzyme 2 (5).

STEROID 5α-REDUCTASES

- **ISOENZYME 1**
  Encoded on chromosome 1; pH optimum 8; expressed in many tissues, largely after puberty
- **ISOENZYME 2**
  Encoded on chromosome 5; pH optimum 5.5; expressed in urogenital tract; deficiency causes male pseudohermaphroditism

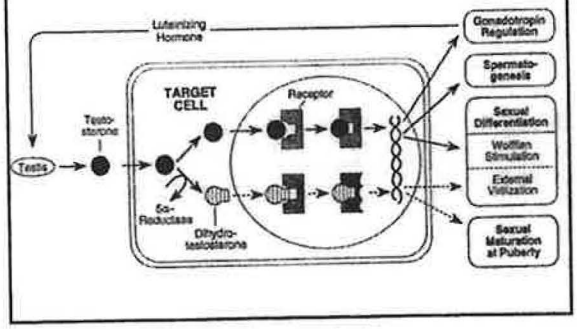
Defining the role of dihydrotestosterone in androgen action was aided enormously by studies of genetic males with steroid 5α-reductase 2 deficiency, a rare autosomal recessive disorder in which males have testes and male ejaculatory ducts but otherwise a female phenotype, including absence of the prostate (6). The disorder is the result of loss of function mutations of the gene that encodes isoenzyme 2 (6).

5α-REDUCTASE 2 DEFICIENCY

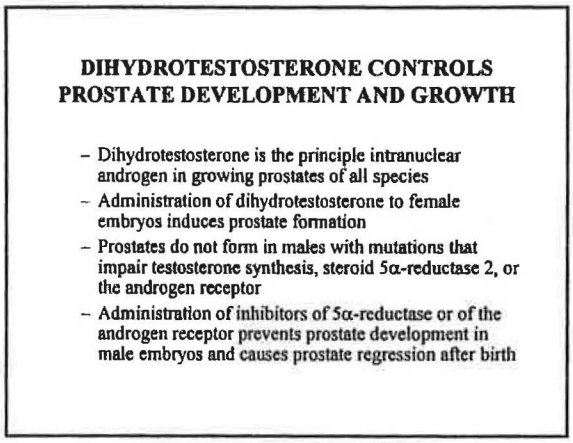
Karyotype	**46,XY**
Inheritance	**Autosomal recessive**
Phenotype	**Female with clitoromegaly, male breasts, variable late virilization**
Urogenital Tract	**Testes, epididymides, vasa deferentia, and seminal vesicles empty into vagina**
Endocrinology	**Normal male levels of testosterone and estradiol; dihydrotestosterone present in plasma after puberty**

As the result of studies of this disorder and of other paradigms, normal androgen physiology can be summarized in the following schematic diagram (7).

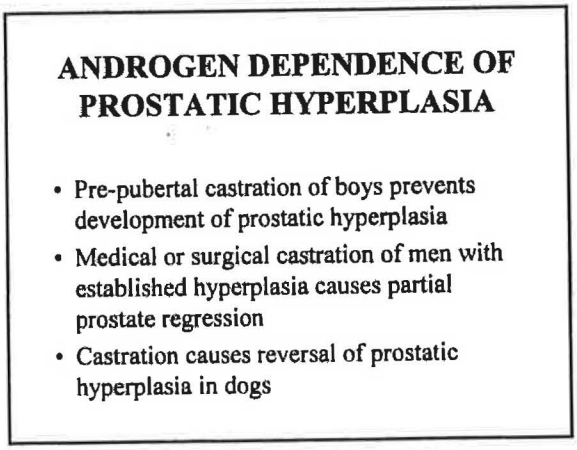
SCHEMATIC DIAGRAM OF NORMAL ANDROGEN PHYSIOLOGY



We established that the development of the prostate during embryogenesis and its growth at the time of sexual maturation are controlled by dihydrotestosterone. Namely, dihydrotestosterone is the principal intranuclear androgen in the growing prostates of all species, administration of dihydrotestosterone to female embryos induces prostate formation, prostates do not form in males with mutations that impair testosterone synthesis, steroid 5α-reductase 2, or the androgen receptor, and administration of inhibitors of 5α-reductase or inhibitors of the androgen receptor prevents prostate development in male embryos and causes prostate regression after birth (8).



This information was then considered in light of what was known about the androgen dependence of prostatic hyperplasia. Namely, prepubertal castration of boys prevents the development of prostatic hyperplasia, medical or surgical castration of men with prostatic hyperplasia causes partial regression of the disease, and castration causes reversal of prostatic hyperplasia in dogs, the only species other than man that develops the disorder. I will come back to studies of medical or surgical castration later, but at the beginning we decided to use the dog model of prostatic hyperplasia to determine the role of dihydrotestosterone in the process.



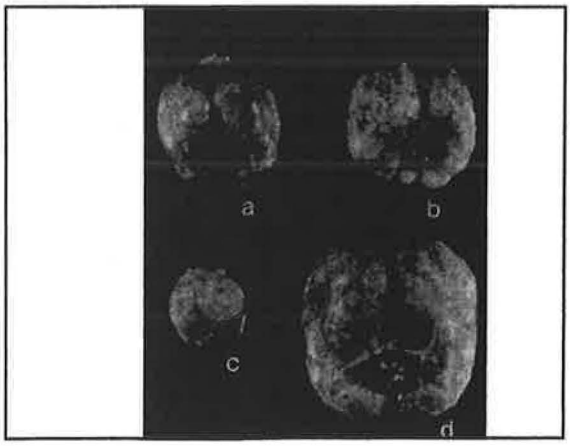
DOG MODEL OF PROSTATIC HYPERPLASIA

Prostatic hyperplasia is a universal feature of aging male dogs, although it is said in the literature to be more severe in some breeds (such as Scottish terriers) than in others. The condition does not occur in castrated dogs, and castration of older dogs with prostatic hyperplasia causes regression of the condition. It differs from the human disorder in at least two ways; namely, the histological picture is predominately an epithelial hyperplasia, involving little stroma, and the absence of a capsule in the dog prostate causes the enlarging gland to grow backward so that the predominant symptom is constipation rather than urinary tract obstruction.

