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Commentary

White's operation: the history of 19th century attempts to treat prostate disease with castration

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Abstract: To understand the roots of 19th century hormonal treatments for BPH in the career of J. William White, a prominent surgeon scientist at the University of Pennsylvania. We reviewed primary and secondary literature available in PUBMED, the University of Pennsylvania Archives, and internet resources. In 1893, Dr. White presented a series of experiments demonstrating atrophy of the canine prostate following castration and advocated for this procedure in men suffering from prostatic hypertrophy. This approach was adopted by many of White's contemporaries. In 1895, White presented findings from 111 patients and reported improvement of urinary symptoms in three quarters of these patients. Improvements in surgical techniques for prostatectomy have predominantly eliminated castration as a clinical procedure for BPH treatment. These early experiments demonstrated the critical dependence of the prostate on testicular androgens and were the basis for subsequent hormonal therapies for BPH. In conclusion, the bold experiments of late 19th century surgeons paved the way for our contemporary understanding of the important role of sex steroid hormones in BPH.

Keywords: History, benign prostatic hyperplasia, castration, testosterone

The problem of prostatic hypertrophy

Benign prostatic hyperplasia (BPH) is a clinical entity known since ancient times. The first written descriptions of urinary retention, a dreaded complication of BPH, were found in the ancient Egyptian Eber Papyrus, written in 1500 BC and believed to be copied from material written in 3400 BC [1]. The first documentation of catheterization for prostate disease was in the first century AD by Romans Celsus and Galen, and this was the mainstay of treatment for obstructive sequelae of BPH for two millennia. The late 19th century was a time of renewed interest in BPH since many men suffered and ultimately succumbed to complications. One prominent physician wrote: "From the commencement of "catheter life" to the death of the patient from bladder or kidney mischief, hypertrophy of the prostate gland is associated with so much worry and pain and danger that we should gladly welcome any means which offer relief from this distressing condition" [2]. Treatment options for men with lower urinary tract symptoms and obstructive uropathy were limited, and included dilatation and catheterization. The 19th century was also a time of great innovation in surgical approaches to disease, enabled by the development of effective anesthesia, and the adoption of antiseptic techniques in the operating theater. This set the stage for advancement in surgical approaches to BPH. While this report will focus on the efforts of J. William White to advocate for castration as a treatment for BPH, concurrent development of prostatectomy surgery advanced in the 1890s and was ultimately adopted and refined by urologists [3].

J. William White, MD, PhD (1850-1916)

Born in Philadelphia, November 2, 1950, James William White (**Figure 1**) was the son of James William White senior, a prominent Philadelphia physician, founder of the Women's Maternity Hospital and longtime president of the S.S. White Dental Supply Company. His mother was Mary Ann McClaranan of New England. White

Figure 1. J. William White, M.D. (portrait photograph, c. 1880, ID 20070227016). University of Pennsylvania Archives, Philadelphia, PA.

was a bright child, and according to his biographer and friend Agnes Repplier, possessed "a tendency to quarrel, and a still more fatal readiness to uphold his dispute by force" [4]. Following "three vigorous years" at the Medical School of the University of Pennsylvania, in 1871 at the age of 21, he graduated at the head of his class with Ph.D. and M.D. degrees. White began residency training at the Philadelphia hospital at Blockley and completed residency training at the Eastern Penitentiary. By the late 1870s, he was working under the prominent Dr. D. Hayes Agnew and is portrayed in Thomas Eakins' famous painting "The Agnew Clinic" (**Figure 2**).

White ultimately achieved a highly productive career as a genitourinary surgeon and scientist. He co-authored numerous medical textbooks and maintained a lifelong connection to the University of Pennsylvania. White was an avid sportsman and advocate for athletics at the University of Pennsylvania. Following his retirement, White traveled extensively in Europe, and was struck by the plight of the Allies in the early years of World War 1 (**Figure 3**). Just months before the sinking of the *RMS Lusitania* in 1915, White founded the American Ambulance Hospital in Paris. He campaigned tirelessly for American involvement in WWI until his death in 1916.

Late 19th century concepts of BPH

As a specialist in genitourinary surgery and venereal disease, White was keenly interested in the problem of prostatic hypertrophy. Late 19th century concepts of BPH etiology ranged from arterial sclerosis, prostate growth compensatory to bladder changes, prolonged ungratified sexual excitement, or second marriages late in life. A French contemporary of White's, Guyon, argued that prostatic hypertrophy was due to a constitutional element unique to arterial sclerosis. Guyon emphasized the role of the bladder in producing symptoms of end-stage "prostatism". Another colleague of White's, Harrison, emphasized that prostatic hypertrophy occurred secondary to changes in the bladder (trabeculation, diverticula and detrusor hypertrophy). While White recognized the many theories of BPH in his time, he adopted the prevailing view that the enlarged prostate caused a "mechanical obstruction, leading to bladder changes" [5]. White believed that BPH depended on a systemic, chemical influence from the testes, analogous to uterine fibromyomata, or fibroids, and that bladder changes and urinary retention were secondary to the prostate disease. He extended this idea to suggest that castration would be followed by prostatic atrophy, which he demonstrated in a canine model.

