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A scientific basis for the therapeutic effects of *Pygeum africanum* and *Serenoa repens*

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Abstract In Europe, phytotherapeutic preparations have been prescribed for the treatment of symptomatic benign prostatic hyperplasia (BPH) for over 20 years [l–4]. In these countries, phytotherapeutic preparations represent approximately 1/3 of total sales of all therapeutic agents sold for the treatment of BPH. In France, and other countries, phytotherapeutic preparations are the most widely used drugs for the treatment of BPH. In Asia, Africa, and India, phytotherapy is considered a first-line treatment for BPH and has been utilized effectively for centuries. In the United States, the multimillion dollar sales of phytotherapeutic preparations for "the health of the prostate and bladder" attests to the widespread utilization of these agents [3, 4].

Two of the most popular phytotherapeutic agents that have undergone both clinical studies to determine their efficacy, and have been the subject of basic science studies to identify the mechanism(s) of action are *Pygeum africanum* (Tadenan), an extract from the bark of the African plum tree, and *Serenoa repens* (Permixon), a lipido-sterol extract of dwarf palm. Tadenan and Permixon are registered therapeutic agents of Debat Pharmaceuticals, and Pierre Fabre Medicament, respectively. Manufacture of both preparations are tightly controlled and subjected to strict quality control for stability of component composition. In regard to phytotherapeutic agents, each individual preparation (even from the same plant source) must be considered individually because of differences in the extraction techniques, preparation of products, composition, and biological activities. Thus, the clinical and biological activities of one preparation cannot be extrapolated to other preparations of the same plant source. Thus, studies described in this review which utilize the preparations that are manufactured by DEBAT (*Pygeum africanum*) or Pierre Fabre Medicament (*Serenoa repens*) are referred to by their trade names, Tadenan and Permixon, to differentiate them from other nonstandardized preparations of the same plants.

Key words *Serenoa repens* · *Pygeum africanum* · Prostate · BPH · Bladder

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There are two aspects to the clinical manifestations of BPH. First is the progressive enlargement of the prostate resulting in compression of the urethra and the initiation of both obstructive and irritative symptoms. These include urgency, frequency, nocturia, hesitancy, reduced flow rate, and incomplete emptying [5–7]. The second is the physical response of the bladder to the enlarged prostate, which includes increased bladder wall thickness, decreased compliance, progressive denervation, collagen infiltration, decreased pressure generation and emptying ability, and unstable bladder contractions during filling [8–12]. Although it has been shown by several studies that there may be no direct relationship between the size of the enlarged prostate and the degree of symptoms [13, 14], most urologists and research scientists in the field would agree that the enlarged prostate is involved in the etiology of the symptoms.

There are several proposed mechanisms involved in BPH pathophysiology including: hormonal stimulation of prostate growth, stroma-epithelial interactions, immune – inflammatory mechanisms, and adrenergic stimulation of cell growth and division. Different agents used in the treatment of BPH have different mechanism of action. In general, current therapies are designed to act at specific aspects of prostate growth and internal prostatic tension, or at the bladder and bladder neck to reduce urethral resistance or reduce the degree of hyperactivity [7, 15, 16]. Finasteride (Proscar) is a 5α-reductase inhibitor which reduces prostatic dihydrotestosterone (DHT) production. Use of finasteride

results in a shrinkage of the prostate, theoretically reducing the degree of obstruction present [17, 18]. Several α-adrenergic antagonists are also available for the treatment of symptomatic BPH [7, 15, 16]. There are high densities of α-adrenergic receptors on the smooth muscle components of the prostate, as well as within the smooth muscles of the internal urethral sphincter and urethra. These agents are believed to improve symptomatic BPH by both reducing the internal tension within the prostate and reduce urethral resistance, thus reducing the level of obstruction. Calcium channel blockers and potassium channel openers have been used with limited success to treat the unstable bladder contractions which contribute to the symptoms of BPH [7, 15, 16].

Clinical studies demonstrate that Tadenan and Permixon are statistically more effective than placebo in relieving urological symptoms, and are similar in efficacy in improving urological function to other medications [19–23].

