Medical treatment of

Benign
Prostatic
Hyperplasia

MASSIMO PORENA

EDIZIONI MINERVA MEDICA
It was with very great pleasure that I accepted the invitation from Edizioni Minerva Medica to coordinate a panel of important Italian urologists, the most influential experts in prostatic disease. I found the suggestion to discuss one of the “hottest” fields in urology to be very stimulating, as well.

The medical therapy for benign prostatic hyperplasia has a short history, which started no farther back than 25-30 years ago. Before then, surgery was the only real treatment for prostatic disease aimed at also resolving the associated lower urinary tract symptoms (LUTS).

Nowadays, several drugs are available for the treatment of prostatic enlargement, which stop or minimize glandular growth, improve bladder neck and urethral hypertonicity or reduce the associated LUTS. They can be used as a monotherapy or in various combinations.

This book is meant to be a summary of the latest developments in the field and a guide to the use of drugs, focusing on their biological mechanisms of action and their adverse events. The Authors involved in this work are the backbone of research in this field in Italy.

Overlapping between topics sometimes occurred. However, I decided not to prune out repetition: firstly because, as the ancient Romans said, *Repetita juvant*; secondly, because the topics discussed in the chapters are closely interrelated; and lastly, because different Authors have addressed similar topics from different points of view.

I wish to congratulate all authors on this endeavour and thank them for their valuable contribution.

Massimo Porena
Walter Artibani
Urology Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Italy

Marco Carini
Department of Urology, University of Florence, Italy

Maria Angela Cerruto
Urology Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Italy

Elisabetta Costantini
Urology and Andrology Clinic, Santa Maria della Misericordia Hospital, Sant’Andrea delle Fratte, Perugia, Italy

Carolina D’Elia
Urology Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Italy

Cosimo De Nunzio
Department of Urology, Sant’Andrea Hospital, Sapienza University, Rome, Italy

Francesco Esperto
Department of Urology, Sant’Andrea Hospital, Sapienza University, Rome, Italy

Marco Franco
Department of Neurosciences, Sciences of Reproduction and Odontostomatolgy, University Federico II of Naples, Italy

Mauro Gacci
Department of Urology, University of Florence, Italy

Antonella Giannantoni
Urology and Andrology Clinic, Santa Maria della Misericordia Hospital, Sant’Andrea delle Fratte, Perugia, Italy
Giorgio Guazzoni
Department of Urology, Humanitas
University, Rozzano, Milan, Italy

Roberto La Rocca
Department of Neurosciences, Sciences
of Reproduction and Odontostomatology,
University Federico II of Naples, Italy

Massimo Lazzeri
Department of Urology, Istituto Clinico
Humanitas IRCCS, Humanitas Clinical
and Research Center, Rozzano, Milan, Italy

Luigi Mearini
Urology and Andrology Clinic,
Santa Maria della Misericordia Hospital,
Sant’Andrea delle Fratte, Perugia, Italy

Vincenzo Mirone
Department of Neurosciences, Sciences
of Reproduction and Odontostomatology,
University Federico II of Naples, Italy

Giuseppe Morgia
Department of Urology, University
of Catania, Italy

Alessandro Palmieri
Department of Neurosciences, Sciences
of Reproduction and Odontostomatology,
University Federico II of Naples, Italy

Massimo Porena
Urology and Andrology Clinic,
Santa Maria della Misericordia Hospital,
Sant’Andrea delle Fratte, Perugia, Italy

Fabrizio Presicce
Department of Urology, Sant’Andrea
Hospital, Sapienza University, Rome, Italy

Giorgio Ivan Russo
Department of Urology, University
of Catania, Italy

Sergio Serni
Department of Urology, University
of Florence, Italy

Pietro Spatafora
Department of Urology, University
of Florence, Italy

Andrea Tubaro
Department of Urology, Sant’Andrea
Hospital, Sapienza University, Rome, Italy

Daniele Urzì
Department of Urology, University
of Catania, Italy

Luca Venturino
Department of Neurosciences, Sciences
of Reproduction and Odontostomatology,
University Federico II of Naples, Italy

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Section 1

Etiopathogenetic and pathophysiologic pathways

M. Porena, E. Costantini, A. Giannantoni, L. Mearini
The disturbances of micturition or lower urinary tract symptoms (LUTS), once categorized as “irritative” and “obstructive” symptoms, nowadays should be described as symptoms of the voiding phase, “voiding” symptoms (hesitancy, straining, decreased urinary stream, postvoid dribbling) and disturbances of the filling phase, “storage” symptoms (frequency, urgency, urgency incontinence, nocturia). The term “prostatism” includes many of these disturbances but is an inaccurate, general term as such symptoms are commonly present even in females or in other conditions, not related to prostatic pathology.

