

# The Pathophysiology of Benign Prostatic Hyperplasia

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**ABSTRACT:** Although benign prostatic hyperplasia (BPH) is one of the most common disease processes affecting the aging male, surprisingly little is known about its pathophysiology. Cause-and-effect relationships have not been established, despite intense research efforts in the last four or five decades aimed at elucidating the underlying etiology of prostatic growth in older men. Previously held notions that the clinical symptoms of BPH (prostatism) are due simply to a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of the symptoms are due to obstruction-induced detrusor dysfunction. Moreover, obstruction may induce a vari-

ety of neural alterations in the bladder and prostate that contribute to symptomatology. Undoubtedly, the constellation of cellular pathologies that give rise to the symptoms of BPH will be far more complex than we currently realize. Only by unraveling these complexities, however, will we be able successfully to design alternative strategies to treat, and possibly prevent BPH.

Key words: Prostatic growth, prostatic smooth muscle, prostatism.

**J Androl 1991;12:356-363.**

This report is not intended as an exhaustive scientific discussion of benign prostatic hyperplasia (BPH) pathophysiology. Rather, the objective is to provide the practitioner with an overview of the pathophysiologic mechanisms to which current therapeutics are directed.

## Pathology

### Anatomic Features

Much of our understanding of pathology of BPH comes from the elegant work of McNeal (McNeal, 1988, 1990). His anatomic studies demonstrate that BPH first develops in the periurethral transition zone of the prostate. The transition zone consists of two separate lobules of tissue immediately external to the preprostatic sphincter. The main ducts of the transition zone arise on the lateral aspects of the urethral wall, at the point of urethral angulation near the verumontanum. Proximal to the origin of the transition zone ducts are the glands of the periurethral zone, which are confined within the preprostatic sphincter and course parallel to the axis of the urethra. McNeal believes that all BPH nodules develop either in the transition zone or in the periurethral region (McNeal, 1988, 1990).

Although early transition zone nodules appear to occur either within or immediately adjacent to the preprostatic

sphincter, they can be found in almost any portion of the transition or periurethral zones as the disease progresses and the number of small nodules increase. However, the transition zone also enlarges with age, unrelated to the development of nodules (McNeal, 1990). In some cases, predominant growth of periurethral nodules at the bladder neck gives rise to the "middle lobe." By McNeal's definition, the middle lobe must be of periurethral origin, since there is no transition zone tissue in this area. It is not clear whether middle lobe growth occurs at random in men with BPH, or whether there is an underlying genetic susceptibility to this pattern of enlargement.

One of the unique features of the human prostate is the presence of the prostatic capsule, which plays an important role in the development of prostatism. In the dog, the only other species known to develop naturally occurring BPH, symptoms of prostatism rarely arise because the canine prostate lacks a capsule. Presumably, the capsule transmits the "pressure" of tissue expansion to the urethra, and leads to an increase in urethral resistance. Thus, the clinical symptoms of BPH in humans may be due not only to age-related increases in prostatic size, but also to the unique anatomic structure of the human gland. Clinical evidence of the importance of the capsule can be found in series that clearly document that incision of the prostatic capsule (transurethral incision of the prostate) results in a significant improvement in outflow obstruction, despite the fact that the volume of the prostate remains the same.

The size of the prostate does not correlate with the degree of obstruction. Thus, other factors such as dynamic urethral resistance, the prostatic capsule, and anatomic pleomorphism are more important in the production of clin-

This manuscript is derived from a lecture presented on April 30, 1991 at the Sixteenth Annual Meeting of the American Society of Andrology.

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ical symptoms than the absolute size of the gland. Perhaps the volume of periurethral/transition zone tissue relates more to the degree of obstruction than the overall volume of the prostate.

### Histologic Features

Benign prostatic hyperplasia is a true *hyperplastic* process. Histologic studies document an increase in the cell number (McNeal, 1990; Rohr and Bartsch, 1980). In addition, thymidine uptake studies in the dog clearly indicate an increase in DNA synthesis (Barrack and Berry, 1987). The term benign prostatic *hypertrophy* is pathologically incorrect.