Although still controversial, it is the opinion of the authors, and of many others, that the clinical studies support the clinical effectiveness of these agents in the treatment of symptomatic BPH. Unlike other agents utilized in the treatment of BPH, phytotherapeutic preparations have not been designed to act at any one specific aspect of either prostatic involvement in the etiology of BPH, or the bladder's response to the presence of the enlarged prostate. The end result is that many physicians now accepted that phytotherapeutic agents are clinically effective in the treatment of symptomatic BPH; the mechanism(s) of action are not well understood.

Of the many phytotherapeutic preparations available, there is mechanistic information available only for *Pygeum africanum* and *Serenoa repens*. The following is a review of the pharmacological actions of these phytotherapeutic agents that may be relevant to their clinical efficacy. It should be noted that most of these studies utilize the identical preparations that are currently used as the prescribed therapeutic agents. As mentioned above, bladder dysfunction secondary to BPH directly involves two inter-related processes, the progressive enlargement of the prostate, and the pathological response of the bladder to the enlarged prostate and concomitant increased urethral resistance. The studies discussed below have been directed at determining the effect of these agents on specific aspects of the growth of the prostate or the response of the bladder to partial outlet obstruction.

Pygeum africanum (Tadenan)

There is evidence that prostatic growth related to BPH involves the proliferative action of one or more growth factors on specific cellular elements within the prostate [24–26]. Tadenan has been shown to be a potent inhibitor of both basal growth of prostatic fibroblasts in culture and the stimulatory effects of a variety of growth factors including basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF) [26, 27]. Table 1 lists the IC_{50} doses for inhibition of basal and stimulated proliferation by bFGF, EGF, IGF-I, and nongrowth factor mitogens. Tadenan was effective in inhibiting basal cell growth at concentrations as low as 5 μg/ml, and growth factor-stimulated proliferation at concentrations as low as 1 μg/ml [26, 27]. It is interesting to note that the IC_{50}, values for Tadenan for inhibition of growth factors and mitogen-stimulated proliferation are in the same order of magnitude (between 4.4 and 14.5 μg/ml). Thus, the action of Tadenan is likely not via direct inhibition at a specific receptor site, but rather related to inhibition of a common pathway by which these growth factors and mitogens stimulate cell proliferation. Since prostate growth and cellular hyperplasia are controlled by multiple factors, an agent that can inhibit more than one of these factors might be more useful than a specific inhibitor of only one factor.

Inflammatory processes are also believed to be involved in the evolution of prostatic growth and BPH symptomology [28, 29]. *Pygeum africanum* extracts have been shown to cause a dose-dependent inhibition of leukotriene synthesis in human polymorphonuclear cell cultures stimulated by the calcium ionophore A 23187. Inhibition of 5-lipoxygenase was demonstrated at *Pygeum africanum* concentrations as low as 3 μg/ml [30].

Prostate growth is androgen dependent and the volume and morphology of the prostate is significantly

Table 1 Effect of Tadenan on mitogen-induced proliferation and 5α-reductase activity in vitro

	Dose range μg/ml	IC_{50} μg/ml	Reference
Fibroblast proliferation			27
Basal	1–100	14.4 ± 4.2	
bFGF-stimulated	1–100	12.6 ± 1.5	
EGF-stimulated	1–100	4.5 ± 1.7	
IGF-I-stimulated	1–100	7.8-U-2.7	
Fibroblast proliferation			27
Basal	1–100	12.3 ± 4	
TPA-stimulated	1–100	12.5 ± 1.9	
PDBu-stimulated	1–100	8.1 ± 2.6	
5α-reductase		63	36
		78	37

affected by alterations in circulatory levels of sex hormones [31–33]. *Pygeum africanum* has been demonstrated to have a "phyto-estrogenic" effect (which can either activate or inhibit estrogen receptors) on the prostate, resulting in a significant effect on the morphology of the glandular epithelium of the prostate, presumably due to a weak anti-estrogen effect [34, 35]. In addition to its "phyto-estrogenic" effect, *Pygeum africanum* has a inhibitory effect on 5α-reductase, although the potency is relatively low compared to its effect on cellular proliferation [36, 37].

In a rat model, prostate hypertrophy/hyperplasia was stimulated by DHT administration resulting in significant alterations in bladder function. Tadenan pretreatment was shown to significantly improve bladder function simultaneous with reducing prostatate weight [38].

