

THE ROLE OF DIHYDROTESTOSTERONE IN BENIGN PROSTATIC HYPERPLASIA

CULLEY CARSON III AND ROGER RITTMASER

ABSTRACT

This article examines the role of the androgen dihydrotestosterone (DHT) in the healthy and diseased prostate and considers the implications of the data on DHT for therapeutic approaches to benign prostatic hyperplasia (BPH). Development and maintenance of the normal prostate, as well as development of BPH, depend on a functional androgen-signaling axis, components of which include: (1) testosterone synthesis in the testes and adrenal glands; (2) conversion of testosterone to DHT; (3) transport of DHT to target tissues; and (4) binding of DHT to the androgen receptor with consequent modulation of genes. DHT plays a beneficial role in the developing prostate but it can be detrimental in the adult prostate in that it causes pathologic prostate growth. The role of DHT in other adult tissues is uncertain. DHT has not been shown to perform beneficial functions unique from testosterone in the adult male, and it is believed that its fundamental effect is to amplify testosterone's weaker hormonal signal. Increased understanding of the cellular mechanisms by which the androgen-signaling axis functions has led to advances in treatment for prostate disease. In BPH, the 5α -reductase inhibitors—the only class of therapy to act at the pathophysiologic substrate of the disease—arrest the disease process, reduce prostate volume, improve symptoms, and reduce the risk of acute urinary retention and BPH-related surgery. The availability of dutasteride, the first dual (Type 1/Type 2) 5α -reductase inhibitor, offers the opportunity for rapid and consistent inhibition of DHT. UROLOGY 61 (Suppl 4A): 2–7, 2003. © 2003, Elsevier Science Inc.

Nearly all men who reach average life expectancy are affected by prostate disease.¹ The most prevalent disease of the prostate is benign prostatic hyperplasia (BPH), histologic evidence of which is apparent in approximately 5 of 10 men (50%) who are 50 years of age, and 9 of 10 men (90%) who are 80 years of age.^{1,2} The mechanisms of BPH are multifactorial and are not yet definitively established. However, BPH is known to depend on androgens—in particular, the androgen dihydrotestosterone (DHT). DHT is also crucial to the early development and normal growth of the prostate. This article examines the role of DHT in the healthy and diseased prostate and considers the

implications of DHT suppression as a therapeutic approach to BPH.

SYNTHESIS OF DIHYDROTESTOSTERONE

The precursor of DHT is testosterone, most of which is produced by the Leydig cells of the testis in response to hormonal signals from the hypothalamus and pituitary ([Video Clip 1: Circulation of testosterone to the prostate](#); <http://www.goldjournal.net>) Figure 1.³ DHT is synthesized from testosterone by 5α -reductase, a highly lipophilic enzyme found on intracellular (ie, nuclear) membranes.⁴ There are 2 isoenzymes of 5α -reductase, designated Type 1 and Type 2 (Table I).⁴ 5α -Reductase Type 2 is found predominantly in the prostate and other genital tissues whereas 5α -reductase Type 1 is found throughout the body wherever 5α -reductase is expressed, including the prostate and the skin.⁵ Both isoenzymes are found in the liver. The isoenzymes differ in optimum pH for activity (5.5 pH for Type 1 vs 7.0 pH for Type 2) and chromosome location (chromosome 5 for Type 1 vs chromosome 2 for Type 2) and are differentially responsive to 5α -reductase inhibitors.⁴ Both Type 1 and Type

From the Division of Urology, Department of Medicine, University of North Carolina, Chapel Hill North Carolina, USA (CC); Clinical Development and Medical Affairs, GlaxoSmithKline, Research Triangle Park, North Carolina, USA (RR).

C.C. Carson III is a member of the speaker's bureau for, and is a study investigator funded by, GlaxoSmithKline.