The above-mentioned micturition symptoms, of various types and intensity, affect many elderly males and have been historically attributed to the increase in prostate volume or benign prostatic enlargement (BPE). The relationship between prostate volume and symptoms is highly variable, as not every man with hyperplasia of the prostate has clinically relevant symptoms or these symptoms may be due to numerous other underlying pathologies. In fact, it is nowadays clarified that LUTS can be attributed to a series of conditions, not directly connected to benign prostatic hyperplasia (BPH), that affect the male urinary system. For example, sleep disturbances can mimic nocturia and pathologies like diabetes mellitus and heart failure can induce polyuria.

Disturbances of the male urinary tract system that may imitate “prostatism” but are completely unrelated to the evolution of prostate gland include urethral stenosis, pathologies of the bladder neck not related to the prostate and neurogenic or myogenic contractile dysfunction of the detrusor, including the overactive bladder.

In essence, any similar clinical situation can attributed to “obstructive” pathology (bladder outlet obstruction – BOO, urethral stenosis), reduced contractile capacity of the detrusor, overactive bladder as well as nonurologic pathologies that induce polyuria or sleep disturbances.

Moreover, it is well documented that only two thirds or three quarters of men with clinically relevant BPH suffer “obstructive” symptoms or have documented obstruction. Therefore, the sequence of LUTS due to BOO as a result of BPE which is a consequence of histologically confirmed BPH, even though frequently encountered in aging males, is not a rule (Figure 1.1).

Finding out whether BPH is responsible for obstruction and/or patient complaints is a considerable task relevant to identifying the patients who really need treatment and selecting the treatment most suitable for them.
Two conditions are necessary for the development of BPH: advanced age and presence of the testicles and thus testosterone. In fact microscopic, macroscopic or clinical BPH very rarely manifest before the age of 40, while at the age of 75 approximately 25% of men requires a therapeutic intervention for problems caused by the presence of BPH. Similarly BPH does not develop in patients castrated before puberty or affected by diseases, generally genetic, that alter the production or action of androgens.

What is a hyperplasia and in particular BPH? From an histological point of view it is an increase in the number of cells, and in the case of the prostate of epithelial and stromal cells that are found at the level of the periurethral zone. This process can be induced by an increase of proliferation of the two cell lines, stromal and epithelial or a decrease/cessation of apoptosis, which is the programmed cell death. In the case of development of hyperplasia of the prostate it seems that the decrease in apoptosis has a predominant role while an increase in proliferative activity is not certain and, in any case, is limited to the initial phase of BPH. Evidence supporting this is the increased expression of anti-apoptotic genes like BCL2 as well as the reduced DNA synthesis that have been observed in experiments in dogs in which BPH was induced with a combination of androgens and estrogens.

These events are manifested during a long period of time which most likely spans from initiation of stem cell proliferation followed by their differentiation to matura- tion, followed by programmed cell death. Any event blocking this maturational process does not allow the differentiation final step and finally reduces the programmed cell death.

Several factors may interfere in this maturation process of the prostatic cells, factors that manifest over time with advancing age: first of all hormonal factors, androgens and estrogens; growth factors either facilitating or inhibiting differentiation; stromal-epithelial interaction; neurotransmitters and neural signaling pathways, in particular α-adrenergic pathways. All these factors have a role in the balance between the proliferation and the programmed death of prostatic cells.

/**/Steroids and their receptors/**/

The relationship between the sex steroids, prostate development and BPH is complex and many factors are involved.

The circulating testosterone is produced mainly by the testicles, which contribute its 90%, and the adrenals, which produce the remaining 10%. The adrenal androgens, dehydroepiandrosterone (DEHA), its sulfate (DEHAS) and androstenedione, undergo metabolic conversion to testosterone and dihydrotestosterone in plasma and in the prostate. Majority of the circulating testosterone (approximately 95%) is reversibly bound to albumin and SHBG (sex hormone binding globulin). The remaining unbound fraction of testosterone acts directly to the level of the brain, the skeletal muscles and the seminiferous tubules of the testis, stimulating respective androgen-dependent processes. At the prostatic level, approximately 90% of the testosterone that reaches the gland is converted by the enzyme 5-α-reductase to...
dihydrotestosterone (DHT), which constitutes the principal prostatic androgen.