McNeal's studies demonstrate that most periurethral nodules are purely stromal in character (McNeal, 1990). These small stromal nodules resemble an embryonic mesenchyme, with an abundance of pale ground substance and minimal collagen. It is unclear whether these early stromal nodules contain mainly fibroblast-like cells, or whether differentiation toward a smooth muscle cell type is occurring. In contrast, the earliest transition zone nodules represent proliferation of glandular tissue, which may be associated with an actual reduction in the relative amount of stroma (McNeal, 1990). The minimal stroma seen initially consists primarily of mature smooth muscle, not unlike that of the uninvolved transition zone tissue. These glandular nodules are apparently derived from newly formed small duct branches that sprout from existing ducts, leading to a totally new ductal system within the nodule. This type of new gland formation is quite rare outside of embryonic development. The proliferative process leads to a tight packing of glands within a given area, as well as an increase in the height of the lining epithelium, and there appears to be hypertrophy of individual epithelial cells as well. Again, the observed increase in transition zone volume with age appears to be related not only to an increased number of nodules, but also to an increase in the overall size of the zone.

McNeal believes that during the first 20 years of BPH development, the disease may be predominantly characterized by an increased number of nodules, whereas the subsequent growth of each new nodule is generally slow (McNeal, 1990). A second phase of evolution occurs where there is a significant increase in large nodules. In the first phase, the glandular nodules tend to be larger than the stromal nodules. In the second phase, when the size of individual nodules is increasing, the large glandular nodules clearly predominate.

There is significant pleomorphism in stromal-epithelial ratios in resected tissue specimens. Studies from primarily small resected glands demonstrate a predominance of fibromuscular stroma (Rohr and Bartsch, 1980, 1983). However, larger glands, chiefly those removed by enucleation, evidence mostly epithelial nodules (Franks, 1954). Although measurement of stromal-epithelial ratios may fur-

ther our understanding of the disease process, and even allow us to predict therapeutic response (eg, to  $\alpha$ -blocker therapy; Shapiro and Lepor, 1991), these morphometric analyses should not be overinterpreted. An increase in stromal-epithelial ratios does not necessarily indicate that BPH is a "stromal" disease; stromal proliferation may well be due to "epithelial" disease.

### Etiology

#### Hormonal Regulation of Prostatic Growth

There is abundant evidence that the development of BPH requires the presence of testicular androgens (Table 1) as well as aging (McConnell, 1990). Patients who are castrated before puberty, or who are affected by a variety of genetic diseases that impair androgen action or production, do not develop BPH. It is also known that prostatic levels of dihydrotestosterone (DHT), as well as the androgen receptor, remain high with aging, despite the fact that peripheral levels of testosterone decrease. Moreover, recent evidence demonstrates that androgen ablation by castration or medical therapy leads to a partial involution of established BPH (McConnell, 1990). In a given organ, the number of cells, and thus the volume of the organ, depends on the equilibrium between cell proliferation and cell death (Coffey and Walsh, 1990; Isaacs, 1987). Thus, an organ can enlarge not only by an increase in cell proliferation, but also by a decrease in cell death. Although androgens and growth factors may stimulate cell proliferation in experimental models, the role of cell proliferation in human BPH must be questioned, as there is no clear evidence of an active proliferative process. Although it is possible that the early phases of BPH are associated with a rapid proliferation of cells, the established disease appears to be maintained in the presence of an equal or reduced rate of cell replication. There is increasing evidence that androgens are not only required for normal cell proliferation and differentiation in the prostate, but may also actively inhibit cell death (Isaacs, 1987). In the dog, experimental BPH can be produced by androgens combined with estradiol (Coffey and Walsh, 1990; DeKlerk et al, 1979; Walsh and Wilson, 1976). Despite a significant increase in gland size, there is actually a reduction in the rate of DNA synthesis compared to untreated controls (Barrack

Table 1. Evidence for the androgen dependence of benign prostatic hyperplasia

Prepubertal castration prevents BPH
Genetic diseases that impair androgen action or production inhibit prostatic growth
Prostatic levels of DHT and androgen receptor remain high with aging
Androgen ablation by castration leads to some degree of prostatic involution

and Berry 1987). These studies demonstrate that, in the dog, androgens and estrogens both inhibit the rate of cell death.

