Tissue Content of Dihydrotestosterone in Human Prostatic Hyperplasia Is Not Supranormal

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ABSTRACT The dihydrotestosterone content of normal peripheral and benign hyperplastic prostates was measured in tissue obtained at open surgical procedures on 29 men of ages 36 to 82 yr. The dihydrotestosterone content in normal prostates (mean±SE, 5.1±0.4 ng/g tissue) and in benign hyperplastic prostates (5.0±0.4) was similar. In 11 patients in whom both normal and hyperplastic prostatic tissue was harvested simultaneously at the same operation, there was no significant difference in the content of dihydrotestosterone in the two types of tissue. These findings fail to confirm the widespread belief that dihydrotestosterone content is elevated in benign hyperplastic prostates. Our data differ from the reported literature in one major respect: the dihydrotestosterone content of normal peripheral prostate in this study is three to four times higher than previously reported. This difference between the present and earlier studies was resolved by experiments performed on cadavers, which were the source of normal prostatic tissue used by other investigators. Dihydrotestosterone content was measured in seven cadavers ranging in age from 19 to 82 yr of age. The results of this experiment indicate that the dihydrotestosterone content of prostatic tissue removed at autopsy is factitiously low (0.7–1.0 ng/g tissue). This finding was confirmed by in vitro incubations of fresh prostatic tissue at 37°C that demonstrated reduction of dihydrotestosterone content to low levels within 2 h. When taken together, these results indicate that when prostatic tissue is harvested appropriately, the dihydrotestosterone content of normal peripheral and hyperplastic tissues is the same. This finding should influence future research into the etiology of benign prostatic hyperplasia.

INTRODUCTION

Dihydrotestosterone is the major intracellular androgenic metabolite within the prostate (1, 2). Recognizing the central regulatory role of dihydrotestosterone in growth of the prostate, Wilson and co-workers (3) first suggested that dihydrotestosterone accumulation might be implicated in the etiology of benign prostatic hyperplasia (BPH).[1] This suggestion was based initially on an investigation of several different animal species to determine whether the capacity of the prostate to form dihydrotestosterone could be correlated with prostatic growth (3). Their study demonstrated that, in most animals, the prostate loses its ability to form dihydrotestosterone with age. However, in two animal species, the dog and man, high rates of dihydrotestosterone formation persist throughout life. Because these are the two animal species that spontaneously develop prostatic hyperplasia, they proposed that BPH might be the result of the unregulated production of dihydrotestosterone over many yers. To explore this possibility further, Siiteri and Wilson (4) measured the androgen content in normal and hyperplastic human prostates. Although they found no significant difference in the content of testosterone in the two types of tissue, the content of dihydrotestosterone was three- to fourfold greater in hyperplastic tissue than in normal glands. Subsequently, this observation has been confirmed by other investigators (5–8), and for the past dozen years,

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[1] *Abbreviations used in this paper:* BPH, benign prostatic hyperplasia; HPLC, high performance liquid chromatography.

research into the etiology of BPH has focused on factors that may be responsible for this accumulation of supranormal levels of dihydrotestosterone and the mechanism by which this induces prostatic hyperplasia.

Recently, while investigating the value of dihydrotestosterone content as a marker for the hormonal responsiveness of prostatic cancer, we noted that the content of dihydrotestosterone in normal and benign hyperplastic tissues obtained at open surgical procedures was similar. In reviewing the literature to determine why we were unable to confirm the findings of others, we learned that the "elevated" levels of dihydrotestosterone in BPH which were reported by others were based upon measurements performed on surgically removed specimens, whereas the "low levels" of dihydrotestosterone in normal tissue were based upon measurements performed on tissues obtained at autopsy (4–8). This observation suggested that the conditions of tissue harvesting may have significantly influenced the endogenous levels of androgens within the prostate. To explore this possibility, the present study was undertaken. Dihydrotestosterone content in normal and benign hyperplastic tissue has been measured in tissues removed at open surgical procedures and at autopsy on men of varying ages. These data suggest that the dihydrotestosterone content of prostatic tissue removed at autopsy is abnormally low. This finding was confirmed by in vitro incubations of prostatic tissue at 37°C that demonstrated rapid disappearance of dihydrotestosterone. These data indicate that when prostatic tissue is harvested appropriately, the dihydrotestosterone content of normal peripheral and hyperplastic tissues is the same. This finding should influence future research into the etiology of BPH.