BENIGN PROSTATIC HYPERPLASIA IN THE DOG

- Universal feature of the aging male, more severe in some breeds
- Does not occur in castrated dogs, and castration of older dogs causes regression
- Predominately involves the epithelial components of the gland
- Backward growth results in constipation rather than urinary tract obstruction

One of our early experiments was to measure dihydrotestosterone levels in the dog prostate. As the average weight went from 10 g in the mature prostate to 28 g in the hypertrophic prostate, the dihydrotestosterone concentration increased approximately 3-fold (9). We then tried to induce prostatic hyperplasia in the castrated dog by the administration of androgens, and we had a variety of problems in administering the drugs in a manner that would sustain plasma levels and spent several futile years in this endeavor. In fact, we did not succeed in inducing prostatic hyperplasia in the castrated dog until Patrick Walsh, then a fellow in the lab, administered androstanediol, another 5α-reduced androgen that is back converted to in the prostate to dihydrotestosterone (10). In the same experiment, the administration of estradiol along with androstanediol caused even greater growth (10).



a. Naturally occurring prostatic hyperplasia in the dog
b. Prostate of a castrated dog treated with androstanediol
c. Prostate of a castrated dog treated with estradiol
d. Prostate of a castrated dog treat with estradiol plus androstanediol (ref. 10)

Estradiol by itself does not induce growth. However, it was known that estradiol enhances the level of the progesterone receptor in breast, and it has a similar effect on the level of the dihydrotestosterone receptor in the prostate (11), almost certainly the explanation for the synergism of the two hormones in regulating prostate growth. On the basis of these studies we proposed a two hormone model for the pathogenesis of prostatic hyperplasia in the dog, namely that dihydrotestosterone is the hormone responsible for the hyperplasia and that estradiol enhances dihydrotestosterone action by increasing the level of the androgen receptor.

TWO HORMONE MODEL FOR THE PATHOGENESIS OF PROSTATIC HYPERPLASIA IN THE DOG

HORMONE	ACTION
• Dihydrotestosterone	• Induce hyperplasia
• Estradiol	• Enhance dihydrotestosterone action by increasing the level of the androgen receptor

Proof of the validity of the model took several years of additional work. Uli Wenderoth was eventually able to induce prostatic hyperplasia in the castrated dog with testosterone given in the form of esters. When he administered an experimental inhibitor of 5α-reductase (DMAA) for 4 weeks to dogs with naturally occurring prostatic hyperplasia, prostate size decreased from an average of 22 g to 5.4 grams; the regression was associated with a profound decline in prostate dihydrotestosterone levels but little change in plasma androgen levels, and recovery was complete within 8 weeks of stopping the inhibitor (12). Even more importantly, he was able to prevent the induction of prostate hyperplasia in the castrated dog given testosterone cypionate by the simultaneous administration of the 5α-reductase inhibitor (12),

EFFECT OF TESTOSTERONE WITH OR WITHOUT DMAA ON CASTRATED DOG PROSTATE

TREATMENT		PROSTATE WT, G
Castration plus Testosterone Cypionate	Week 0	11.4 ± 0.9
	4	21.4 ± 2.4
Castration plus Testosterone Cypionate plus DMAA	Week 0	11.2 ± 1.2
	4	5.6 ± 0.7

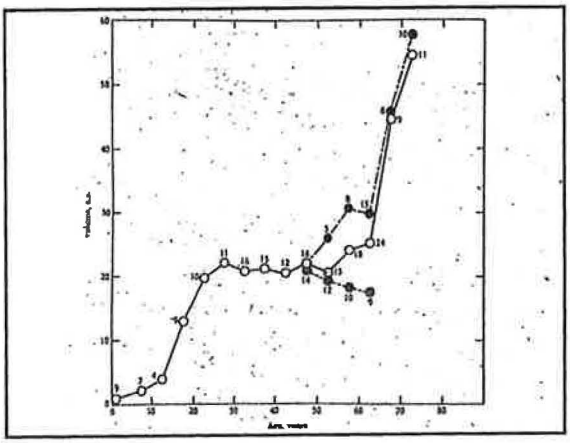
These findings clearly indicate that the hyperplastic process in this species is due to continued androgen action and that dihydrotestosterone and not testosterone mediates the process. The true etiology may be failure to downregulate the androgen receptor, and other downstream mediators

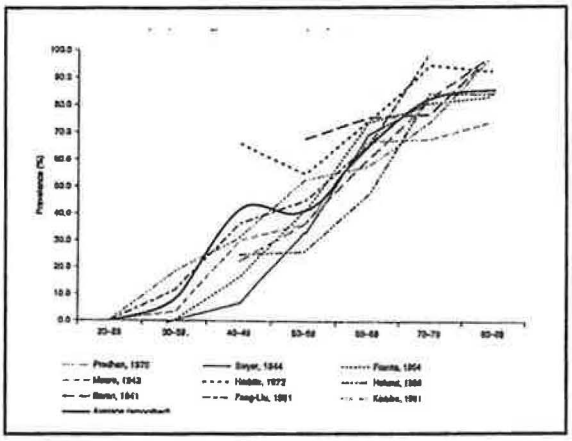
of androgen action are certainly involved in the hyperplasia (13). The two-hormone scheme for canine prostatic hyperplasia has been confirmed by many other groups and is one of the best established animal models for disease.