Isaacs (1987) and Naslund and Coffey (1987) have developed the hypothesis that BPH is a "stem cell" disease. Presumably, dormant stem cells in the normal prostate rarely divide, but when they do, they give rise to a second type of transiently proliferating cell capable of undergoing DNA synthesis and proliferation, thus maintaining the number of cells in the prostate. Once the proliferating cells mature through a process of terminal differentiation, they have a finite lifespan before undergoing programmed cell death. These investigators have postulated that a block develops in the maturation process that reduces the progression to terminally differentiated cells, thus decreasing the overall rate of cell death. Indirect evidence for this hypothesis comes from the observation that secretion, one parameter of epithelial cell differentiation, decreases with age. This suggests that the number of differentiated cells capable of secretory activity may be decreasing (Isaacs, 1987).

Hormones may exert their influence over the stem cell population not only with advancing age, but also during embryonic and neonatal development (Naslund and Coffey, 1987). The size of the prostate may be defined by the absolute number of potential stem cells present in the gland, which in turn may be dictated at the time of embryonic development. Studies in animal models have suggested that early imprinting of prostatic tissue by postnatal androgen surges is critical to subsequent, hormonally induced, prostatic growth (Naslund and Coffey 1986, 1987).

### **The Role of Dihydrotestosterone (DHT) and the Androgen Receptor**

The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life. In the penis, androgen receptor expression decreases to negligible rates at the completion of puberty (Roehrborn et al, 1987; Takane et al, 1991). Thus, despite high circulating levels of androgens, the adult penis loses its ability for androgen-dependent growth. If the penis maintained high levels of androgen receptor throughout life, presumably the organ would grow until the time of death. In contrast, androgen receptor levels in the prostate remain high throughout aging (Barrack et al, 1983; Husmann et al, 1990; Rennie et al, 1988; Takane et al, 1991). In fact, there is evidence to suggest that nuclear androgen receptor levels may be higher in hyperplastic tissue than in normal controls (Barrack et al, 1983). Age-related increases in estrogen, as well as other factors, may increase androgen receptor expression in the aging prostate, leading to further growth (or to a decrease in cell death), despite decreasing levels of androgens in the peripheral circulation and "normal" levels of DHT in the

prostate. The regulation of androgen receptor expression in BPH, which can now be studied at the transcriptional level (Tilley et al, 1989; Takane et al, 1991), will be a major focus of future research.

Initial studies of resected prostatic tissue suggested that prostatic DHT levels were higher in the hyperplastic gland than in normal control tissues (Table 2). However, the controls used for these early studies were largely accident victims. Ongoing metabolism of DHT after death lowers the level of this androgen in cadaveric tissues.

This was clearly shown in a study by Walsh et al, where prostatic surgical specimens from men without BPH were used as controls (Table 2; Walsh et al, 1983). These investigators demonstrated that DHT levels are the same in hyperplastic and normal glands. However, the aging prostate maintains a high level of DHT, as well as a high level of androgen receptor; thus, the mechanisms for androgen-dependent cell growth are maintained. There is little question that androgens have at least a permissive role in the development of the disease process.

The testes are clearly required for the development of BPH. However, testosterone is not the principle androgen within the prostate. Rather, 80% to 90% of intraprostatic testosterone is converted into a more active metabolite, DHT, by the enzyme 5 $\alpha$ -reductase. High levels of 5 $\alpha$ -reductase are found in nuclear membrane microsomes of prostatic epithelial cells (McConnell, 1990). This enzyme does not appear to have any other important function, since its absence in the 5 $\alpha$ -reductase deficiency syndrome, as well as inhibition by finasteride, does not appear to result in other medical problems (McConnell, 1990; McConnell et al 1990).

Androgens are not the only important factors contributing to the development of BPH. All mammalian prostates studied have testosterone, DHT, and androgen receptor; however, only dogs and man develop BPH. Interestingly, another glandular organ that remains androgen-responsive throughout life, the seminal vesicle, does not develop hyperplasia. Obviously, other mechanisms or cofactors must be present in these two species that make them susceptible to the disease. Nonandrogenic substances from the testis,

Table 2. Published data on prostatic dihydrotestosterone levels\*

	Normal	BPH
Siiteri and Wilson (1970)	1.3 $\pm$ 0.5	6.0 $\pm$ 1.0
Geller et al (1976)	21 $\pm$ 0.3	5.6 $\pm$ 0.9
Hammond (1978)	1.3 $\pm$ 0.3	5.5 $\pm$ 0.5
Meikle et al (1978)	1.3 $\pm$ 0.6	4.0 $\pm$ 1.9
Kreig et al (1979)	1.6 $\pm$ 1.0	4.5 $\pm$ 1.4
Walsh et al (surgery; 1983)	5.1 $\pm$ 0.4	5.0 $\pm$ 0.4
Walsh et al (autopsy; 1983)	0.7 $\pm$ 0.1	1.0 $\pm$ 0.2

\* Dihydrotestosterone levels are expressed as nanograms per gram tissue.

perhaps transmitted through the vas deferens or deferential blood vessels, for example, may play some role (Darras et al, 1991).