METHODS

Materials. Testosterone and dihydrotestosterone were obtained from Steraloids, Inc. (Pawling, NY) and crystalized to constant melting point before use. [1,2,6,7-^{3}H]testosterone (98.8 Ci/mmol) was obtained from New England Nuclear, (Boston, MA) and [1,2-^{3}H]dihydrotestosterone (56 Ci/mmol) from Amersham Corp. (Arlington Heights, IL), and they were purified within 2 wk of use by thin-layer chromatography on precoated plates (250 μm, Analtech, Inc., Newark, DE). Reagent grade ethyl ether (Mallinckrodt Inc., St. Louis, MO) was used for sample extraction. Acetonitrile, which was used for high performance liquid chromatography (HPLC), was Photrex grade and was obtained from J. T. Baker Chemical Co. (Phillipsburg, NJ). Ethylene glycol, isooctane, and benzene (all Nanograde, which were used for celite-column chromatography, were obtained from Mallinckrodt Inc. The Celite analytical filter was obtained from Fisher Scientific Co. (Pittsburgh, PA).

Tissue. The prostates of 29 men who ranged in age from 36 to 82 yr were obtained at the time of simple retropubic prostatectomy for the treatment of BPH (six patients), radical retropubic prostatectomy for the treatment of stage B carcinoma of the prostate (eight patients), and radical cystoprostatectomy for the treatment of carcinoma of the bladder (15 patients). Seven additional prostates were removed at autopsy from men who ranged in age from 19 to 82 yr. The bodies were brought to the morgue and refrigerated within 4 h of death. The average time from death to removal of the prostate was 14 h (range 4.5–17 h). Normal testicular volumes were documented in all autopsied patients. After removal, all prostatic tissue was placed immediately in iced saline and examined by a surgical pathologist. Those specimens that were found to be hyperplastic were dissected into hyperplastic and normal peripheral segments. The tissue was then rinsed in iced saline, weighed, and stored in liquid nitrogen. A representative segment of each specimen was placed in formalin and later analyzed by the surgical pathologist to confirm the histological diagnosis.

Homogenization. The tissue frozen in liquid nitrogen was pulverized with a Thermovac tissue pulverizer (Redi-Industries Corp., Copiague, NY). The powdered tissue was added to 10 vol buffer (10 mM Tris, 1.5 mM EDTA, and 10% [wt/vol] glycerol, pH 7.4, at 22°C) and homogenized in an all glass Duall homogenizer (Kontes Co., Vineland, NJ) for three 5–10-s periods (pestle speed, 1,350 rpm) with a 60-s 4°C cooling-off period in between. An aliquot (0.5 ml) was saved for DNA determination, which was measured by the method of Burton (9) by using calf thymus DNA as standard. Results were expressed as nanograms of steroid per gram tissue or per milligrams of DNA±SE. The data were analyzed statistically by the *t* test (10) or the Wilcoxon rank sum test (11).

Extraction and defatting. [^{3}H]Testosterone (2,000 dpm; 3 pg) and [^{3}H]dihydrotestosterone (2,000 dpm; 5 pg) were added to each extraction tube for recovery measurement. Each sample was then extracted three times with 5 ml of ethyl ether (12). Each sample was defatted by passing the residue of the ether extract through a Bond-Elut column (octadecyl-C_{18}; 200 mg Sorbent) obtained from Analytical International Inc. The columns were first washed with 2 vol each of methanol, acetonitrile, and water. The residue of the ether extract was dissolved in 1 ml of water, which was added to the column. The steroids were eluted from the column with 3 ml of acetonitrile into a 12 × 75-mm collection tube and dried under nitrogen in a water bath at 45°C.