There are two isoforms of 5-α-reductase, type 1 and type 2, that are coded by different genes. Type 1 is the predominant type in extraprostatic tissues (skin, liver) and is inhibited by dutasteride and not finasteride. Type 2 is the predominant 5-α-reductase in the prostatic gland and is inhibited by either dutasteride or finasteride.

Type 1 seems to be involved more in prostate cancer than in the development of BPH. Type 2 is essential for both the normal and hyperplastic growth of the prostate. This is evidenced by the atrophy of the prostate gland noted in cases of 5-α-reductase deficit, caused by a mutation of the gene coding isoform 2.

Immunohistochemical studies have demonstrated the predominant presence of isoform 2 within the stromal cells which hence assume a determining role in prostate growth.

The cascade of events can thus be summarized like this: testosterone diffuses in both the epithelial and stromal cells. In the former it is able to bind directly to the androgen receptor. In the stromal cells, conversely, testosterone is almost completely converted to DHT by the isoform 2 of 5-α-reductase. In the form of DHT it is able to act in an autocrine fashion in the stromal cells and also diffuse in the adjacent epithelial cells in a paracrine fashion. Finally, the DHT produced in the periphery from the liver and skin can equally dif-
fuse in stromal and epithelial prostatic cells in the classic endocrine fashion. The fraction of DHT which is produced in the periphery by either isoform of the 5-α-reductase is inhibited by medications that inhibit the respective isoforms. In these events interfere in a determinative way growth factors inside the prostatic cells (Figure 1.2).

Both free testosterone and DHT bind on the same cytosolic specific receptor located on the nuclear membrane but DHT has higher affinity for the receptor, compared to testosterone, and the complex receptor-DHT is more stable compared to the complex receptor-testosterone. Therefore, DHT is proved to be the most important prostatic androgen. The androgen receptor (AR) is a 100 kDa protein, composed by two subunits, α and β. The binding of the hormone to the receptor is reversible.

The DHT-AR complex is activated by drastic conformational change which allows its passage into the nucleus. The β subunit of the receptor binds to a acceptor site while the α subunit binds to DNA allowing the activation of RNA polymerase and the transcription of messenger RNA, which, at the end, initiates the synthesis of the coded protein. In contrast, the withdrawal of androgen from androgen-sensitive tissues promotes the reduction of protein synthesis and the involution of these tissues. This demonstrates the irrefutable necessity of androgen for the development of BPH to which, however, does not correspond an evident mitogenic activity of these hormones on prostatic cells but their evident and direct regulatory effect on numerous growth factors. Moreover the volume of the prostate in advanced age does not correlate to the level of circulating androgens but is seems to correlate to the estrogen/androgen ratio which tends to increase with age. The variation of the estrogen/testosterone ratio in favor of the estrogen is therefore one of the fundamental factors for the development of BPH.

In conclusion, there is not a direct cause-and-effect relationship between androgens and BPH but, certainly, the development of BPH requires the lifelong presence of androgens. Moreover, there is evidence that, while the level of circulating testosterone decreases with age, the level of intraprostatic DHT as well as its receptors remain constant throughout life.

This last piece of information is really significant. In fact, all the other organs whose growth is androgen-dependent stop their growth at the end of puberty. On the contrary, in the prostate the level of androgen receptors remain high throughout life and, therefore, the prostate gland can show a growth response even at advanced age. Probably the high expression of ARs that is found in the prostate of the elderly and their definite increase in BPH, compared to normal controls, are sustained by the already mentioned increase of estrogens, which coincides with the advance in age. This over-expression of ARs is evident despite the decrease with age in the level of circulating androgens and the constant, without any increase, levels of intraprostatic DHT.10, 11

This fact introduces to the role of estrogens in the pathogenesis of BPH. Numerous experimental studies support the role of estrogens in the development of BPH. These studies are indirectly confirmed by the finding of estrogen alterations in aging men. In fact estrogen levels increase with ad-
vancing age, either absolutely or in comparison to testosterone levels. The result of this will be an imbalance between estrogen and testosterone in favor of estrogen in the elderly man, as previously mentioned. Moreover, it has been observed that intraprostatic estrogen levels are always increased in BPH and that patients with voluminous BPH have higher levels of circulating estrogens. Therefore, in contrast to what is observed for testosterone, the levels of circulating estrogen are positively correlated to prostatic volume. In conclusion, despite the fact that the role of estrogens is not as clear as that of androgens, there is undoubtedly an important influence of estrogen on the normal and pathologic growth of the prostate.