*The Role of Estrogens*

There is increasing evidence to suggest that estrogens play a role in the pathogenesis of BPH (Table 3). In the dog, where estrogens act synergistically with androgens to produce experimental BPH (Barrack and Berry, 1987; Walsh and Wilson, 1976), estrogen appears to be involved in induction of the androgen receptor (Moore et al, 1979). Estrogen may, in fact, "sensitize" the aging dog prostate to the effects of androgens (Barrack and Berry, 1987). The canine prostate contains an abundance of high-affinity estrogen receptors (Trachtenberg, 1985). In the dog, estrogen treatment stimulates the stroma, causing an increase in the total amount of collagen (Berry, 1984; Berry and Isaacs, 1984).

The role of estrogens in the development of human BPH is less clear. Serum estrogen levels increase in men with age, absolutely or relative to testosterone levels. There is also suggestive evidence that intraprostatic levels of estrogen are increased in men with BPH. Patients with larger volumes of BPH tend to have higher levels of estradiol and estratriol in the peripheral circulation (Coffey and Walsh, 1990). Although there are relatively low concentrations of classic high-affinity estrogen receptors in human BPH (Berry et al, 1984), there may be a sufficient amount for biologic activity. From experimental studies with aromatase inhibitors, it appears that decreases in intraprostatic estrogen in animal models may lead to reduction in drug-induced stromal hyperplasia. At present, the role of estrogens in human BPH is not as firmly established as the role of androgens. Species variation and cause-effect relationships are problematic. There are high levels of progesterone receptor in the normal and hyperplastic prostate. However, the role of the progesterone receptor in normal prostatic physiology, as well as in BPH, remains to be defined.

*Stromal-Epithelial Interaction*

Abundant experimental evidence demonstrates that prostatic stromal and epithelial cells maintain a sophisticated para-

crine-type communication. The growth of the canine prostate epithelium can be regulated by cellular interaction with the basement membrane and stromal cells. Isaacs et al, using a marker of canine prostatic epithelial cell function, have shown that epithelial cells grown on plastic quickly lose their ability to secrete this protein (Isaacs et al, 1983). In addition, the cells begin to grow rapidly, and change their cytoskeletal staining pattern. In contrast, if the cells are grown on prostatic collagen, they maintain their normal secretory capacity and cytoskeletal staining pattern, and do not grow rapidly. This is strong evidence that one class of stromal cell excretory protein (ie, extracellular matrix) partially regulates epithelial cell differentiation. Thus, BPH may be due to a defect in a stromal component that normally inhibits cell proliferation, resulting in loss of a normal "breaking" mechanism for proliferation. This abnormality could also act in an autocrine fashion to lead to proliferation of stromal cells.

Further evidence of the importance of stromal-epithelial interactions in the prostate comes from the developmental studies of Cunha (1976) and Cunha et al (1980), which demonstrate the importance of the embryonic prostatic mesenchyme in dictating differentiation of the urogenital sinus epithelium. The process of new gland formation in the hyperplastic prostate suggests a "reawakening" of embryonic processes where the underlying prostatic mesenchyme directs epithelial cell development (Cunha et al, 1980; McNeal, 1990). As our understanding of stromal-epithelial cell relationships in the prostate increases, it is possible that therapies may be designed to induce regression of established BPH by modulating these autocrine/paracrine mechanisms.

*Growth Factors*

Growth factors are small peptide molecules that stimulate or, in some cases, inhibit cell division and differentiation. Cells that respond to growth factors have surface receptors specific for that growth factor that in turn are linked to a variety of transmembrane and intracellular signaling mechanisms. Jacobs and coworkers were the first to demonstrate that extracts of BPH stimulate cellular growth (Jacobs et al, 1979). This putative prostatic growth factor was subsequently found through sequence analysis to be basic fibroblastic growth factor ( $\beta$ -FGF; Story et al, 1984).