The preoccupation for 20 years has been whether this formulation has any relevance for the human disorder. To anticipate the thesis of my talk, the cumulative evidence supports the key role of dihydrotestosterone in the human disorder, but a role for estrogen is not established.

NATURAL HISTORY OF PROSTATIC HYPERPLASIA IN MEN

To describe the quest for medical therapy it is necessary to consider the natural history of prostatic hyperplasia. The weight of the prostate as a function of age was originally described by Swyer (13), namely, the gland weighs about 1.4 g at birth, increases to about 4 g prior to puberty, and then grows to about 20 g by age 20. On average, there is no change in weight until the mid 50s when a second growth spurt ensues 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.





Prostate size as a function of age (13) **Prostate histology with age** (14)

Actually, assessment of prostate volume does not provide much functional insight into the disorder for two reasons. First, the histological manifestations of prostate hyperplasia start many years before the overall volume increases (14). This discrepancy is due to the fact that the condition 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, sometimes requiring 25 years (15). Second, there is no clear relation between prostate size and symptomatology. On the one hand, obstruction to urine outflow can occur in normal sized prostates with periurethral pathology, and on the other only a fraction of men with prostatic enlargement become symptomatic (16). Nevertheless, in the Olmsted County, Minnesota prospective study, average prostate volume increased 1.6 % per year in normal men between the ages of 40 and 79 (17), and this increase in size was accompanied by a 2.1% decline in average peak urine flow rates per year (18). The disorder occurs in all ethnic groups; it seems to be most common in blacks, caucasians, and Jews and less common in Asia, and the course on average is accelerated in blacks (19) Whatever these mean changes may imply, in a prospective study of 81,000 men it was deduced that 45 % of asymptomatic 46 year old men will develop lower urinary tract symptoms within 30 years (20). Although the likelihood of

developing urinary tract obstruction is not great, in the Olmsted County study, 1 in 4 men in the eighth decade required treatment, and the presence of an enlarged prostate, a prostate specific antigen greater than 1.3 ng/ml, peak urinary flow rates < 12 ml per second, or severe symptoms was associated with a 4 fold risk of surgical treatment (21).

In summary, although histological development of prostatic hyperplasia is virtually universal not all men develop symptoms. In addition, during the course of the therapeutic trials during the past 20 years, our understanding of the natural history has undergone additional refinement. For example, it is not clear is how much of lower urinary tract symptoms in aging men (hesitancy, urgency, frequency, incontinence) is caused by prostatic hyperplasia and how much is due to dysfunction of the detrusor muscle of the bladder related to aging or other causes (22). From my standpoint, the fact that lower urinary tract symptoms in men are usually relieved by prostate surgery strongly suggests that prostatic hyperplasia is the usual, admittedly not invariable, cause.

UNRESOLVED ISSUES IN BPH

- Although histological features are universal, only a fraction of men develop symptoms and fewer have obstruction
- In many aging men lower urinary tract symptoms may not be due to prostatic hyperplasia
- Symptoms may stabilize or improve with time
- All therapeutic interventions are plagued by major placebo effects
- Incidence of prostate surgery has declined independent of medical therapy

It is also clear that symptoms may stabilize or actually improve with time, and a variety of studies of watchful waiting have been reported (reviewed in 13). Perhaps the most important of these studies was the five year VA cooperative study of Wasson and his colleagues (23) in which 556 men with lower urinary tract symptoms and prostatic hyperplasia were randomized to undergo transurethral resection or be watched conservatively. There were twice as many treatment failures in the conservatively managed group, and a fourth of the conservatively managed group underwent surgery. Strikingly, however, some of the conservatively treated group had a small but noticeable improvement in all outcomes measured. The most significant predictor for men deciding to cross over to surgery was high symptom score at the time of commencing the study (23).

Related to the "watchful waiting" phenomenon, placebo effects have plagued all pharmacological studies of prostatic hyperplasia (24-26). A major element in the placebo effect is the fact that subjects are chosen for studies on the basis of abnormal urine flows and high symptom scores, and these parameters tend to regress to the mean with time (26), and the fact that urine flow and urinary tract symptoms, both under complex neurogenic and physiological control and subject to influence by many variables (drugs, concurrent conditions, dietary intake, etc.) vary with time is hardly surprising. The probability for a patient to experience improvement is around 40 % in the watchful waiting and the placebo arms, and the changes in peak flow rates and residual urines are similar for these groups as well (13). The subjective improvement and the fluctuations in peak flow rate constitute the background placebo effect against which changes achieved by active treatment modalities of all kinds must be compared.

Be this as it may, in many, if not most, men lower tract urinary symptoms do not worsen very much with time, and for this reason the American Urological Association has developed guidelines for transurethral prostatectomy (1,27). These guidelines have gained widespread acceptance here and abroad, and the frequency of transurethral prostatectomy has fallen; in Europe, the decline between 1991 and 2000 was from 5.2 to 2.6 operations per 1000 men per year (28), and there was a similar decrease in the United States between 1984 and 1997 (29). These declines occurred too rapidly to be explained by any beneficial effects of medical therapy.

With these various confounding issues in mind, let us turn to the issue that is of special interest to me, namely the question of whether the dog two-hormone model is applicable to the human disorder. There are a variety of ways in which the model could be tested.