HPLC purification of testosterone and dihydrotestosterone. Testosterone and dihydrotestosterone in the defatted ether extracts of prostatic tissue were purified with a Waters Associates (Milford, MA) 6,000 A liquid chromatograph equipped with a Whatman Chemical Separation, Inc. (Clifton, NJ) Partasil ODS-3 column (4.6 mm × 25 cm). The steroids were eluted from the column with acetonitrile:water (50:50, vol/vol) at a flow rate of 3 ml/min. Testosterone, 5α-androstane-3α,17β-diol, dihydrotestosterone, and androsterone eluted from the column at 3.2–3.8, 4.0–4.6, 4.8–5.6, and 7.0–7.8 min, respectively. Eluates of testosterone and dihydrotestosterone were aliquoted for radioimmunoassay and for a recovery estimation via liquid scintillation spectrometry.

Radioimmunoassay. The radioimmunoassay procedures used were identical to those described elsewhere (12).

Validation of the assay. The defatting procedure removed material from the tissue extract that interfered with the radioimmunoassay of testosterone and dihydrotestosterone. 5α-androstan-3α,17β-diol, and androsterone were eluted separately from dihyrotestosterone in the HPLC system, and therefore did not interfere with the dihydrotestosterone assay.

The recovery of testosterone and dihydrotestosterone was determined on every biological sample and was 49 and 54%,

respectively. The recovery counts added to the prostatic tissue samples never exceeded 5% of the total radioactive counts used in the assay. The sensitivity of the assay for testosterone and dihydrotestosterone (defined as the mass of steroid that bound 90% on the displacement curve) was 12 and 11 pg, respectively. The blank values for both steroids averaged 7 pg for testosterone and 3 pg for dihydrotestosterone (well below the sensitivity of the assay). Any values that fell below 80% binding on the standard curve were reported as zero. This value was determined for each assay and varied from 15 to 30 pg/sample.

Precision of the assay was determined by measuring testosterone and dihydrotestosterone on five replicates of the same prostatic homogenate on five different days. The within-assay coefficients of variation for testosterone and dihydrotestosterone were 15.01 and 10.28%, respectively. The between-assay coefficients of variation for testosterone and dihydrotestosterone were 16.27 and 14.4%, respectively.

The accuracy of the assay for testosterone and for dihydrotestosterone was measured by the quantitative recovery of authentic testosterone and dihydrotestosterone that was added to 200 mg prostatic tissue from normal dogs. The testosterone and dihydrotestosterone concentrations were 0.806 and 8.33 ng/g, respectively. The amount determined after addition of 1 ng of testosterone and 1 ng of dihydrotestosterone (equivalent to 5.70 ng/g) was 6.24 ng/g for testosterone and 14.72 ng/g for dihydrotestosterone. Therefore, the recovery of testosterone and dihydrotesterone were 95.5 and 101%, respectively.

The specificity of the testosterone and dihydrotestosterone assay was confirmed by comparing the testosterone and dihydrotestosterone concentration in three samples of human prostatic tissue purified via Celite column plus HPLC chromatography vs. the single HPLC purification used routinely in the radioimmunoassay. There was no significant ($P > 0.25$) difference between prostatic testosterone and dihydrotestosterone concentrations that were obtained when the prostatic tissue was purified by the double vs. the single chromatographic purification procedure.