Reprint requests: Culley Carson III, MD, Division of Urology, Department of Medicine, University of North Carolina 2140 Bioinformatics Building, CB# 7235, Chapel Hill, North Carolina 27599-7235. E-mail: carson@med.unc.edu

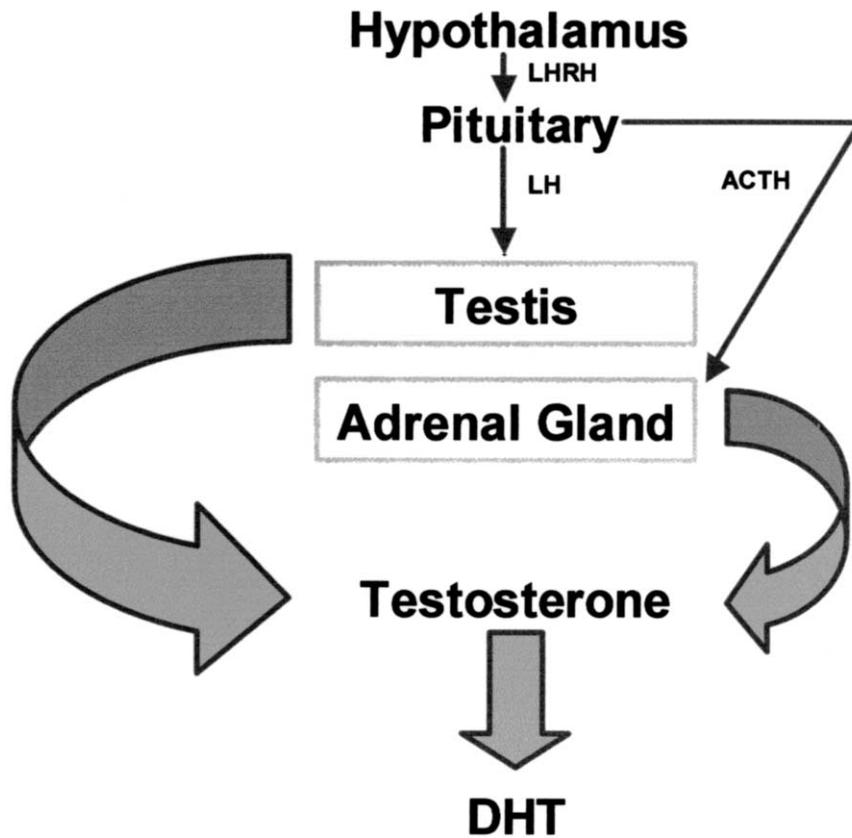


FIGURE 1. Schematic of the hypothalamic-pituitary-testicular-adrenal axis. ACTH = adrenocorticotropin hormone; DHT = dihydrotestosterone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone.³

TABLE I. Characteristics of human 5 α -reductase isoenzymes^{4,5}

	Type 1	Type 2
Chromosome location	Chromosome 5	Chromosome 2
Found in prostate?	Yes	Yes
pH optimum	Neutral to basic	Acidic
Inhibition by finasteride	No ($K_i \geq 300$ nmol/L)	Yes ($K_i = 5$ nmol/L)
mRNA expression increased in BPH tissue	Yes	Yes
Inhibition by dutasteride	Yes	Yes

2 isoenzymes are sensitive to inhibition by 5 α -reductase inhibitors: At their respective therapeutic doses, finasteride is an inhibitor of Type 2 isoenzyme, and dutasteride inhibits Type 1 and Type 2 isoenzymes (Video Clip 2: Conversion of testosterone to DHT by 5 α -reductase; <http://www.goldjournal.net>).⁵

THE ANDROGEN-SIGNALING AXIS

Development and growth of the normal prostate, as well as development of BPH or prostate cancer, depend on a functional androgen-signaling axis, components of which include: (1) testosterone synthesis in testes and adrenal glands, (2) conversion of testosterone to DHT, (3) transport of DHT to target tissues, and (4) binding of DHT to its

target receptor with consequent modulation of genes.⁶ DHT becomes physiologically active by binding to the androgen receptor, a member of the (intracellular) nuclear receptor superfamily that includes steroid-hormone receptors and thyroid-hormone receptors.^{7,8} The most potent endogenous androgen, DHT has substantially greater affinity for the androgen receptor than does testosterone making DHT the primary driver of this complex process.⁹