POTENTIAL WAYS TO TEST THE TWO HORMONE THESIS IN MAN

- **Role for Estrogen**
  Antiestrogens
  Aromatase Inhibitors
- **Role for Dihydrotestosterone**
  5α-Reductase Inhibitors

The question of a role for estrogens in the human disorder has been reviewed in the recent past (14, 30), and the easiest way to summarize the studies is to say that a great deal of indirect evidence supports such a relation [relative or absolute increase in estradiol levels in aging men, increased estrogen levels and prostate size in the massively obese, high levels of both estrogen receptors (α and β) in the hyperplastic prostate, etc.], but the critical experiments have not been done, namely to administer effective inhibitors of the aromatase enzyme or the estrogen receptor and demonstrate inhibition of prostate growth or regression in prostate size.

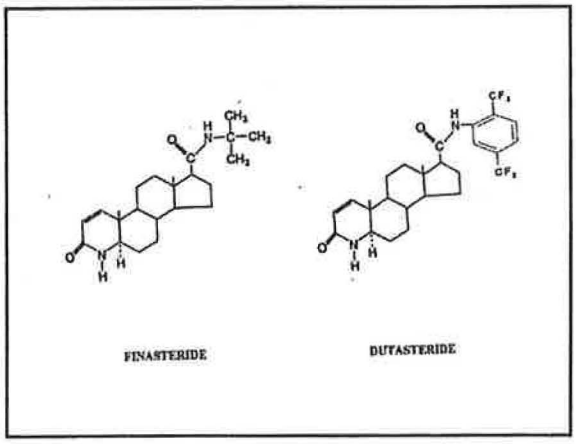
5α-reductase inhibitors were not initially available for testing in humans, but a number of pharmaceutical companies invested in their development because of suggestive evidence that they might be effective. Indeed, in the 19th century prior to the development of techniques first for open and then for transurethral prostatectomy, castration was a standard therapy for the condition (31,32), and it is interesting that surgical castration (33,34) and medical castration with the use of gonadotropin hormone-releasing hormone analogues (35, 36) have similar effects, namely about a 30 percent decrease in the size of the hyperplastic prostate including occasional dramatic improvement (37) in men who were poor candidates for surgery. Anti-androgens produce similar side effects to those of chemical castration (38). All forms of androgen deprivation cause hot flashes and impotence, but the studies indicated that the testes play a continuing role in the maintenance of prostatic hyperplasia. The implication was that a more selective inhibitor might

block the action of androgens selectively in the prostate, but the androgen deprivation studies also implied that the maximal benefit one would predict in men with advanced disease would be a decrease in size of 30 %.

This brings us to the subject of 5α-reductase inhibitors in men.

5α-REDUCTASE INHIBITORS

Several pharmaceutical companies developed candidate drugs, but the critical break-through was made by Brooks and his colleagues at Merck, namely the discovery that steroids in which the 4-carbon is replaced with a nitrogen (so called azosteroids) have the capacity to inhibit 5α-reductase without impairing the function of the androgen receptor (39). The agent that has been safest and most useful in clinical testing is finasteride (40), and the clinical studies that I am going to describe have been done with finasteride, which is a more effective inhibitor of human isoenzyme 2 than isoenzyme 1. [GlaxoSmithKline is now testing dutasteride, which inhibits both isoenzymes (41); it is not clear whether dutasteride is clinically more effective than finasteride.]



Finasteride is a potent inhibitor of steroid 5α-reductase 2; it is absorbed efficiently by mouth and has a turnover time in plasma of 6-8 h but a much longer biological effect in that plasma dihydrotestosterone levels do not return to normal for several days after stopping the drug (40). It passes across the placenta and causes a phenocopy of 5α-reductase 2 deficiency in male rat pups (42). The mechanism of action is complicated in that it is both a competitive and an irreversible inhibitor of the enzyme, and more importantly, like castration, it causes a decrease in the content of the enzyme and its messenger RNA in the rat prostate (43). Also, like castration, finasteride treatment causes an increase in the rate of apoptosis in the human prostate (44).

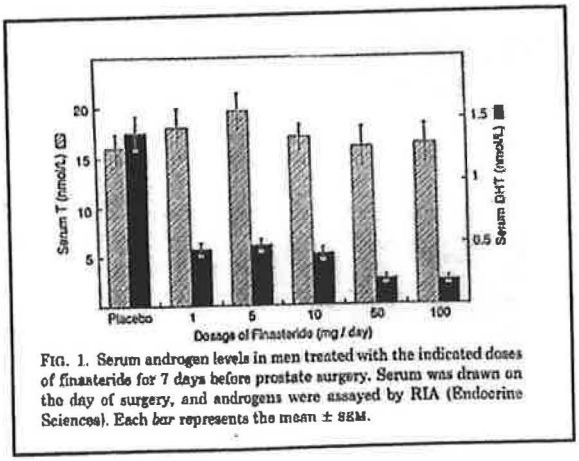


FIG. 1. Serum androgen levels in men treated with the indicated doses of finasteride for 7 days before prostate surgery. Serum was drawn on the day of surgery, and androgens were assayed by RIA (Endocrine Sciences). Each *bar* represents the mean ± SEM.