In the rabbit, and in man, bladder function can be characterized by the response to autonomic stimulation [39–42]. In the presence of an enlarged prostate (man) and partial outlet obstruction (rabbit), bladder function can remain relatively "normal" for prolonged periods of time during the progression of response to obstruction. This is because the bladder can compensate for the progressive increase in urethral resistance by increasing its mass. During this compensated period of functioning, although there may be changes in micturition pressure and flow characteristics, the urodynamic changes are not severe, and thus do not require medical attention. It is not until decompensated function occurs that the patient seeks medical attention [5–7, 39–41]. These clinical changes may leave the patient susceptible to subsequent renal injury and frequent infections, in addition to the considerable discomfort experienced prior to and during urination.

In man, it is difficult to investigate the cellular mechanisms by which progressive bladder dysfunction occurs. However, many of the functional changes associated with human bladder pathology can be induced in experimental animal model systems and this has been demonstrated prominently in a rabbit model of bladder outlet obstruction [41–43]. The progressive response to partial outlet obstruction can be divided into three distinct phases: (1) an initial response to surgical induction of partial outlet obstruction (days 1–14) characterized by bladder distension followed by a progressive increase in bladder mass and specific contractile and metabolic dysfunctions; (2) compensated bladder function immediately follows the "initial response" and lasts an indefinite and variable length of time; this period is characterized by a relatively stable bladder mass, and stable contractile responses to field stimulation (FS), bethanechol, and KC1 stimulation, but during this period there are progressive morphological changes in bladder cell structure; and (3) at some point, the functional ability to empty degenerates and the bladder becomes "decompensated". This decompensated phase is characterized by a progressive deterioration in contractility and function (i.e., ability to empty), a rapid increase in mass, and a progressive decrease in the volume fraction of smooth muscle elements within the bladder wall. The end result is either an organ with a thick fibrous wall, small capacity, poor compliance, and little or no contractile function, or a dilated bladder with a thin fibrous wall, large capacity, and little or no contractile function [41–43].

The following are characteristics of the rabbit model of partial outlet obstruction: The weight of the bladder increases rapidly over the first 2–4 weeks, and then slowly thereafter. This is accompanied by a decreased compliance and a progressive decrease in the contractile responses to all forms of in vitro stimulation [41–43]. However, the rate of contractile dysfunction in response to FS (mediated by the release of neurotransmitters) is faster than the rate of contractile dysfunctions in response to all other forms of stimulation [41–43].

Virtually all bladder cellular elements are involved in the response to partial outlet obstruction [43]. The urothelium undergoes an early rapid period of hyperplasia, the connective tissue component undergoes rapid changes in localization and content, the smooth muscle elements undergo both hyperplasia and hypertrophy, and fibroblasts differentiate into functional smooth muscle cells [44–47]. In general, partial outlet obstruction induces a rapid and marked remodeling of the bladder wall which includes compartment-specific cellular hypertrophy (growth and enlargement of individual cells), hyperplasia (cell division), and re-organization (structural relationship between connective tissue and smooth muscle elements).

We have identified in the rabbit three major cellular alterations which are induced by partial outlet obstruction and directly result in the reduction in the ability of the hypertrophied bladder to generate pressure and empty (1) progressive denervation [48, 49], (2) selective dysfunction of the sarcoplasmic reticulum (SR) to store and release calcium [50, 51], and (3) selective mitochondrial dysfunction [51, 52]. In men with obstructive dysfunctions secondary to BPH, there is a significant increase in bladder mass and wall thickness [54], selective denervation [55, 56], and specific decreases in mitochondrial and SR function [57], indicating that the rabbit model of partial outlet obstruction is a relevant model of obstructive dysfunction secondary to BPH in men.

Several sets of studies on the effects of Tadenan on the response of the rabbit bladder to partial outlet obstruction have been published [58–60]. In the first, rabbits were pretreated for three weeks with vehicle, 1 mg/kg, 10 mg/kg, or 100 mg/kg Tadenan orally [58]. After the pretreatment period, the rabbits were subjected to partial outlet obstruction and continued treatment for an additional two weeks. At the end of 2 weeks' obstruction, the rabbits were euthanized, the bladders excised and weighed, and in vitro contractility studies were performed. Nonobstructed rabbits were treated with Tadenan or vehicle for 5 weeks [58]. Tadenan had

no effects on bladder mass in obstructed rabbits. In obstructed rabbits, the contractile response of bladder strips to FS and bethanechol was impaired. Tadenan pretreatment resulted in a dose-dependent protection of the contractile responses of bladder strips to FS and bethanechol [58]. Tadenan administration to nonobstructed animals had no effects on any parameter studied.