Binding of DHT to the androgen receptor complex results in a cascade of events necessary for the formation of signaling factors that regulate cellular growth.¹⁰ In the nucleus, 2 DHT-receptor complexes bind as a dimer to high affinity nuclear DNA sequences (ie, androgen response elements) that

can modulate the expression of genes (Video Clip 3: Molecular effects of DHT–receptor complex; <http://www.goldjournal.net>).^{11,12} In the prostate, for example, binding of the DHT/androgen complex to specific androgen response elements causes the production of proteins, such as prostate-specific antigen and regulatory proteins that modulate growth and cellular function.¹² When it is not bound with ligand, the androgen receptor is thought to be located in the cytoplasm and is inactive.¹⁰

The prostate is composed of approximately 40 to 50 ducts lined with epithelial cells and surrounded by a fibromuscular stroma. Although they are distinct tissue types, the stroma and the epithelium interact via cellular signaling mechanisms—including those mediated by DHT and DHT-dependent growth factors.¹³ 5 α -Reductase, DHT, and androgen receptors are present in both the stroma and the epithelium of the prostate.^{10,14} DHT is hypothesized to act on prostate cells via any of several mechanisms including endocrine, paracrine, or autocrine (Figure 2).⁸ (Video Clip 4: Signaling factors via paracrine mechanism modulate growth of prostate; <http://www.goldjournal.net>)

- With an endocrine mechanism, a hormone released from a gland is carried via the circulation to act at target cells. For example, DHT synthesized in organs distant from the prostate can reach androgen receptors in the prostate stroma via the circulation.

- With a paracrine mechanism, a hormone released from a cell is carried via diffusion to adjacent target cells. For example, DHT synthesized in the stroma can diffuse to adjacent stromal and/or epithelial cells to influence their function.

- With an autocrine mechanism, the cell that releases the hormone and the target cell are one and the same.

As with DHT, DHT-dependent mediators, such as growth factors, can act via paracrine or autocrine mechanisms to influence cellular function. Through these mechanisms, DHT and DHT-dependent growth factors regulate normal prenatal and postnatal development of the male genitalia and the prostate, as well as abnormal prostate growth.⁸

ROLE OF DIHYDROTESTOSTERONE IN NORMAL DEVELOPMENT

During normal development, DHT is responsible for differentiation of the fetal prostate and the development of male external genitalia.¹⁵ The integral role of DHT in prostate development is illustrated by observations of individuals with Type 2 5 α -reductase deficiency arising from a genetic mutation. These individuals have underdeveloped

prostates and genitalia at birth, and the prostate remains underdeveloped at puberty despite partial virilization (presumably occurring because of the action of testosterone).^{16,17}

In addition to these effects, DHT modulates prostatic function in the adult. In the adult prostate, DHT and other androgens are hypothesized to contribute to the maintenance of homeostasis between the processes of cell proliferation and cell death (ie, apoptosis) (Figure 3).^{12,18} Cell proliferation and apoptosis are androgen-dependent mechanisms affected by intermediaries set in motion by the binding of DHT to the androgen receptor. DHT indirectly mediates expression of genes that control cellular proliferation and death by controlling the expression and secretion of growth factors.^{12,19} Animal studies show that growth factors secreted by prostatic stromal cells can act on epithelial cells in paracrine fashion to affect proliferation and apoptosis.^{12,19} In humans, DHT may stimulate production and secretion of growth factors, such as growth-stimulatory epidermal factor (EGF), keratinocyte growth factor (KGF), and insulinlike growth factors (IGFs)—all of which modulate cellular proliferation.¹² Likewise, DHT affects the activity of transforming growth factor- β (TGF- β), which modulates apoptosis.^{19,20}

DHT plays a beneficial role in the developing prostate, but it can be detrimental in the adult prostate, in that it causes pathologic prostate growth.^{5,7,12} The role of DHT in nonprostate adult tissues, other than the skin, is uncertain. DHT has not been shown to perform beneficial functions unique from testosterone in the adult male, and it is believed that its fundamental effect is to amplify testosterone's weaker hormonal signal.¹⁷