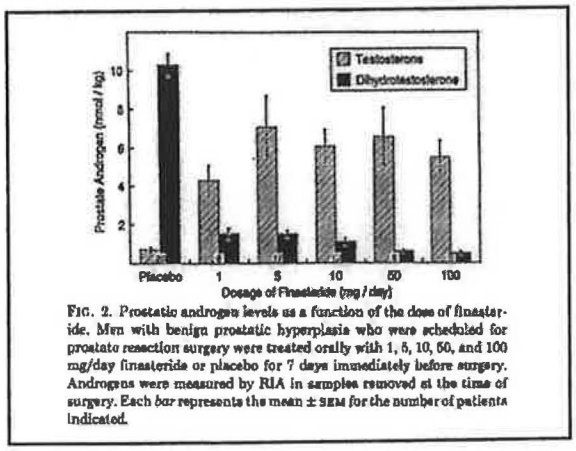
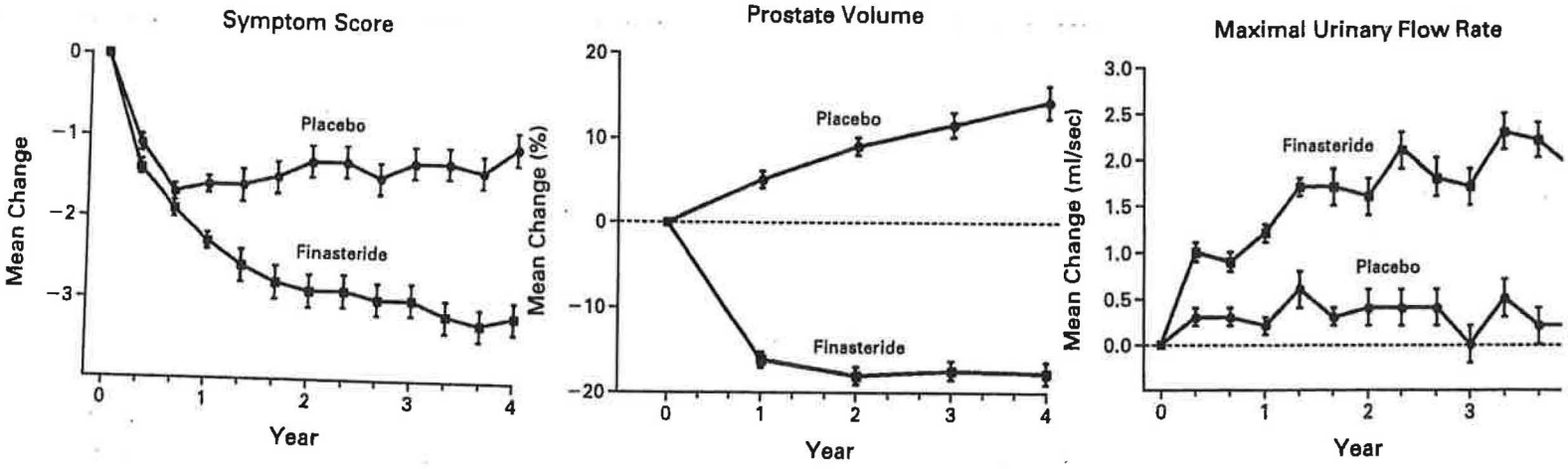


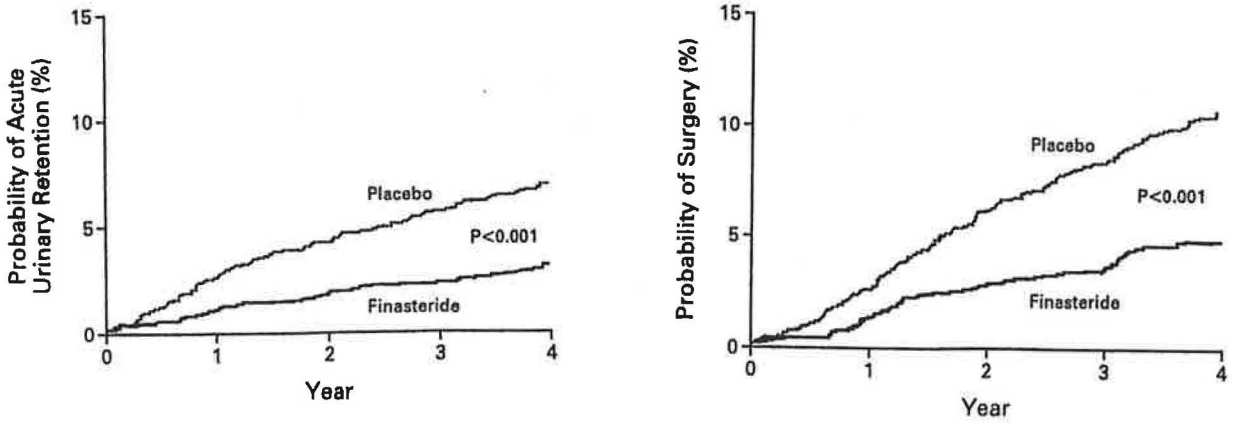
FIG. 2. Prostatic androgen levels as a function of the dose of finasteride. Men with benign prostatic hyperplasia who were scheduled for prostate resection surgery were treated orally with 1, 5, 10, 50, and 100 mg/day finasteride or placebo for 7 days immediately before surgery. Androgens were measured by RIA in samples removed at the time of surgery. Each *bar* represents the mean ± SEM for the number of patients indicated.

Finasteride causes a profound decline in plasma dihydrotestosterone levels in plasma of men with no reciprocal rise in testosterone, but the decrease in prostatic dihydrotestosterone is associated with an increase in tissue testosterone levels, a phenomenon that may limit the effectiveness of the drug (45).

Since the completion of the phase 3 testing in the early 90s there have been many articles from the US and abroad on various aspects of finasteride treatment for prostatic hyperplasia, but the most important of these was the publication of the Finasteride Long-Term Efficacy and Safety Study in 1998 (46). In this study 3040 men with moderate to severe lower urinary tract symptoms and enlarged prostate glands were randomized in a double-blind fashion to receive 5 mg of placebo or finasteride for four years. Symptom scores and urinary flow rates were measured every four months in all, and prostate volume was measured in a subset. The baseline characteristics were similar; 1000 finasteride-treated and 883 placebo-treated men completed the study.