The second series of experiments determined the effects of Tadenan pretreatment (100 mg/kg) on rabbits partially obstructed for 1–14 days [59]. Similar to the first series of studies, Tadenan had no effects on bladder weights of the obstructed rabbits. Tadenan pretreatment prevented or reduced the severity of the contractile dysfunctions associated with partial outlet obstruction. In addition, Tadenan pretreatment prevented the development of both mitochondrial (citrate synthase) or SR (Ca^{2+} ATPase) dysfunction [59]. In addition, it was shown that Tadenan pretreatment resulted in an overexpression of HSP-70, which is believed to be involved in the protective effect of Tadenan on bladder function [60].

In the next two series of studies [61], Tadenan was administered after 2 weeks of partial outlet obstruction. In the mild obstruction studies, the bladder weight of the Tadenan treated obstructed rabbits was lower than in the vehicle-treated obstructed rabbits. Tadenan treatment reversed the contractile dysfunctions to FS and also reversed the reduction in compliance induced by partial outlet obstruction. In the severe model of partial outlet obstruction, the increase in bladder was greater in the vehicle-treated group than in the Tadenan treated group. Partial outlet obstruction reduced compliance equally in both the vehicle and Tadenan treated groups. Tadenan partially reversed the contractile dysfunction to FS and nearly completely reversed the contractile dysfunction to carbachol [61]. The conclusion from these studies is that Tadenan pretreatment prevented or reduced the progression from compensated bladder function to decompensated bladder function, and Tadenan therapy completely reversed the effects of mild partial outlet obstruction, including improving the compliance of the obstructed bladders; and improved the contractile responses of the severely obstructed bladders. These results are consistent with the theory that Tadenan is acting directly on the bladder by either preventing or delaying the shift from compensated to decompensated function.

Additional studies demonstrated that the reversal of the contractile dysfunctions induced by mild partial outlet obstruction were paralleled by a reversal of the molecular changes to smooth muscle myosin isoforms induced by partial outlet obstruction [62].

Using an established mathematical model of micturition which evaluates the pressures at the bladder neck and the prostatic urethra, Valentini et al. demonstrated that Tadenan administration results in a significant increase in detrusor contractile function that is consistent with the animal data described above [63, 64].

There is evidence that the shift from compensated to decompensated bladder function associated outlet obstruction results from cyclical ischemia and reperfusion [64–66]. Specifically, partial outlet obstruction has been demonstrated to stimulate proteolytic and hydrolytic enzymes [64], which cause progressive damage to specific neuronal and cellular membranes resulting in denervation and mitochondrial and SR damage. The current theory is that Tadenan protects membranes from hydrolytic damage from the activated enzymes [57, 58–60].

If this hypothesis is true and one of the mechanisms of action of Tadenan is protection against ischemic-induced injury, then pretreatment with Tadenan should prevent or reduce the level of injury in an ischemic model of bladder dysfunction. A recently completed study was designed to determine if Tadenan pretreatment of rabbits protected the bladder against the development of contractile dysfunctions induced by unilateral ischemia, and to correlate the contractile effects in the presence and absence of Tadenan with the activation of Hsp-70 [68]. These studies demonstrated that Tadenan pretreatment protected the nonischemic side of the bladder from the development of contractile dysfunctions. In addition, unilateral ischemia (and partial outlet obstruction [60]) resulted in a significantly greater expression of Hsp-70 both in the bladders isolated from the Tadenan treated rabbits and those from the vehicle-treated rabbits [68]. These results indicate that Tadenan has a protective effect against ischemic damage to the bladder, similar to that shown for the obstructed bladder, and this protection may involve an enhanced expression of Hsp-70 and other genetic factors.

Summary

Tadenan has multiple effects on a variety of systems relevant to both prostate growth and bladder function.The summation of these effects would be a reduced growth potential in the prostate and improved bladder function in the presence of mild-moderate obstructive symptoms. The most obvious question concerns whether each of the individual specific actions of Tadenan is mediated by a single component or a select combination of components.