ROLE OF DIHYDROTESTOSTERONE IN BENIGN PROSTATIC HYPERPLASIA

Consistent with its role in maintaining balance between cellular proliferation and death in the normal prostate, DHT plays an important role in the development of BPH—that is, pathologic prostate enlargement caused by an increase in cell number arising from both cellular hyperplasia and reduced apoptosis.¹⁰ Although the role of DHT in BPH has been defined relatively recently, the importance of androgens in the development of BPH has been appreciated for decades on the basis of circumstantial evidence. For example, BPH does not develop among those undergoing early castration or with hypopituitarism (which leads to hypoandrogenism).¹² Moreover, the size of the enlarged prostate can be reduced with antiandrogen manipulations, including administration of antiandrogen medications and surgical castration.¹²

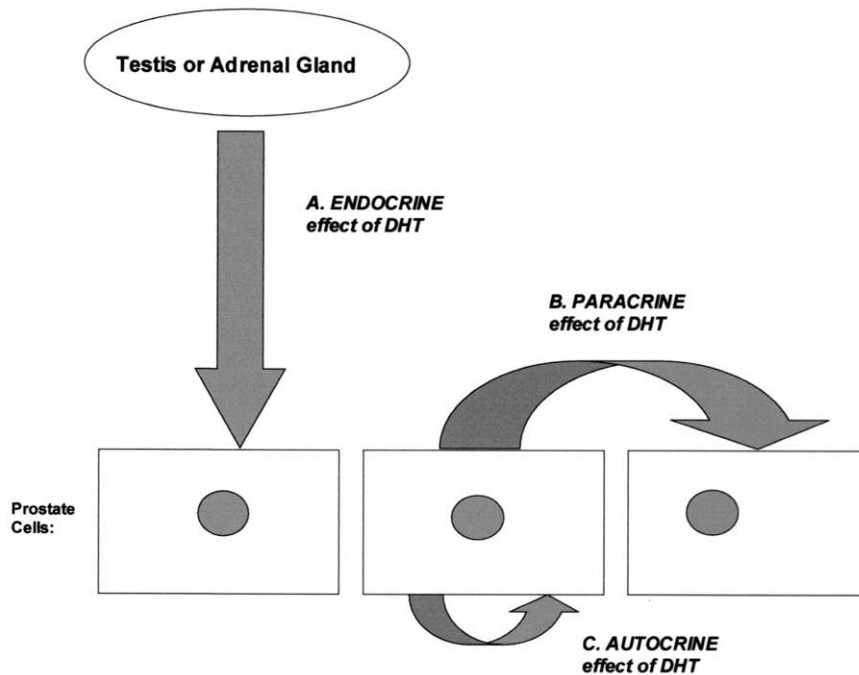


FIGURE 2. Autocrine, paracrine, and endocrine effects of dihydrotestosterone (DHT) in the prostate.⁸