TABLE I

Content of Testosterone and Dihydrotestosterone in Normal Peripheral Prostatic Tissue Removed at Radical Prostatectomy or Cystoprostatectomy

	Patient	Age	Testosterone		Dihydrotestosterone	
			ng/g tissue	*ng/mg DNA*	*ng/g tissue*	*ng/mg DNA*
1.	A	36	0	0	5.2	2.4
2.	B	41	1.1	0.6	5.7	3.1
3.	C	44	1.7	1.1	4.1	2.6
4.	D	46	0.9	0.3	4.8	1.4
5.	E	47	0	0	7.5	2.5
6.	F	49	0	0	5.9	2.3
7.	G	53	6.5	2.8	6.8	3.0
8.	H	56	0	0	5.2	4.1
9.	I	57	2.7	1.2	8.8	3.8
10.	J	61	1.2	0.6	6.5	3.1
11.	K	61	0.7	0.3	1.5	0.6
12.	L	61	1.1	0.7	4.9	3.0
13.	M	62	1.4	0.7	3.6	1.9
14.	N	62	1.1	0.4	8.1	3.0
15.	O	64	2.3	0.9	4.9	2.0
16.	P	65	0	0	4.7	1.9
17.	Q	66	0.9	0.4	3.2	1.4
18.	R	69	0.9	0.5	4.0	2.3
19.	S	72	2.6	1.1	5.3	2.3
20.	T	74	0	0	2.7	1.1
21.	U	82	0.9	0.5	3.4	1.7
	Mean±SE		1.2±0.3	0.6±0.1	5.1±0.4	2.4±0.2

RESULTS

The content of testosterone and dihydrotestosterone in prostatic tissue removed at surgery. The content of testosterone and dihydrotestosterone was measured in normal peripheral prostatic tissue removed from 21 men at the time of radical prostatectomy or cystoprostatectomy (Table I). When these levels were compared with similar studies performed on benign hyperplastic tissue that was removed from 20 patients at open surgical procedures (Table II), there was no significant difference ($P > 0.25$) in the levels. Specifically, the dihydrotestosterone content of normal tissue, whether expressed as nanograms per gram of tissue (5.1±0.4 SE) or nanograms per milligrams of DNA (2.4±0.2 SE), was not different from the levels in benign hyperplastic tissue (5.0±0.4 ng/g tissue and 1.8±0.1 ng/mg DNA). When these data are plotted vs. age, once again there is no age or tissue correlation with dihydrotestosterone content (Fig. 1). Both normal peripheral and benign hyperplastic tissue were removed simultaneously at the same operation in the 11 patients who are listed in Tables I and II. When the dihydrotestosterone content in these specimens was compared, there was no significant difference (11) between the levels in normal peripheral and benign hyperplastic tissue (Table III). Thus, these results fail to support the prior observations of others which suggest that the dihydrotestosterone content of benign hyperplastic tissue is elevated above normal levels (4–8). In an effort to reconcile this difference, we reviewed the reports of others and learned that the levels of dihydrotestosterone in hyperplastic tissue reported herein correlated closely with those reported previously (4–6 ng/g tissue) (4–8, 13). However, the levels of dihydrotestosterone in normal peripheral prostate reported by others (1.3–2.1 ng/g tissue) (4–8) were much lower than those that we observed. On further scrutiny of the literature, we learned that the dihydrotestosterone values in BPH were measured in surgically resected specimens whereas the measurements in normal peripheral prostate were performed on tissue obtained at autopsy (4–8). This prompted us to investigate the content of androgens in prostatic tissue obtained at autopsy.

Content of testosterone and dihydrotestosterone in prostatic tissue removed at autopsy. Prostatic tissue was obtained at autopsy from seven men ranging in age from 19 to 82 yr (Table IV). The content of

TABLE II

Content of Testosterone and Dihydrotestosterone in Benign Hyperplastic Prostatic Tissue Removed at Radical Prostatectomy, Cystoprostatectomy, or Simple Retropubic Prostatectomy