Subsequently, a variety of growth factors have been characterized in normal, hyperplastic, and neoplastic prostatic tissue. In addition to  $\beta$ -FGF, other heparin-binding growth factors ( $\alpha$ -fibroblastic growth factor), transforming growth factors (TGF- $\beta$ ), and epidermal growth factor (EGF) have been found in hyperplastic and BPH tissue. Transforming growth factor is a potent inhibitor of proliferation in normal cells in a variety of tissues. In models of prostatic cancer, there is evidence suggesting that malignant cells have escaped the growth inhibitory effect of TGF- $\beta$

Table 3. Evidence of an estrogen role in benign prostatic hyperplasia

Age-related increase in plasma estrogen levels
Estrogens are synergistic with androgens in the production of experimental canine BPH
Estrogens may up-regulate androgen receptor levels
Estrogens may increase stromal cell growth and collagen expression
Stromal cell nuclei contain estrogen receptors
Increase in intraprostatic estrogen in men with BPH

(McKeehan and Adams, 1988); similar mechanisms may operate in BPH.

There is mounting evidence of an interdependency between growth factors, growth factor receptors, and the steroid hormone milieu of the target tissue (Rennie et al, 1988; King, 1990; Kyprianou and Isaacs, 1988). Although data on the absolute level of growth factor and growth factor receptors in hyperplastic and normal tissue are conflicting, it is likely that growth factors play some role in the pathogenesis of BPH. However, further research will be necessary to establish the role of growth factors in a disease process where cellular proliferation is not obvious.

### **Importance of Prostatic Smooth Muscle**

Regardless of the exact proportion of epithelial to stromal cells in the hyperplastic prostate, there is no question that prostatic smooth muscle represents a significant volume of the gland (Table 4; Rohr and Bartsch, 1980, 1983). Although the smooth muscle cells in the prostate have not been extensively characterized, presumably their contractile properties are similar to those seen in other smooth muscle organs. The spatial arrangement of smooth muscle cells in the prostate is not optimal for force generation, but there is no question that both resting and dynamic prostatic smooth muscle tone play a major role in the pathophysiology of BPH (Shapiro and Lopor, 1991). The factors that determine resting smooth muscle tone in the prostate remain to be elucidated. However, stimulation of the adrenergic nervous system clearly results in a dynamic increase in prostatic urethral resistance. Blockade of this stimulation by  $\alpha$ -receptor blockers clearly diminishes this response. It is not clear, however, that  $\alpha$ -blockade decreases resting tone and prostatic smooth muscle.

Smooth muscle cells at the bladder neck and prostatic capsule, as well as stromal prostatic smooth muscle cells, are richly populated with  $\alpha_1$ -adrenoreceptors. The detrusor smooth muscle itself does not contain a significant number of  $\alpha_1$ -receptors. Thus,  $\alpha$ -blockade results in a selective diminution in urethral resistance without a measurable effect on detrusor smooth muscle contractility. This selective localization of the  $\alpha$ -receptor in the lower urinary tract un-

derlies the rationale of  $\alpha$ -blocker therapy for the treatment of BPH. In addition to producing relaxation of the smooth muscle, it is possible that  $\alpha$ -blockers may have other effects, since prostate denervation produces histologic alteration (Wang et al, 1991). In the heart, adrenergic stimulation and subsequent blockade can modulate myocyte growth as well as the expression of the extracellular matrix. In theory, therefore,  $\alpha$ -blockers may have effects in the prostate that transcend their relaxation properties.

Several additional observations on the stromal/smooth muscle cells are appropriate. It is generally assumed that stromal cells are resistant to the effects of androgen withdrawal. In short-term studies, androgen ablation appears to affect primarily the epithelial cell population. In general, however, stromal cells have much slower turnover rates than epithelial cells. If the primary effect of androgen ablation is to increase cell death rates, a decrease in stromal cell numbers may not be appreciated until a year or more of therapy has passed. Thus, further study will be required to determine whether the stromal cell is really "resistant" to androgen withdrawal. Likewise, it cannot be assumed that hormonal therapy has no effect on the stroma, even if stromal cell volumes are not decreased. In a variety of smooth muscle cell systems (eg, vascular and myometrial), contractile proteins, neuroreceptors, and extracellular matrix proteins are known to be regulated by several hormones and growth factors. Thus, a given therapy may affect stromal cell function without decreasing the absolute number or volume of cells.