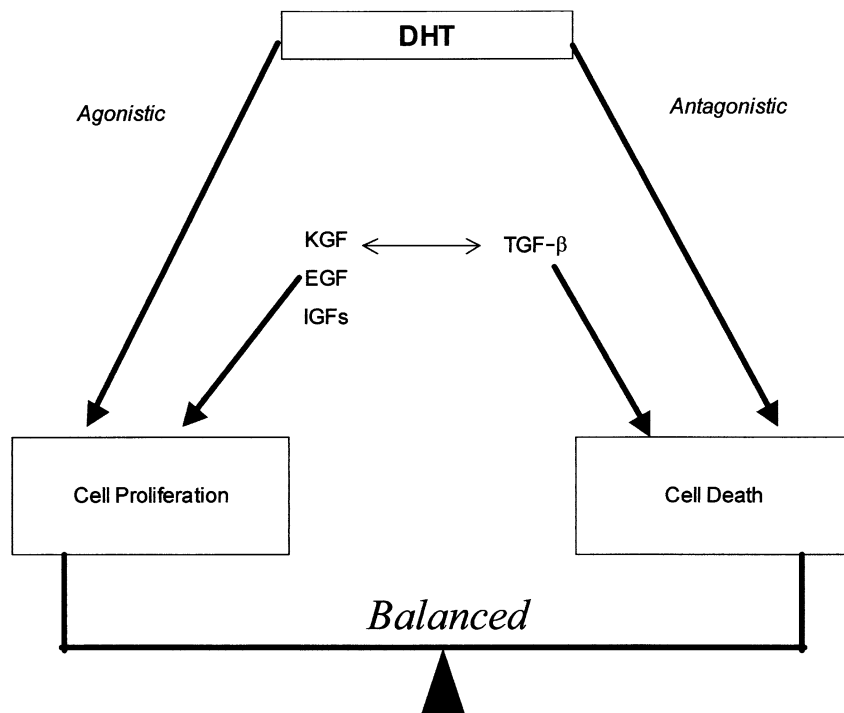


FIGURE 3. Diagrammatic representation of factors involved in maintaining homeostasis between cellular proliferation and cellular death in the prostate. DHT = dihydrotestosterone; EGF = epidermal growth factor; IGFs = insulinlike growth factors; KGF = keratinocyte growth factor; TGF- β = transforming growth factor- β .¹²

These data demonstrating an important role of androgens in BPH are extended by observations suggesting that DHT rather than testosterone is the causative androgen in BPH. For example, concen-

trations of both total and free testosterone in the plasma decrease as a function of age so that incidence of clinical BPH coincides with a time of decreasing circulating testosterone levels.⁴ Unlike

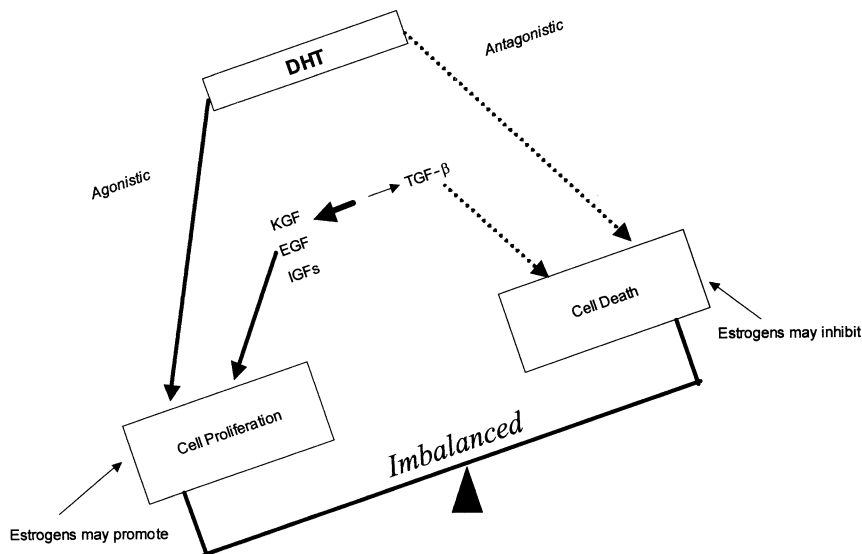


FIGURE 4. Diagrammatic representation of the prostatic imbalance between cellular proliferation and cellular death hypothesized to underlie benign prostatic hyperplasia. DHT = dihydrotestosterone; EGF = epidermal growth factor; IGFs = insulinlike growth factors; KGF = keratinocyte growth factor; TGF- β = transforming growth factor- β .¹²

circulating testosterone, which decreases with age, DHT levels do not appreciably decrease.⁴ Thus, DHT levels, unlike testosterone levels, remain constant throughout the time that clinical BPH is most likely to appear. These data are congruent with a role of DHT in hyperplastic prostate growth and suggest that testosterone, per se, is not critically involved directly.

The precise pathophysiologic mechanism of BPH has not been established, but the evidence described above supports an important role for DHT. Specifically, animal and human studies suggest that development of BPH entails disruption of the DHT-supported homeostasis between cell proliferation and cell death such that proliferative processes predominate and apoptotic processes are inhibited (Figure 4).^{8,12} The disruption of homeostasis could arise from perturbations in androgen levels or function (eg, from altered responsivity of the androgen receptor to stimulation with DHT) and/or from perturbations in levels or function of growth factors that are mediated by DHT.

TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

For some men, BPH is a progressive disease, defined as continued prostate growth, worsening of symptoms, and an increased risk of long-term complications such as acute urinary retention and BPH-related surgery. Two classes of medications with different mechanisms of action are available for the treatment of symptomatic BPH. Alpha-

blockers are effective in improving the symptoms of BPH regardless of prostate volume, but do not reduce the size of the prostate or arrest the disease process. In men with BPH and an enlarged prostate, 5 α -reductase inhibitors reduce prostate volume, arrest the disease process, and improve symptoms over time.²¹⁻²³ In clinical studies of men with BPH, 5 α -reductase inhibitors reduce prostate volume by approximately 20% to 30%.^{23,24} As discussed above, DHT plays an important role in the development of BPH. Furthermore, in BPH tissue, Type 1 and Type 2 5 α -reductase mRNA expression is slightly but significantly increased.¹⁴ These observations support the role of dual 5 α -reductase inhibition in the treatment of BPH. (Video 5).

Dutasteride inhibits both Type 1 and Type 2 5 α -reductase isoenzymes (Video Clip 5. Inhibition by dutasteride of both type 1 and type 2 5- α reductase; <http://www.goldjournal.net>).²¹ This dual inhibition reduces median serum DHT levels by 90% at 2 weeks and 93% at 2 years.²¹ Data collected from large (N = 4325) pivotal trials demonstrated the effectiveness of dutasteride in reducing prostate volume, arresting the disease process, and improving symptoms. (Video Clip 6: Clinical effect of prostate shrinkage by dutasteride; <http://www.goldjournal.net>).²³ In the pivotal trials, the most common drug-related adverse events in men taking dutasteride were impotence (4.7% dutasteride patients and 1.7% placebo patients, months 0 to 6; 0.8% dutasteride patients and 0.9% placebo patients, months 19 to 24), decreased libido (3.0%

dutasteride and 1.4% placebo, months 0 to 6; 0.3% dutasteride and 0.1% placebo, months 19 to 24), ejaculation disorder (1.4% dutasteride and 0.5% placebo, months 0 to 6; 0.1% dutasteride and 0.0% placebo, months 19 to 24), and gynecomastia (0.5% dutasteride and 0.2% placebo, months 0 to 6; 0.6% dutasteride and 0.1% placebo, months 19 to 24).²¹

CONCLUSIONS

Development and maintenance of the normal prostate as well as development of BPH depend on a functional androgen-signaling axis, components of which include: (1) testosterone synthesis in testes and adrenal glands; (2) conversion of testosterone to DHT; (3) transport of DHT to target tissues; and (4) binding of DHT to the androgen receptor with consequent modulation of genes. DHT plays a beneficial role in the developing prostate but can be detrimental in the adult prostate in that it causes pathologic prostate growth. DHT has not been shown to perform beneficial functions unique from testosterone in the adult male, and it is believed that its fundamental effect is to amplify testosterone's weaker hormonal signal.¹⁷ Increased understanding of the cellular mechanisms by which the androgen-signaling axis functions has led to advances in treatment for prostate disease. In BPH, the 5 α -reductase inhibitors—the only class of therapy to act at the pathophysiologic substrate of the disease—arrest the disease process, reduce prostate volume, improve symptoms, and reduce the risk of acute urinary retention and BPH-related surgery.

ACKNOWLEDGMENT. The author acknowledges the assistance of Jane Saiers, PhD, in writing the manuscript.

