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Invited Review

Prostate development and growth in benign prostatic hyperplasia

Barry G. Timms *, Luke E. Hofkamp

Division of Basic Biomedical Sciences, Sanford School of Medicine, The University of South Dakota, 414. E. Clark St., Vermillion, SD 57069, USA

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ABSTRACT

The etiology of benign prostatic hyperplasia [BPH] in elderly men has intrigued anatomists, pathologists and scientists for centuries. Studies of morbid anatomy, clinical observations and contemporary cellular biology have contributed to an evolving interpretation of the causality of the disease. Insights into the detailed microanatomy and ductal architecture of the prostate during stages of fetal and early postnatal development suggest that mechanisms involved in the early growth period become aberrantly expressed in elderly men. Age, hormones and epithelial–mesenchymal interactions are all contributing factors to the pathogenesis of BPH. Control of the microenvironment in normal and abnormal growth is a multifactorial process. Susceptibility to the disease may include clinical comorbid diseases, region-specific changes in cell–cell interactions and a variety of signaling pathways including a novel hypothesis regarding the role of the primary cilium as a regulator of signal transduction mechanisms. Recent work in animal models has shown that there are region-specific differences within the prostate that may be significant because of the dynamic and intricate interplay between the epithelium and mesenchyme. Because of the focal nature of BPH a closer examination of normal morphogenesis patterns, which defines the gland's architecture, may facilitate a detailed understanding of the atypical growth patterns.

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1. Historical aspects of BPH

> "When the hair becomes grey and scanty, when specks of earthy matter begin to be deposited in the tunics of the arteries and when a white zone is formed at the margin of the cornea, at this same period the prostate gland usually, I might perhaps say invariably, becomes increased in size." Sir Benjamin Brodie—1843

Within the preceding poetic description of impending senescence, Brodie (1843) aptly defines aging as a major risk factor for the development of benign prostatic hyperplasia [BPH] in men. He was one of the several pioneering investigators who made careful clinical and post mortem observations of the male urogenital system, paying particular attention to the pathology of urethral constriction at the bladder neck. The latter, currently termed bladder outlet obstruction [BOO], along with BPH, is considered to be a contributing factor in lower urinary tract symptoms (LUTS; (Roehrborn, 2008, 2011)). Aside from the aging process, the permissive role of androgens is known to be another important factor in the etiology of the disease. Men castrated before puberty do not develop BPH (Wilson and Roehrborn,

* Corresponding author. Tel./fax: +1 605 677 5144.
E-mail address: btimms@usd.edu (B.G. Timms).

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1999). In addition to age and the influence of androgens, other factors involved in the pathogenesis of BPH are still being proposed and discovered.

From a clinical standpoint, the noted French physician and anatomist, Jean Riolan, speculated that bladder neck obstruction was a possible consequence of prostate enlargement in the mid17th century (Riolan and Anatomica, 1649). Described as the "Prince of Anatomists" by William Harvey (van Gulik and Schoots, 2005), he writes:

> "When, therefore, there is pain accompanied with a desire to urinate, but the urine is retained, one may suspect that either a spongy growth or a little stone is sticking in the orifice, or that the orifice of the bladder is hardened because it cannot be expanded, or that the prostate glands have become swollen or are indurated, all of which I have observed in various bodies."

During the same period, Samuel Collins proffered a rather vague description of the disease and ascribes its cause as the result of "*indulgence in venery*" [the pursuit of sexual pleasure], but did note the presence of many "*hydatides*" [cysts] within the gland (Zuckerman, 1936). More elaborate descriptions ensued. One of the founders of modern pathology, Giambattista Morgagni, kept meticulous medical history notes. In his examination of the bladder from a sixty year-old man who had suffered from urine retention, he states: '*…a greater or less impediment is thrown in the way of the egress of the urine, by excrescences of the prostate gland*' (Morgagni, 1769). In a review of the pathology of BPH Franks (Franks, 1953) comments on the fact that Morgagni was a perceptive observer. He was able to identify not only the site of origin for prostatic hyperplasia but also the association and prevalence of the disease in elderly men. He noted that "… *a caruncle* [an outgrowth] … *was found to grow out in the very middle of the internal, and upper, circumference of the gland, posteriorly*." An interesting array of other potential causes for this disorder were hypothesized at the time, including the following: a scrofulous habit, over indulgence in pleasures of the table, celibacy, sedentary habits or professions, bladder irritation, alcohol consumption and horse riding (Thompson, 1868). Interestingly, these early observations had also determined a significant association with aging and report that one in three males aged 60 and above presented with prostatic enlargement (Thompson, 1868), matching the current published evidence for macroscopic BPH [palpably enlarged prostate; (Oesterling, 1991, 1996)].