Finasteride treatment caused an improvement in symptom score (after a year), a decrease in prostate volume, and an improvement in urine flow. Even more interestingly, the incidences of prostate surgery and of acute urinary retention were decreased in half by finasteride. These results may be skewed somewhat by the fact that the only subjects entered into the study were men with enlarged prostates, and it has been observed in several studies that the larger the prostate the more likely a beneficial response.



These differences are statistically significant and they are consistent. From my own standpoint, the most interesting feature of the studies was the fact that finasteride therapy stopped the growth of the hyperplastic prostate. [This concept is strengthened by the findings in the study to determine whether finasteride could prevent prostatic cancer (46) in which 18,882 55 year-old men were randomized to receive finasteride or placebo for seven years. Although there was a slight decrease in the development of cancer, the most striking finding was that the incidence of urinary retention was cut from 6.3 to 4.2 % and the incidence of transurethral resection from 1.9 to 1.0 % (46.] These studies constitute the strongest evidence to date that dihydrotestosterone is critically involved in the pathogenesis of the disease and validate our dog work in a major way.

Furthermore, since the criteria for entry into the BPH efficacy trial (45) were stringent, the fact that any therapeutic benefit occurred is impressive. However, there are problems with the findings in this study. One is that total adverse events (surgery or acute urinary retention) over four years in the 1883 men completing the study totaled 199 in the placebo group and 100 in the finasteride-treated group; in other words, it took 4000 treatment years to prevent 99 serious adverse events or 40 treatment years to prevent one adverse effect. What is needed is a means of predicting the subset of men who will develop adverse effects, and work is in progress to attempt to use genetic markers for such a purpose (47). [Also see Combined Treatment section below.] If such were available it might be more practical to treat the subset of men at high risk, A second problem is that the improvement in symptom score was not as dramatic as either the increase in urine flow or decrease in prostate volume. The symptom score is a reproducible and effective way to classify symptoms in numerical terms (mild symptoms 6.3 ± 2.0; moderate symptoms 14.4 ± 4.6; severe symptoms 23.2 ± 4.3) (48). The mean initial symptom scores were 15.5 in each group, and in the men who completed the study, the mean decrease was 3.3 in the finasteride group and 1.3 in the placebo group so that on average the men were left with moderately severe symptoms. Even more worrisome, many men had no improvement in symptoms, and the improvement in symptoms did not correlate with changes in prostate volume or urine flow. A third problem is that similar effects might have been achieved with a lower dose of finasteride. In the initial efficacy trials 1 mg/day produced a similar decrease in prostate size as 5 mg/day (49), and it is possible that low dose or intermittent therapy could be equally effective long term as the 5mg/day dose.

What about adverse effects? Because the men were also at risk for prostate cancer, they were carefully monitored with serial digital rectal examinations and measurements of PSA (45). Prostate biopsies were performed in 320 finasteride-treated men and 325 of the placebo group, and cancers were detected in 5 % of each group. The drug-related adverse events consisted of sexual dysfunction and either breast enlargement or tenderness; the reasons for these effects are not clear in that men with 5α-reductase 2 deficiency never have breast enlargement and do not appear to have diminished sexual drive or potency. Diminished ejaculate volume is almost certainly a consequence of the role of dihydrotestosterone in the normal function of the seminal vesicles and prostate. It is interesting that most adverse events occurred during the first year of therapy, a phenomenon that has been observed by others (50). Sexual dysfunction may be increased in men with lower urinary tract symptoms (51), but that could not explain the effects of finasteride therapy.

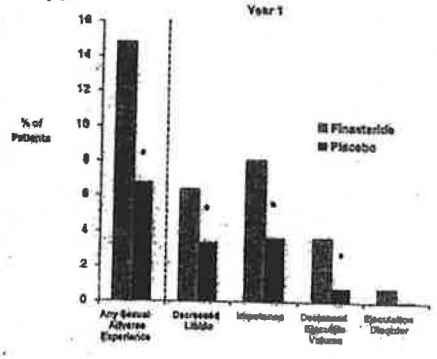


FIGURE 1. *Percentage of patients with drug-related sexual AEs during the first year of treatment with finas-*

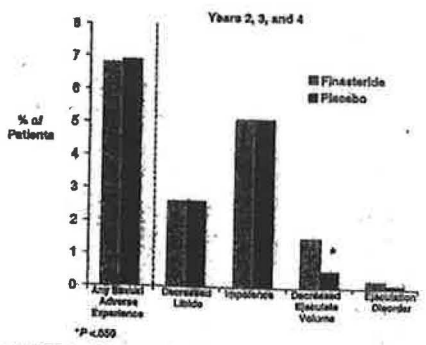


FIGURE 2. *Percentage of patients with new drug-related sexual AEs during years 2 to 4 of treatment with finasteride 5 mg or placebo.*

ALPHA BLOCKERS

α1-Adrenergic receptor antagonists were first used empirically approximately 25 years ago to treat the lower urinary tract symptoms associated with prostatic hyperplasia, and over the ensuing years many well designed, adequately powered, randomized, placebo-controlled studies have established a role for such agents in the treatment of this disorder (52, 53). The empiric data are impressive, but the subsequent development of a pathophysiological rationale for the therapy is confusing. The predominant receptor subtype in the human prostate appears to be the α_{1a}-adrenergic receptor and that specific blockade of this receptor would work without systemic side effects (54), but in fact the urospecific receptor antagonists tested to date appear less effective than nonspecific α1-receptor antagonists (55, 56). This finding plus the fact that the antagonists work in patients with lower urinary tract irritative symptoms of other etiologies suggests that the primary effect of the agents is at the level of the bladder rather than the prostate itself. Interpretation of the literature is also confused by the fact that different agents and different study designs have been employed (titration to fixed dose, titration to response, titration to maximal dose, etc.) and because the placebo response also compounds these studies. Finally, agents with varying degrees of receptor subtype selectivity and different systemic side effects have been used. Terazosin, doxazosin, and tamsulosin have been studied most extensively. In the table below is my summary of eleven placebo-controlled studies involving more than 5000 men described in Ref 52. The data are consistent in that all three agents produced a mean improvement in urine flow rates and in symptom scores, and symptom improvement included virtually all categories (nocturia, hesitancy, urgency, etc.). Although side effects become intolerable at the higher doses, beneficial effects were achieved with well-tolerated doses. However, the improvements, like those from finasteride, are modest so that most men at the end of the studies were left with moderately severe symptoms and with abnormal flow.