### **The Bladder's Response to Obstruction**

Current evidence suggests that the bladder's response to obstruction is largely an adaptive one (Fig 1). However, it is also clear that many of the clinical symptoms of prostatism are related to obstruction-induced changes in bladder function, rather than outflow obstruction. Approximately one-third of the men continue to have significant voiding dysfunction after surgical relief of obstruction (Abrams et al, 1979). Obstruction-induced changes in the bladder are of two basic types. First, changes that lead to *detrusor instability* are clinically associated with symptoms of frequency and urgency. Second, those changes that lead to decreased *detrusor contractility* are associated with further deterioration in the force of the urinary stream, hesitancy, intermittency, increased residual urine, and, in a minority of cases, detrusor failure. Acute urinary retention should not be viewed as the inevitable result of this process. Many patients presenting with acute urinary retention have more than adequate detrusor function, with evidence of a precipitating event leading to the obstruction.

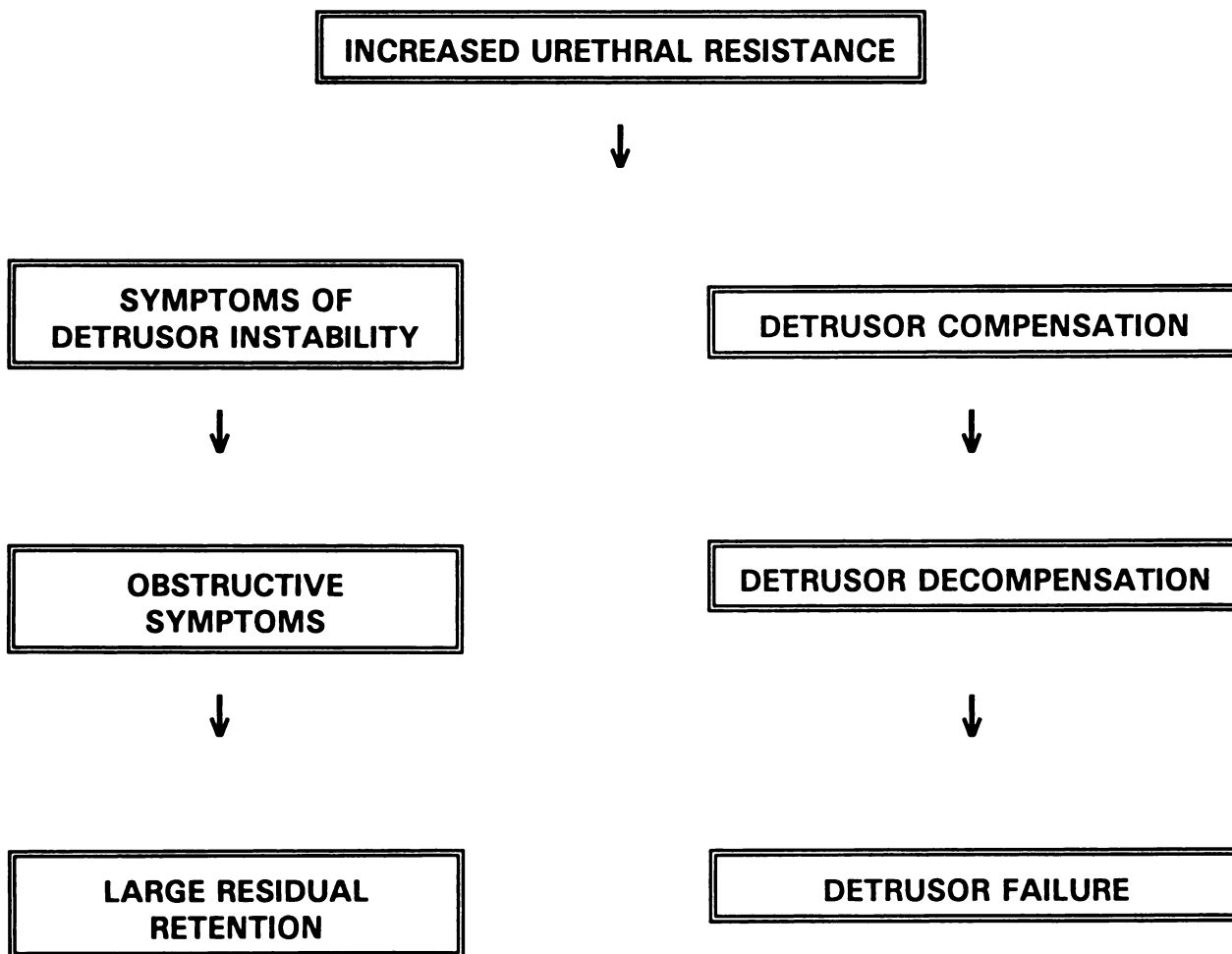
Much of our knowledge of the detrusor's response to obstruction is based on experimental animal studies. Lim-