Another early advocate of pathologic investigation, John Hunter, began to unveil the obscurity surrounding the functional activity of the male accessory sex glands. In 1786 (Hunter, 1786) he stated that

> "The prostate and Cowper's glands, and those of the urethra, which in the perfect male are soft and bulky, with a secretion salt to the taste, in the castrated animal are small, flabby, tough and ligamentous, and have little secretion."

As a treatment, castration was found to alleviate the symptoms of BPH (Huggins and Stevens, 1940). However, as Zuckerman (1936) points out, even though the implication of this observation would advocate that castration might serve as a treatment to relieve prostatic enlargement, the physiological relationship between androgens and BPH would not be discovered until almost a hundred years later. These independent paths of observation regarding the development of BPH with age and the dependence of prostate growth on androgens eventually merged with the classic studies performed by Huggins and Clark (1940).

2. Regional anatomy of the prostate

The eminent British surgeon, Sir Henry Thompson, published several essays regarding the anatomy and pathology of the male accessory sex glands. He is credited with the noteworthy statement that "*In order to study the Pathology of the Prostate, it is necessary to observe accurately its normal structure, conformation and anatomical relations*" (Thompson, 1868). This fundamental principle has become the backbone of numerous subsequent studies and has led to significant advancement in the knowledge of the structure, function and disease condition of the organ. The adult human prostate is a compact gland that does not exhibit the distinct lobes seen in many mammals (Timms et al., 1994). However, the focal nature of prostatic diseases, including BPH,

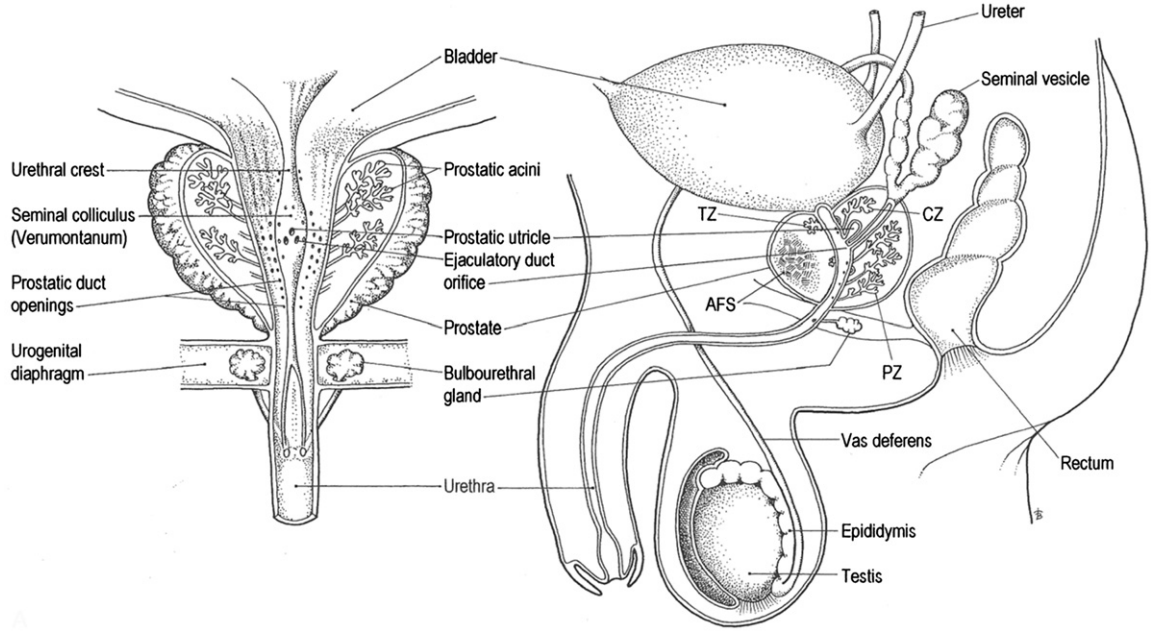

Fig. 1. Diagram of frontal and sagittal sections of the male urogenital complex illustrating the anatomical position of the adult prostate and associated structures. The prostatic zones described by McNeal (McNeal, 1983) are indicated: central zone [CZ], peripheral zone [PZ], anterior fibromuscular stroma [AFS] and transition zone [TZ]. Adapted from Timms (Timms, 2008).