With regards to their mechanism of action, estrogens seem to provoke an over-expression of AR and an increase of the isoform 2 of 5-α-reductase, ultimately promoting the increase of prostate volume in the elderly. Moreover, the administration of estrogen in experimental animals stimulates the growth of the prostatic stroma with a definite increase in collagen.

Experimental dog studies have demonstrated an abundance of estrogen receptors (ER) in the prostate in two different forms: ER-α, expressed in stromal cells, and ER-β, expressed in prostatic epithelial cells. Other studies on prostatic stromal cell-cultures have demonstrated that up-regulation of ER-α is associated with up-regulation of growth factors, among which particularly the fibroblast growth factors (FGF-2 and FGF-7). On the contrary, the reduction of intraprostatic estrogen with aromatase inhibitors provokes an involution of stromal hyperplasia. The two types of estrogen receptors promote different actions on the prostate and are involved in the etiology of either BPH or prostate cancer modulating effects either proliferative or antiproliferative. They show different expression either in the two pathologic conditions, cancer and BPH, or in the natural history of both.

**GROWTH FACTORS**

It has been previously highlighted that the growth factors modulate the action of androgens on the prostatic cells and their role in modifying the balance between cell proliferation and death, which may lead to the evolution of BPH. Evidence keeps emerging on the interaction and inter-dependence between steroids, extracellular matrix, growth factors and their receptors.

The growth factors are small peptides able to act on cellular division and differentiation, with either facilitatory or inhibitory mechanism. The existence of growth factors came to light by the work of Lawson who demonstrated that BPH extracts stimulate cellular growth. Based on these observations, further studies demonstrated the presence in the prostatic tissue, either normal or pathologic, of a long series of growth factors; from the first identified, the basic fibroblast growth factor bFGF2, to other fibroblastic growth factors like FGF1, FGF3 and the FGF7, the keratinocyte growth factor (KGF), the transforming growth factor-β (TGF-β), the epidermal growth factor (EGF), the insulin-like growth factor (IGF).

Nowadays it is believed that certain growth factors, such as FGF-1, FGF-2, FGF-7, FGF-17, the vascular endothelial growth factor (VEGF) and the IGF, under DHT stimulation and modulation, provoke epi-
thelial cell proliferation, one of the steps in the development of BPH. On the contrary, the TGF-β, an important inhibitor of epithelial cell proliferation, may either be down-regulated in BPH or the prostatic cells escape its inhibitory control, similarly to what also happens in the neoplastic cells of prostate cancer.

It must be kept in mind that TGF-β is expressed in the stromal prostatic cells on which it exerts, on the contrary, a potent mitogenic effect, either by means of an autocrine mechanism or by up-regulating bFGF-2 which, in turn, is a known growth factor for the prostatic stromal cells.

It is therefore plausible that, in different moments, the TGF-β can be up-regulated, thus inducing an expansion of the stromal compartment, or down-regulated and therefore unable to exert its inhibitory role on the proliferation of the epithelial cells. All this leads to equilibrium between cellular proliferation and apoptosis which is under the influence not only of steroids but also of growth factors, either inhibitory or facilitatory.

The steroids play a “permissive” role of modulation while the growth factors are the actual effectors of cellular modification towards proliferation or, on the contrary, towards maturation and cell death.

**EXTRACELLULAR MATRIX (ECM)**

There are severe experimental evidences that extracellular matrix, one class of stromal cell excretory proteins, can regulate epithelial cell differentiation maintaining a paracrine type of communication among prostatic stromal and epithelial cells.

The importance of stromal-epithelial interactions were confirmed by a study that demonstrated the decisive role of the embryonic prostatic mesenchyme for the differentiation of the urogenital sinus epithelium. The same process of induced epithelial cell development by prostatic stroma could be on the basis of the new proliferation in prostate hyperplasia.

The soluble growth factors into the extracellular matrix may be the mediators of the prostatic stromal epithelial interactions. In addition, many growth factors increase the expression of CYR61, an ECM-associated protein that promotes proliferation of...
both, epithelial and stromal prostatic cells. CYR61 is iper-expressed in BPH tissues.

**OTHER FACTORS INVOLVED IN THE PROSTATIC HYPERPLASTIC PROCESS**

1) *Sympathetic pathways* have been identified as important factors.\(^{18}\)

In experimental animal models it has been observed that \(\alpha\)-adrenergic blockade can induce apoptosis and therefore have an effect on prostatic volume and can act as a modulator of the smooth musculature phenotype in the prostate. On the other hand, \(\alpha\)-blocking therapy is already established in the treatment of LUTS precisely because the sympathetic signaling pathways are decisively involved in the pathophysiology of BOO and associated LUTS.