REFERENCES

1. Meigs JB, and Barry MJ: Natural history of benign prostatic hyperplasia, in Kirby R, McConnell JD, Fitzpatrick JM, *et al* (Eds), *Textbook of Benign Prostatic Hyperplasia*. Oxford, UK, Isis Medical Media Ltd, 1996, pp 139–148.
2. Berry SJ, Coffey DS, Walsh PC, *et al*: The development of human benign prostatic hyperplasia with age. *J Urol* 132: 474–479, 1984.
3. Rane A: Endocrine and adrenergic pharmacological intervention in disease of the prostate. *Br J Clin Pharmacol* 45: 329–337, 1998.
4. McConnell JD: 5 Alpha-reductase in prostate disease, in Kirby R, McConnell JD, Fitzpatrick JM, *et al* (Eds), *Textbook of Benign Prostatic Hyperplasia*. Oxford, UK, Isis Medical Media Ltd, 1996, pp 85–90.
5. Bartsch G, Rittmaster RS, and Klocker H: Dihydrotestosterone and the concept of 5 α -reductase inhibition in human benign prostatic hyperplasia. *Eur Urol* 37: 367–380, 2000.
6. Buchanan G, Greenberg NM, Scher HI, *et al*: Collocation of androgen receptor gene mutations in prostate cancer. *Clin Cancer Res* 7: 1273–1281, 2001.
7. Snyder PG: Androgens, in Hardman JG, Limbird LE (Eds), *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York, McGraw-Hill. 2001, pp 1635–1648.
8. Griffiths K, Morton MS, and Nicholson RI: Androgens, androgen receptors, antiandrogens and the treatment of prostate cancer. *Eur Urol* 32(suppl 3): 24–40, 1997.
9. Grino PB, Griffin JE, and Wilson JD: Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. *Endocrinology* 126: 1165–1172, 1990.
10. Marcelli M, and Cunningham GR: Hormonal signaling in prostatic hyperplasia and neoplasia. *J Clin Endocrinol Metab* 84: 3463–3468, 1999.
11. Gnanapragasam VJ, Robson CN, Leung HY, *et al*: Androgen receptor signaling in the prostate. *BJU Int* 86: 1001–1013, 2000.
12. Griffiths K: Molecular control of prostate growth, in Kirby R, McConnell JD, Fitzpatrick JM, *et al* (Eds), *Textbook of Benign Prostatic Hyperplasia*. Oxford, UK, Isis Medical Media Ltd, 1996, pp 23–26.
13. Foster CS: Pathology of benign prostatic hyperplasia. *Prostate Suppl* 9(suppl): 4–14, 2000.
14. Lehle C, Radvanyi F, Gil Diez de Medina S, *et al*: Differences in steroid 5 α -reductase isoenzyme expression between normal and pathological human prostate tissue. *J Steroid Biochem Mol Biol* 68: 189–195, 1999.
15. Wilson JD: Androgens, in Hardman JG, Limbird LE (Eds), *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York, McGraw-Hill. 2001, pp 1441–1458.
16. Imperato-McGinley J, Guerrero L, Gautier T, *et al*: Steroid 5 α -reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 186: 1213–1215, 1974.
17. Wilson JD: The role of 5 α -reduction in steroid hormone physiology. *Reprod Fertil Dev* 13: 673–678, 2001.
18. Isaacs JT: Antagonistic effect of androgen on prostatic cell death. *Prostate* 5: 545–557, 1984.
19. Niu Y, Xu Y, Zhang J, *et al*: Proliferation and differentiation of prostatic stromal cells. *BJU Int* 87: 386–393, 2001.
20. Kim IY, Zelner DJ, Sensibar JA, *et al*: Modulation of sensitivity to transforming growth factor-beta 1 and the level of type II TGF- β receptor in LNCaP cells by dihydrotestosterone. *Exp Cell Res* 222: 103–110, 1996.
21. Dutasteride tablets [package insert]. GlaxoSmithKline, Research Triangle Park, NC, 2002.
22. Finasteride tablets [package insert]. Merck & Company, Inc., Whitehouse Station, NJ, 2001.
23. Roehrborn CG, Boyle P, Nickel JC, *et al*: Efficacy and safety of dual inhibitor of 5 α -reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia (BPH). *Urology* 60: 434–441, 2002.
24. McConnell JD, Bruskewitz R, Walsh P, *et al*: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 338: 557–563, 1998.