His theories were the logical extension of previous literature, although it is unknown whether White was aware of these experiments. Known as the father of behavioral endocrinology, Arnold Berthold in 1849 autotransplanted the testicles of roosters into the abdominal cavity and demonstrated that regression of the comb and wattle (a consequence of castration) did not occur. He concluded that a substance produced by the testicles, secreted into the bloodstream, affects behavior and physiology [6]. In 1889, Charles Edouard Brown-Sequard (1817-1894) self-injected a preparation of dog and guinea pig testicles and claimed that it had favorable effects on his physical and mental abilities [6]. This so-called "Elixir of Life" was administered by more than 12,000 physicians in Europe and the United States for a variety of

Figure 2. Agnew Clinic, painting by Thomas Eakins, commissioned by the Medical School Class of 1889 (portrait photograph, 1889, ID 20070111005). University of Pennsylvania Archives, Philadelphia, PA.

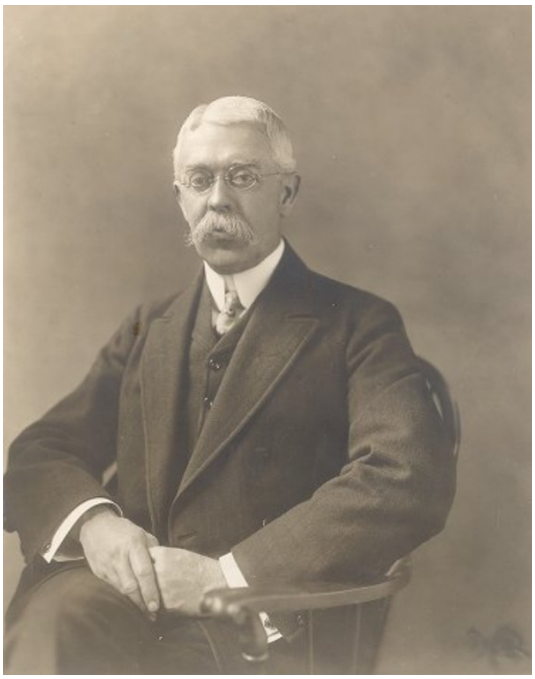

Figure 3. J. William White, M.D. (portrait photograph, c. 1910, ID 20070227017). University of Pennsylvania Archives, Philadelphia, PA.

ailments despite questionable evidence supporting its benefits and inherent risk of infection.

Castration for prostatic hypertrophy

In an address to the American Surgical Association on June 1st, 1893 in Buffalo, NY, White presented his theories on the development of BPH, and advocated for castration as a possible treatment [5]. He first presented the results of his experiments performed on dogs. To establish the prostate mass, 35 dogs and their prostate glands were weighed, yielding an average prostate mass of 15.3748 grams. Following castration, the average prostate mass was 3.93 among 10 dogs, and atrophy was present in most prostates. He then went on to comment on the experiments of John Hunter (1728-1793) who observed that castration of bulls changed the consistency of the secretory glands from soft and bulky to "small, flabby, tough and ligamentous". Hunter also observed that the prostate of hedgehogs, moles and sparrows changed in size (increased) dramatically with rutting season [5, 7]. White followed this discussion with an observation of prostatic atrophy after castration of a human patient [5]. While he understood that the embryologic origins of the prostate and uterus are distinct, White reasoned that if oophorectomy caused regression of uterine fibroids, then castration should lead to a decrease in size of the hypertrophied prostate. He argued that if castration could be applied therapeutically to "prostatics" it was a simple operation with low mortality and considerably less morbidity than contemporary prostatectomies. In the closing remarks of his address, White clearly lacked the motivation to apply his discovery. "I must admit, finally, that I have not had the courage of my convictions, and have never seriously sought to recommend the operation" [5].

The medical community responds

Just one year after his address, on June 23, 1984, he reviewed seven cases submitted by several colleagues. Francis L. Haynes performed "White's operation" and proclaimed of one case, "the patient is practically cured" [8]. White himself performed castration for a catheter-dependent 69-year-old patient with a prostate "half the size of an orange", with clinical improvement. While he suggested therapeutic castration to three more of his patients, it

appears that due to his honest communication about of the experimental nature of the procedure, these patients declined the operation.