	Patient	Age	Testosterone		Dihydrotestosterone	
			ng/g tissue	*ng/mg DNA*	*ng/g tissue*	*ng/mg DNA*
1.	V	51	9.5	4.1	5.3	2.3
2.	H	56	0	0	5.6	1.6
3.	I	57	0.5	0.3	3.2	1.6
4.	W	58	1.2	0.3	9.4	2.5
5.	X	60	1.1	0.4	7.6	2.5
6.	Y	61	0	0	5.5	1.8
7.	K	61	0.8	0.2	4.1	1.1
8.	L	61	0.7	0.3	3.6	1.7
9.	N	62	1.4	0.5	1.2	0.4
10.	O	64	1.0	0.3	5.5	1.9
11.	P	65	0.6	0.2	5.4	1.7
12.	Q	66	0	0	4.6	2.2
13.	Z	68	7.8	2.7	4.5	1.5
14.	R	69	1.1	0.9	3.2	2.6
15.	AA	70	5.6	1.6	6.6	1.9
16.	S	72	1.2	0.4	6.0	2.1
17.	T	74	0	0	2.4	1.3
18.	BB	74	1.5	0.5	6.4	2.1
19.	CC	77	1.5	0.6	4.8	1.8
20.	U	82	1.0	0.3	5.7	1.6
	Mean±SE		1.8±0.6	0.7±0.2	5.0±0.4	1.8±0.1

dihydrotestosterone in normal peripheral (0.7±0.2 ng/g tissue; 0.3±0.1 ng/mg DNA) and hyperplastic prostatic tissue (1.0±0.3 ng/g tissue; 0.3±0.1 ng/mg DNA) was five- to sixfold lower than in similar tissue that was removed surgically.

Influence of temperature on dihydrotestosterone content in prostatic tissue. Several investigators have justified the use of prostatic tissue procured at autopsy for the measurement of dihydrotestosterone content by performing incubation experiments at 20°C. These

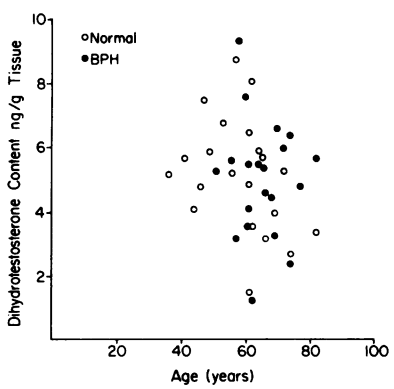

FIGURE 1 Dihydrotestosterone content in normal and benign hyperplastic prostatic tissue as a function of age. Each circle represents a single sample of prostatic tissue.

TABLE III

Dihydrotestosterone Content in Normal Peripheral and Benign Hyperplastic Prostatic Tissue Removed Simultaneously from the Same Patient at Radical Prostatectomy or Cystoprostatectomy

	Patient	Age	Normal tissue		Benign hyperplastic tissue	
			ng/g tissue	*ng/mg DNA*	*ng/g tissue*	*ng/mg DNA*
1.	H	56	5.2	4.1	5.6	1.6
2.	I	57	8.8	3.8	3.2	1.6
3.	K	61	1.5	0.6	4.1	1.1
4.	L	61	4.9	3.0	3.6	1.7
5.	N	62	8.1	3.0	1.2	0.4
6.	O	64	4.9	2.0	5.5	1.9
7.	P	65	4.7	1.9	5.4	1.7
8.	Q	66	3.2	1.4	4.6	2.2
9.	R	69	4.0	2.3	3.2	2.6
10.	S	72	5.3	2.3	6.0	2.1
11.	U	82	3.4	1.7	5.7	1.6
	Mean±SE		4.9±0.6	2.4±0.3	4.4±0.4	1.7±0.2

earlier studies demonstrated that when BPH tissue, which was surgically removed, was incubated at room temperature for 4–12 h and then refrigerated for another 8–16 h, there was no significant decrease in dihydrotestosterone content (4, 14). However, the unclothed body of an adult in an environmental temperature of 60°F only cools at 1°F/h during the first 3 h after death, and then at 2°F/h during the next 3 h (15). If the body is clothed, the rate of cooling is 66% slower. (16). These facts indicated the need to determine the influence of incubations performed at 37°C on dihydrotestosterone content. Normal peripheral and hyperplastic prostatic tissue obtained from a patient undergoing radical cystoprostatectomy was divided into 150-mg aliquots. A sample was frozen immediately and the remainder of the tissue was incubated at 37°C for intervals up to 4 h (Fig. 2). By 1 h, the content of dihydrotestosterone in normal and