Serenoa repens (Permixon)

Permixon is a lipido-sterolic extract of *Serenoa repens*. Studies have demonstrated that it has three relevent biological activities: antiandrogenic, antiproliferative, and anti-inflammatory. The 5α-reductase is a membrane bound enzyme which catalyzes the reduction of testosterone into its active form dihydrotestosterone (DHT). The prostate is androgen sensitive, and the growth of the prostate in BPH is linked in part to DHT-mediated cell proliferation [3l–33]. The source of the DHT is both

from the circulation and from 5α-reductase activity of the prostate [3l–33]. It is clear from the many studies on finasteride, a specific inhibitor of 5α-reductase type 2, that inhibition of the conversion of testosterone to DHT can significantly reduce the prostate volume in men with symptomatic BPH [69–71].

There are two major isoforms of 5α-reductase in the human prostate, identified as type 1 and type 2 [72, 73]. The isoforms have different kinetics, pH activity curves, and sensitivities to drugs [72, 73]. Finasteride is a competitive inhibitor of 5α-reductase type 2, whereas Permixon is a noncompetitive inhibitor of types 1 and 2. Finasteride has a 50-fold greater sensitivity for type 2 5α-reductase, whereas Permixon has approximately equal potencies for both isoforms. Since Permixon contains multiple components, one cannot directly compare the potencies of finasteride against Permixon. However, the Ki of Permixon for type 1 5α-reductase is 7.2 μg/ml and for type 2 is 4.9 μg/ml [72, 73] (see Table 2). In other studies, extracts of *Serenoa repens* have been shown to inhibit 5α-reductase activity in extracts from human prostatic epithelium and stroma [74] and significantly interfere with testosterone metabolism [75].

Further studies on the effect of the lipo-sterol extract from Permixon demonstrated that although unsaturated free fatty acids can inhibit type 2 5α-reductase and saturated free fatty acids can inhibit type 1 5α-reductase, only the mixture of components of Permixon was able to inhibit both forms [76]. Recent evidence indicates that Permixon may act at the nuclear level to noncompetitively inhibit the enzyme, and may have a selectivity for the prostate over other tissues [77].

The rat prostate is androgen sensitive [78, 79]. Castration results in a substantial shrinkage of the prostate; testosterone administration to the castrate restores prostate volume. In a recent study, Paubert-Braquet demonstrated that the administration of Permixon to castrated rats receiving testosterone significantly inhibited the growth of the prostate, demonstrating that Permixon by its actions on 5α-reductase inhibited androgen-stimulated growth of the prostate [79].

Recent studies in man demonstrated that three month treatment with Permixon significantly decreased DHT content of the prostate (biopsy analysis) with an associated increase in testosterone and decrease in EGF [80]. These changes in testosterone, DHT, and EGF content of biopsies of BPH-prostate tissue confirm the ability of Permixon to inhibit DHT synthesis in vivo. Additional in vivo studies demonstrated that Permixon may stimulate apoptosis and inhibit proliferation [81].

As previously mentioned, the effects of specific growth factors on prostate cells are believed to be involved in the etiology of BPH [24–26]. Permixon at concentrations of 30 μg/ml, significantly inhibited the ability of bFGF and EGF to stimulate hyperplasia in a primary culture of prostate epithelial cells. However, basal proliferation was not affected [82, 83]. In other in vitro studies, Permixon was shown to be a potent noncompetitive inhibitor of lipoxygenase [84] and cyclooxygenase, both of which are involved in inflammatory processes. As indicated above, infiltration of inflammatory mediators are believed to play a major role in the etiology of BPH through the action of chemotactic mediators such as leukotrienes [28, 29], and recent in vivo studies demonstrate that treatment with Permixon reduces the accumulation of mast cells in the central region of the prostate (rats) [85]. These results are consistent with the idea that Permixon may act in part by reducing the influence of these inflammatory mediators by inhibiting the synthesis of leukotrienes and arachidonic acid metabolites.

In addition to androgen control of prostate growth, prolactin (PRL) has also been demonstrated to significantly stimulate prostate cell hyperplasia [86]. The lipido-sterolic extract from *Serenoa repens* (LSESr) has been shown to be a potent noncompetitive inhibitor of the PRL receptor. Both PRL-stimulated K^+ conductance and Ca^{2+} mobilization in Chinese hamster ovary cells were significantly inhibited by concentrations of LSESr as low as 1 μg/ml [87].