In 1895, White followed his initial address and subsequent clinical reports with a very detailed case series of 111 patients suffering from BPH who were treated by White and his colleagues with surgical castration. His first case was a 60-year-old man with an 18-month history of obstructive lower urinary tract symptoms managed with catheterization. He was debilitated with foul-smelling purulent, bloody urine. Initially refusing castration, he was admitted and underwent daily bladder irrigation and was treated with salol (phenyl salicylate) and boric acid and a carefully regulated diet of mostly milk. He was discharged but returned clinically worse and consented for castration. The surgery was performed in just three minutes and his urination improved in the first post-operative day. The patient himself reported to White's class of medical students that he was feeling like "...when he was a boy in the fields" [9].

Of the 111 patients White reported in this case series, 87% of patients had rapid atrophy of the enlarged prostate, 52% had improvement in cystitis, 66% had return of "vesical contractility" and 83% had improvement of their most troublesome urinary symptoms following castration. Forty-six percent of these patients were reported to have "a return to local conditions nor very far removed from normal". He was meticulous in reporting clinical courses, as well as ensuing complications, although some reports were much more detailed than others. Notable contributors to this case series included four cases submitted by William Halsted (1852-1922) and one from Charles McBurney (1845-1913). Among the 111-patient cohort, 20 (18%) died following surgery, although many of these patients were very ill and likely poor candidates for surgical intervention. One unfortunate 82-year-old patient was "nearly dead" prior to surgery but did urinate spontaneously four days after castration. White reviewed all cases and determined some patients were apparently moribund prior to castration; excluding these, the mortality rate was 7 of 98 cases (7%). Even in these patients, three quarters showed some improvement in symptoms or a decrease in prostate size before they died. Compared to a mortality rate of 20% in suprapubic prostatectomies and substantial risk of fistula and infection in the late 1890s, the advantages of castration for BPH were apparent to White and many of his colleagues. White's operation was adopted by many of his contemporaries, although his approach spurred spirited discussion between advocates for castration and early proponents of prostatectomy.

In his 1895 report, White elaborated more on the possibility of a chemical product of the testicles being responsible for male sexual characteristics and spermatogenesis [9].

White also referenced the theories of his contemporary, Roger Williams, regarding neoplasms, which were conceived to form as a result of their cells, as well as a "*force* that regulates the cellular activities". White extended this theory to uterine and prostatic overgrowths as being caused by a "failure of the general restraining force". At length, he discussed the analogy that uterine fibroids are to the ovaries as the prostate is to the testes. He also reported the results of several experiments done on dogs, where he showed that ligation of the vas deferens and spermatic cord decreased prostate size and produced prostatic atrophy with concurrent "sloughing" of the testicle [9].

Following White's series in 1895, Alfred Wood addressed the American Association of Genitourinary Surgeons in 1900 and synthesized the series of White and several others findings. A German surgeon, P. Bruns in 1896, presented 148 cases of men with BPH treated by castration, with 83% showing a decrease in prostate size. Another American, A. T. Cabot, in 1896, presented 99 cases and reported that 84% showed substantial or very great improvement. Wood compiled 159 cases not previously presented by White or Cabot, with reduction in prostate size in 51.5%, improvement in urinary symptoms in 57% and general clinical improvement in 67%. Wood's case series mortality rate was 8% although many of these patients had improvement in urinary function prior to their demise. Interestingly, Wood also presented 193 cases of patients treated with vasectomies for BPH. Admittedly, the details were limited compared to his castration series, but 17 patients (9%) had reduction in prostate size, 15% noted improvement in urinary function, and general improvement was reported in

67%. The surgical approach was not fully described, it is unclear whether this procedure included ligation of the testicular blood supply in some of these cases, which might account for the clinical efficacy. It is perhaps more likely that the general improvement resulted from the surgeon or patient's expectation of a clinical improvement from the procedure, rather than a biologically feasible mechanism.

A contemporary perspective on White's operation

The structure of testosterone was elucidated in 1935 [10], and in 1941, the seminal work of Charles Huggins and colleagues demonstrated the hormonal dependence of prostate cancer [11]. Castration or administration of exogenous estrogens to men with advanced prostate cancer caused regression of tumor growth and clinical improvement, and these therapies also dramatically impacted BPH. While the precise molecular etiology of BPH remains unknown today, aging and androgens are associated with its development. The critical role of testicular androgens in development, maintenance and diseases of the prostate gland is well acknowledged. Indeed, therapies that impact androgen action, primarily by inhibiting the conversion of testosterone to dihydrotestosterone via 5-alpha reductase, are a mainstay of modern medical management for benign prostatic hyperplasia (BPH). The contributions of White and his colleagues in promoting castration for BPH is an important chapter in the history and development of hormonal therapies for BPH.

Conclusions

The late 19th and early 20th centuries were important times for innovation in surgical and "hormonal" approaches to BPH. Late 19th century surgeons performed castration as a treatment for men with advanced prostate hypertrophy, with reduction in prostate size and improvement in urinary function and clinical course for most patients.

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Disclosure of conflict of interest

None.

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