TABLE IV

Dihydrotestosterone Content in Normal Peripheral and Benign Hyperplastic Prostatic Tissue Removed at Autopsy

Patient	Age	Normal tissue		Benign hyperplastic tissue	
		ng/g tissue	*ng/mg DNA*	*ng/g tissue*	*ng/mg DNA*
1	19	0.8	0.2	—	—
2	24	0.4	0.3	—	—
3	68	0.9	0.2	1.2	0.3
4	71	1.3	0.5	1.3	0.4
5	74	0.7	0.7	1.3	0.7
6	78	0.9	0.5	1.2	0.3
7	82	0	0	0	0
Mean±SE		0.7±0.2	0.3 + 0.1	1.0±0.3	0.3±0.1

BPH tissue was reduced by 27 and 47%, respectively, and by 2 h, the content in both tissues was reduced to levels similar to those presented in normal and BPH tissue obtained at autopsy (0.8–1.1 ng/mg DNA; 1.2–1.4 ng/g tissue) (Fig. 2).

DISCUSSION

The major finding in this study is that the content of dihydrotestosterone in normal prostatic tissue is similar to the content in the hyperplastic gland. The dihydrotestosterone content in normal prostatic tissue has been studied previously by six different laboratories (Table V). In five of the six reports, the measurements on normal tissue were performed on specimens obtained at autopsy and in these cases, dihydrotestosterone content was low (1.3–2.1 ng/g tissue) (4–8, 13). In addition, Hammond (6) found similar low levels in the periurethral tissue removed from five normal men. The use of material obtained at autopsy has been justified on two grounds: (*a*) prostatic tissue removed from cadavers which have been refrigerated for up to 16 h retains its capacity to grow in tissue culture in some cases (16); and (*b*) the content of dihydrotestosterone in hyperplastic prostatic tissue remains stable during incubations at room temperature for 4–12 h when followed by refrigeration for another 8–16 h (4, 14). However, as discussed earlier, the body temperature after death decreases by only 1°F/h during the first 3 h after death, or less if the body is clothed (15). Furthermore, in many patients, the peripheral perfusion of organs is compromised for several hours before death. Thus, the finding in this study that dihydrotestosterone content falls to low levels within 2 h of incubation at 37°C suggests that prostatic tissue obtained at autopsy is unsuitable for the measurement of dihydrotestosterone content.

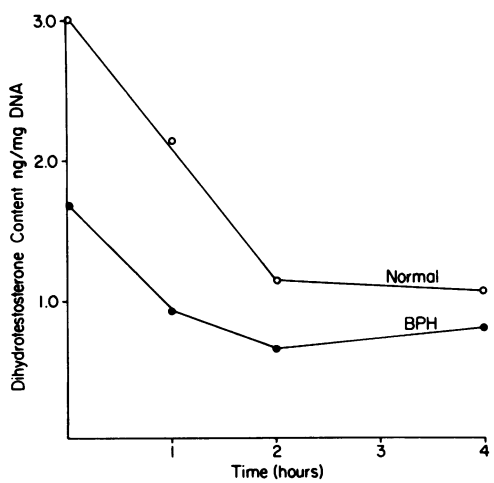

FIGURE 2 The influence of incubation in vitro at 37°C on dihydrotestosterone content in normal and benign hyperplastic prostatic tissue. Normal and benign hyperplastic tissue obtained from a patient at the time of cystoprostatectomy was incubated at 37°C in 250 μl of saline for the time indicated and then frozen in liquid nitrogen until assayed.