Distribution studies of ^{14}C-oleic acid or ^{14}C-sitosterol-supplemented *Serenoa repens* in rats demonstrated that both of these components of Permixon are accumulated in the prostate to a greater extent than in the seminal vesicles, brain, or urinary bladder [88]. Since the prostate is a glandular tissue, it would be expected that lipophilic substances would accumulate in the prostate to a greater extent than the bladder, seminal vesicles or

Table 2 Effect of Permixon on hormones, enzyme activities and mitogen-induced proliferation in vitro

	Dose range tested μg/ml	IC_{50} μg/ml	Competitive / noncompetitive	Reference
5α-Reductase				
Type 1	0.1–1000	4 ± 1	Noncompetitive	72, 73
Type 2	0.1–1000	7 ± 2	Noncompetitive	
Binding of DHT to receptor	1–1000	370	Competitive	80
Lipoxygenase	0.5–50	13		84
Cyclooxygenase (prostate primary culture proliferation)				
Basal	1–30	NS		83
bFGF-stimulated	1–30	App 30		
EGF-stimulated	1–30	App 30		
Prolactin signal transduction	1–30	1	Noncompetitive	87

brain. Although accumulation in a tissue does not necessarily equate to specific activities in this tissue, if the activities of the agent are related to accumulation in specific membranes, and the activity is through localization within the membrane, then this distribution study may be very important.

Summary

Permixon has been shown to be a potent inhibitor of a variety of enzymes and cellular processes which have been implicated in the etiology of BPH. The question of which components of Permixon are responsible for which action is of interest, but does not take away from the specific nature of the actions described above. For example, finasteride is a selective competitive inhibitor of 5α-reductase, whereas Permixon is a noncompetitive inhibitor.

Finasteride has no specific cellular actions other than its inhibition of 5α-reductase whereas Permixon has a variety of other actions. The end result is that both agents inhibit the conversion of testosterone to DHT. The advantage of Permixon may be that in addition to inhibiting 5α-reductase, it also can inhibit growth factor-stimulated proliferation within the prostate and inhibit lipoxygenase activity.

These pharmacological activities of Permixon may in part explain the clinical efficacy of this agent in the treatment of BPH patients.

Summary and conclusions

Tadenan and Permixon have significant effects on a variety of prostate and bladder relevant cellular and biochemical systems. The fact that these agents are noncompetitive inhibitors of several different enzyme systems localized in the prostate indicates that their mechanisms of action are probably not the result of specific receptor or substrate-binding linked mechanisms. It is possible that their ability to inhibit several enzyme systems at similar concentrations is related to the lipophilic nature of the components of these preparations and thus kinetically they appear as noncompetitive inhibitors. The anti-proliferative actions of both Tadenan and Permixon may also be related to the lipophilic nature of the components and their penetration and accumulation within specific cellular and subcellular membranes which results in interference with the ability of a variety (but not all) growth factors to stimulate cell proliferation. The demonstration that many of the actions of both preparations occur at similar concentrations (between 1 and 30 μg/ml) is consistent with the above hypothesis.

Tadenan can both prevent and reverse the bladder dysfunctions induced by partial outlet obstruction in rabbits, and these physiological effects may be directly related to the protection of specific cellular and subcellular membranes from hydrolysis by activated hydrolytic enzymes. One common link between the effects on the prostate and on the bladder is the protection of membranes from the action of specific enzymes. The effect of Permixon on the obstructed bladder is currently under investigation.

Unlike therapeutic agents that are designed to have one mechanism of action, it is likely that phytotherapeutic agents have multiple mechanisms of action. Since there are multiple pathophysiological mechanisms involved in the etiology of symptomatic BPH, the phytotherapeutic agents might be effective in a wider range of patients than conventional therapy.

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ANNOUNCEMENTS

2000

28th Munich Endourological Symposium with Nursing Staff Seminar 5–6 October 2000, Munich, Germany

Chairman: Prof. Dr. R. Hartung,

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4th International Symposium on Uro–Onkology: Advances in Diagnosis and Treatment of Prostate Cancer 19–21 October 2000, Marburg, Germany

Topics: Live Surgery (ascending, descending, nerve-sparing retropubic prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, art. Sphincter implantation, penile prosthesis implantation), pathology and molecular biology of PCA, therapeutic options in organ confined PCA, treatment of locally advanced and metastatic PCA.

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