Table 4. Importance of prostatic smooth muscle (SM) in the pathophysiology of BPH

Prostatic stroma, capsule, and bladder neck contain a high concentration of SM cells
Dynamic "tone" of prostatic SM can be partially inhibited by selective $\alpha_1$ -blockade
Hyperplastic prostatic growth involves a significant increase in SM volume
SM cells may secrete a significant portion of prostatic extracellular matrix

## CLINICAL RESPONSE

## BLADDER RESPONSE



**FIG. 1.** A model of the natural history of BPH. It is highly unlikely that the actual process is this simple. It is also clear that only a minority of patients actually progress to detrusor failure.

ited information is available on the natural history of the human bladder's response to obstruction. Gosling has demonstrated that the major endoscopic detrusor change, trabeculation, is due to an increase in detrusor collagen (Gosling and Dixon, 1980). Severe trabeculation, however, is seen in fairly advanced states of disease. In experimental animal models, the initial response of the detrusor to obstruction is the development of smooth muscle hypertrophy. It is likely that this increase in muscle mass, although an adaptive response to increased intravesical pressure and maintained flow, is associated with significant intra- and extracellular changes in the smooth muscle cell that lead to detrusor instability. This hypothesis, however, remains to be validated in future studies.

In experimental animal models, unrelieved obstruction is

associated with the development of significant increases in detrusor extracellular matrix (collagen). This also appears to be the case in man, although cause-and-effect relationships have not been established (Gosling and Dixon, 1980). In addition to obstruction-induced changes in the smooth muscle cell and extracellular matrix of the bladder, there is increasing evidence that obstruction may modulate neural responses as well. Further research and development of alternative treatment strategies must take into account the detrusor's response to obstruction. If a therapy is designed primarily to relieve the symptoms of obstruction, but does not result in a decrease in outflow resistance, progressive detrusor changes may lead to treatment failure. It should be stressed, however, that the probability of detrusor failure developing in patients with untreated BPH is largely un-

known. Fortunately, it does not appear to be a common event.

In summary, our current knowledge of the pathogenesis of BPH is limited. Although steroid hormones and their receptors, prostatic smooth muscle, neuroreceptors, and detrusor responses all appear to be important in age-related prostatic growth and the development of clinical prostatism, the actual cause of BPH is undefined. Truly effective alternate therapies will probably elude discovery until basic research provides further insight into the underlying disease process.

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## International Symposium on Andrology and Assisted Fertility

Sao Paulo, Brazil—March 26–28, 1992

(Maksoud Plaza Hotel)

The symposium will focus on recent advances in treating impotence, sexual disorders, and male factor infertility, and on assisted fertilization and human reproduction. An international array of speakers has been assembled:

A. Galvao-Teles (Portugal), A. Isidori (Italy), A. Negro-Vilar (USA), C. Nahoum (Brazil), D. DeKretser (Australia), D. Pereira (Brazil), D. Adamopoulos (Greece), E. Coutinho (Brazil), E. Lucena (Colombia), F. Comhaire (Belgium), F. Zegers (Chile), F. Admoelja (Indonesia), G. Baker (Australia), G. Perez-Palacios (Mexico), G. Waites (WHO), H. Burger (Australia), I. Huhtaniemi (Finland), J. Frick (Austria), J. Garcia (USA), J. Paulson (USA), L. Centa (Brazil), L. Martini (Italy), M. C. Orgebin-Crist (USA), N. Neuspiller (Argentina), P. Serafini (USA), P. Troen (USA), P. Van Look (WHO), R. Abdelmassih (Brazil), R. Andrade (Brazil), S. Marina (Spain), S. Pavlou (USA), T. Hargreave (United Kingdom), T. Tan (USA), V. Izzo (Brazil), and W. Schill (Germany).

This symposium is sponsored by the International Society of Andrology, the Pan American Congress of Andrology Association, and the Brazilian Society for Andrology.

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