Other factors involved in prostate growth have also been identified: the early growth response gene-1 (EGR1), \(\alpha2\)-macroglobulin and components of the renin-angiotensin system.

2) *EGR1*, a transcription regulator, is active in BPH cell culture lines.\(^{19}\)

3) The renin-angiotensin system (RAS), with all its components, is present in prostatic tissue and it is activated in BPH. It can contribute to cellular proliferation and contraction of prostatic smooth musculature, either alone or in association with \(\alpha\)-sympathetic modulation.

**GENETIC FACTORS**

Epidemiologic observations and studies in twins have demonstrated a hereditary component in BPH.

In fact, monozygotic twins show an incidence of BPH much higher than that observed in dizygotic twins; in epidemiologic surveys conducted by Roberts\(^ {20}\) in 2,000 men, an increased risk of severe LUTS in those with a family history of BPH, compared to those without family history, was observed.

Such observations were confirmed in a clinical trial which demonstrated a clear difference in average prostate volume: 82 mL in 69 patients with a family history of BPH versus 55 mL in those with sporadic BPH, without family history.

Moreover, a retrospective case-control study conducted by Partin\(^ {21}\) in patients operated for BPH and a similar control group, showed a noteworthy frequency of first-degree relatives treated for BPH in patients being operated compared to first degree relatives in the control group, in accordance to a model of dominant autosomic inheritance. This has allowed the development of a theory that supports susceptibility or heredity in 50% of men undergoing an operation for BPH at an age lower than 60 years, compared to only 9% in patients operated at an age greater than 60 years.

From this it is inferred the existence of a gene to which the development of such pathology is attributed. This gene has not yet been identified, while various situations of genetic polymorphism, DNA mutations and hypomethylation of DNA have been observed.

**PROSTATITIS**

The association between chronic prostatic inflammation and BPH is an everyday observation in biopsies performed for suspected prostate cancer or in histologic examination of surgical specimens from patients operated for BPH.
The frequency of this association has led to the hypothesis that there is an etiopathogenic link between the two conditions. This link has been attributed to T-cells that are present in the prostate, capable to secrete potent epithelial and stromal mitogens, which, in turn, cause hyperplasia of the prostatic epithelium and stroma. In fact abundant activated T-cell infiltration is found in hyperplastic prostatic tissue. These activated T-cells are known to produce growth factors that promote cellular proliferation, such as bFGF2, FGF-1, HB-EGF and VEGF, well-known mitogens of either stromal or epithelial cells.

An association, even though not yet well-established, is believed to exist between inflammation-related cytokine pathways and stromal or epithelial hyperplasia of the prostate. In fact, a great number of cytokines (IL-2, IL-4, IL-7, IL-17) and interferon-β with their respective receptors have been identified in BPH tissue. Many of these inflammatory mediators have in vitro a stimulating activity for the proliferation of stromal prostatic cells. It has been also observed that the macrophage inhibitory cytokine-1 is expressed in normal prostatic tissue but down-regulated in BPH.22

A cause-and-effect relationship between these mediators and BPH, as already mentioned, is not yet well-defined.

**MECHANISMS OF OBSTRUCTION**

The factors that cause obstruction to urine outflow are diverse and can be divided in a static component and a dynamic component.

**Static component**

The static component, in turn, is associated to several factors, which are not all simultaneously present:

- presence of the median lobe that protrudes into the bladder and may fall onto the internal urethral meatus during micturition, obstructing it in a valve-like mechanism.25 This mechanism may be exacerbated when the patient uses abdominal straining in an attempt to maintain micturition (Figure 1.4). Obstruction can be verified even in cases where the vesical prostatic protrusion is not that critical as to completely “close” the bladder neck. As Zeng et al.26 demonstrated using a computerized model of urine flow dynamics, the principal cause of obstruction is a greater propen-
MediCAL trEAtMEnt of bEniGn proStAtiC hYPERPlASiA

Section 1

The act of micturition starts with the opening of the bladder neck followed by the initial entrance of urine in the prostatic urethra. This provokes, through a reflex mechanism, the opening of the urethral sphincter and thus the flow of urine.

**Lack of bladder neck funneling.** The act of micturition starts with the opening of the bladder neck followed by the initial entrance of urine in the prostatic urethra. This provokes, through a reflex mechanism, the opening of the urethral sphincter and thus the flow of urine. In a morphological level the first event is the “funneling” of the bladder neck as shown in figure 1.5. The lack of funneling of the bladder neck, in other words its incomplete opening (Figures 1.6, 1.7),