TABLE V
Summary of Published Data on Dihydrotestosterone Content in Normal and Hyperplastic Prostatic Tissue

Authors (reference)	Source of tissue: Normal	Source of tissue: Benign hyperplastic	Dihydrotestosterone content: Normal	Dihydrotestosterone content: Benign hyperplastic
			ng/g tissue±SE	
Siiteri and Wilson (4)	Autopsy	Surgery	1.3±0.5	6.0±1.0
Geller et al. (5)	Autopsy	Surgery	2.1±0.3	5.6±0.9
Hammond (6)	Autopsy	Surgery	1.3±0.3	5.5±0.5
Meikle et al. (7)	Autopsy	Surgery	1.3±0.6	4.0±1.9
Krieg et al. (8)	Autopsy	Surgery	1.6±1.0	4.5±1.4
Belis (13)	Surgery	Surgery	3.6±0.4	5.7±0.5
Present series	Surgery	Surgery	5.1±0.4	5.0±0.4
	Autopsy	Autopsy	0.7±0.1	1.0±0.2

In this study, the levels of dihydrotestosterone in normal and benign hyperplastic tissues removed surgically were identical. This finding differs from that of Belis (13); he reported dihydrotestosterone levels of 3.6±0.4 ng/g tissue in normal tissue removed surgically from men under 45 yr of age. This level was significantly lower than in the patients that he studied who had BPH (Table V). In our series, the content of dihydrotestosterone in normal prostatic tissue obtained from three men under age 45 (5.0±0.3 ng/g tissue) did not differ significantly from the levels in 18 patients that were 45 yr or older (5.1±0.4). In this series, we also measured the levels of dihydrotestosterone content in normal peripheral prostate from seven patients (patients A–G) before the gross appearance of BPH. The levels of dihydrotestosterone in this group (5.7±0.4 ng/g tissue) were not different from the levels of dihydrotestosterone in patients with established BPH. Furthermore, we were able to measure the levels of dihydrotestosterone in normal peripheral prostate and BPH tissue removed simultaneously from 11 patients at the same operation. Once again, these levels did not differ. Thus, we conclude that the content of dihydrotestosterone in human BPH is similar to the level in normal peripheral prostatic tissue and is not supranormal, as previously reported by others (4–8, 13).

The finding that the dihydrotestosterone content in BPH is identical to levels in normal tissue questions the role of dihydrotestosterone accumulation as a causative factor in the etiology of BPH. The speculative role of dihydrotestosterone as a causative factor in BPH has been supported experimentally by studies in the

dog, which demonstrated that: (*a*) canine BPH is characterized by increased prostatic dihydrotestosterone concentration (17); and (*b*) steroid treatment regimens that increase prostatic growth in the dog increase prostatic dihydrotestosterone concentrations (18). However, recent studies from our laboratories have questioned these findings. In age-matched dogs, we could demonstrate no difference in dihydrotestosterone content between dogs with histologically normal prostates and those with spontaneous BPH.[2] Secondly, although a positive correlation was observed between prostatic weight and dihydrotestosterone content in castrated or intact beagles that were treated with 11 of 15 different steroid hormone regimens, there were four additional treatment regimens (intact or castrated beagles treated with either dihydrotestosterone or 3α-androstanediol alone) which resulted in high concentrations of prostatic dihydrotestosterone that failed to evoke equivalent increases in prostatic weight. Finally, there was a dramatic biphasic change in prostatic dihydrotestosterone concentrations with advancing age in the beagle. After 4 yr of age, the incidence of BPH continued to increase although dihydrotestosterone content in the prostate fell.[2] In another study, we observed that the prostatic secretory function in the beagle peaks at ~4 yr of age and then declines dramatically (19). However, as the secretory capacity of the prostate diminishes, the gland continues to grow and histologic changes of BPH become more evident. These data suggest that factors that regulate growth of the canine prostate and at least one differentiated function (i.e., secretion) may be controlled separately; also, the fact that abnormal growth continues in the face of declining dihydrotestosterone levels suggests that regulatory factors other than dihydrotestosterone may be involved in the etiology of the hyperplastic growth of the dog prostate. The recognition that human BPH occurs in the presence of normal tissue levels of dihydrotestosterone should focus research efforts to identify other factors that may sensitize this tissue and accelerate growth.

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