Effect of α-Adrenergic Blockers in Men with Prostatic Hyperplasia

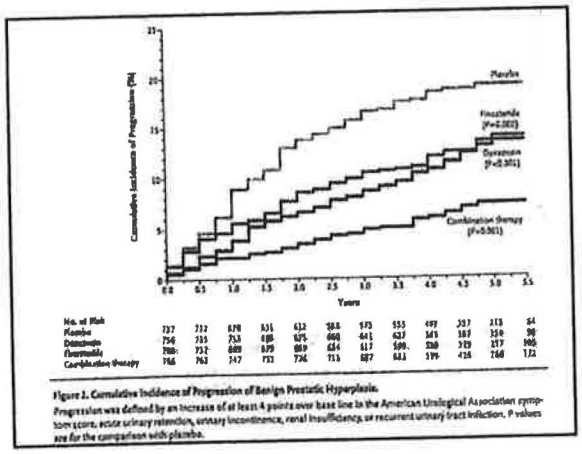
DRUG	SUBJECTS	LENGTH	DOSE	DIFFERENCE IN FLOW SYMPTOMS
TERAZOCIN (3)	2773	3.5 mo	2-8 mg	+1.3 ml -2.3
DOXAZOCIN (4)	483	6.8 mo	2-10 mg	+2.3 ml -3.3
TAMSULOSIN (4)	2074	2.2 mo	0.1-0.8 mg	+1.4 ml -2.2

It should be stressed that relief of symptoms with α blockers is very prompt, but the number of long term studies is small, the tendency being to switch all subjects to therapy after a year or so. In summary, although it has been suggested that α-blockade might impair prostate growth or cause regression (57) in fact change in prostate size has not been documented. Thus, although improved urine flow probably has no permanent beneficial effects, the therapy results in relatively consistent symptomatic improvement.

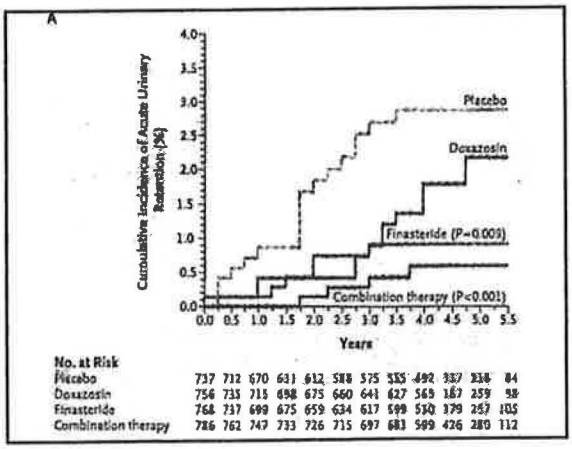
COMBINATION THERAPY WITH FINASTERIDE AND α-BLOCKERS

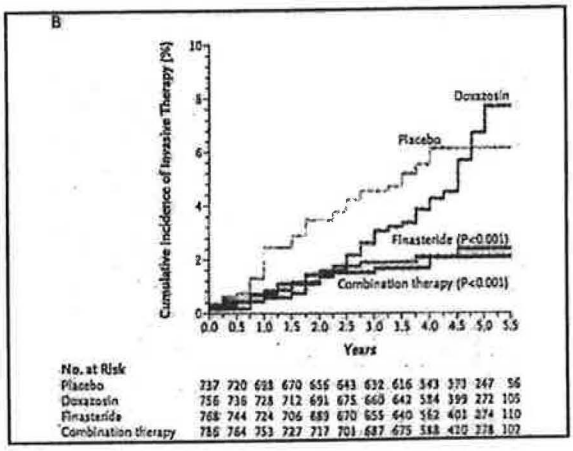
Two large cooperative trials compared therapy with finasteride and α-blockers, alone and in combination and reported that α-blockers [terazosin in the VA Cooperative study (58) and

doxazosin in the European study (59)] were more effective in relieving symptoms and improving urine flow than finasteride and that combination therapy was no more effective than α-blockers alone. Both studies were short in duration (one year). Since most workers in the field had predicted that combination therapy would in fact be superior, the NIH undertook the Medical Therapy of Prostatic Symptoms (MTOPS) trial, a long-term (mean time 4.5 years) double blind study involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia (1,60). The participants had an average age of 62, AUA symptom score of 17, prostate volume of 36 ml, maximal urinary flow rate of l0 ml/sec, and post residual volume of 68 ml. The risk of overall clinical progression—defined as an increase above base line of 4 AUA points, acute urinary retention, or recurrent urinary tract infection—was reduced 39 percent by doxazosin, 34 percent by finasteride, and 66 percent by the combined therapy.



When one looks at the severe outcomes—acute urinary retention and prostatic surgery, the data are equally impressive.





The conclusions from this study seem clear; namely, finasteride prevents the surgical complications, α-blockers prevent the progression of symptoms, and the combination is superior to the individual drugs alone.

Once again, however, to keep these data in perspective, the various improvements are all risk reductions in comparison with placebo. The actual number of adverse events is much smaller.

MTOPS 4 YEAR SUMMARY

	Placebo	Doxazosin	Proscar	Both
Patients	737	756	768	786
Progression	122	73	78	42
⇑Symptoms	97	55	65	36
Retention	18	9	6	4
Incontinent	6	7	7	1
Surgery	37	26	14	12

For example, only 17 percent of the men treated with placebo experienced serious progression, and only 5 % of these men wound up with surgery. Combination therapy reduced these numbers to 5% for progression and 1 % for surgery. Stated otherwise, treatment for 3832 patient years with the combination regiment prevented 14 episodes of acute urinary retention and 25 surgeries—hardly a miracle regimen.

This is even more disturbing when one considers the adverse events reported among the various groups. The most common side effects in the doxazosin group were dizziness, postural hypotension, and asthenia, and the most common adverse events in the finasteride group were erectile dysfunction, decreased libido, and abnormal ejaculation. The individual adverse events for the combination therapy were similar to those for each drug alone. These data are reported as adverse events per 100 patient years, and they would probably look worse if reported as cumulative percentage of subjects who developed adverse events during the entire duration of the study.

ADVERSE EVENTS IN THE MTOPS STUDY

	Placebo	Doxazosin	Finasteride	Both
⇓ Erection	3.3	3.6	4.5	5.1
Dizzyness	2.3	4.4	2.3	5.4
Hypotension	2.3	4.0	2.6	4.3
Asthenia	2.1	4.1	1.6	4.2
⇓ Libido	1.4	1.6	2.4	2.5
⇓ Ejaculation	0.8	1.1	1.8	3.0

Data are given as rates per 100 person years of followup.

As discussed above, the only way that combination therapy could have a major clinical impact would be in the subset of men (if they could be identified) who are destined to undergo overall clinical progression. Perhaps the most interesting finding in the MTOPS study relates to the prediction of men at high risk. Univariate analysis indicated that the risk of overall clinical progression increased with increasing base-line serum PSA levels and base-line prostate volume in the placebo and the doxazosin groups but not in the finasteride or combination-therapy groups. In the total sample, the number of men needed to treat to prevent overall progression was 8.4 for combination therapy, 13.7 for doxazosin, and 15.0 for finasteride. However, among men either with baseline PSA levels > 4 ng/ml or baseline prostate volume > 40 ml the number needed to treat to prevent progression was 7.2 for finasteride and 4.8 for combination therapy. Although this is a promising lead, better means are needed for identifying the subset of men headed for trouble.

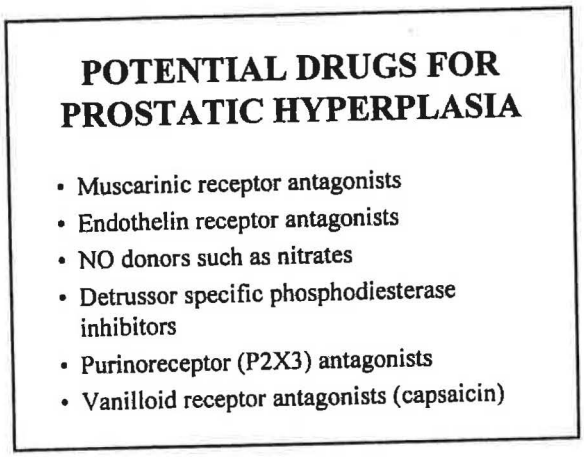
CONCLUSIONS

PROSTATIC HYPERPLASIA: CONCLUSIONS

- Continuing presence of dihydrotesotosterone in the prostate is essential for its development.
- Consequences include obstructive symptoms and lower urinary tract irritation.
- Only a subset of affected men develop obstruction or progressive symptoms.
- α-Adrenergic blockers ameliorate irritative symptoms; 5α-reductase inhibitors prevent obstruction; combination therapy is more effective and should be considered in men with documented progression or contraindications to surgery.
- Better therapies and/or better means of identifying men with progressive disease are needed.

These less than sensational results can be viewed either as a cup half empty or a cup half full. Over the last 40 years, considerable insight has been obtained into the natural history of prostatic hyperplasia. First, development of the process requires an intact testis, and the critical hormone involved is the testosterone metabolite dihydrotestosterone. This is not to imply that dihydrotestosterone is the cause, only that its continuing presence is essential for progression. Estradiol may or may not play a role in the process. Second, the functional consequences of prostatic hyperplasia can be separated into two broad categories: lower urinary tract symptoms, which do not correlate necessarily with prostate size and appear to result from instability of the detrussor muscle of the bladder, and obstructive symptoms, which appear to be due directly to prostate enlargement (either regional or generalized). Third, although development of the anatomic disorder is almost universal in aging men, only a minority of men develop symptoms or complications that require surgical intervention. Consequently, watchful waiting is always an option. Furthermore, surgical technologies for prostatectomy are undergoing a constant evolution. Fourth, lower urinary tract symptoms can be ameliorated with α-adrenergic blockers, the obstructive complications respond to steroid 5α-reductase inhibitors, and combination therapy is more effective than either alone. Fifth, to be cost effective, much better means are needed to identify the subset of patients at risk for progressive symptoms and/or obstruction itself. At present, the only clear indications for combined therapy at present are in candidates for prostatectomy who have some contraindication for surgery or in men with documented progression of disease. More effective (and safer) means of treating the disorder would be a boon.

In fact, a variety of potential therapeutic agents for prostatic hyperplasia are under investigation (61).



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