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- Benjamin Franklin and the rise of the double blind clinical trial
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# PRAETERITUM DOCET

‘The past teaches’

# On the Cover



Medieval medical practitioners viewed disease in Galenic terms, of a balance (or imbalance) of the four humors of phlegm, blood, yellow bile, and black bile and their psychological temperaments: phlegmatic, sanguine, choleric, and melancholic, respectively.(1,2) They also viewed disease as entwined within the world as they saw it, influenced by the months, the seasons, the stars, and their astrological signs. The diagnosis of diseases, and their treatments, required the practitioner to take such variables into account, and a complex system of ridiculous rules and traditions that had no basis on the way we view pathophysiology today. Still, there were examples of medieval medicine that

hint of innovators attempting to systematically study pathological variation. Urine was a useful almost “divine” medium.(3) The fluid could be easily obtained and differences reliably demonstrated on visual, olfactory, and sometimes gustatory terms. Uroscopy was the pseudo-science of diagnosing disease based on such an exam of urine. As published materials were rare, and teaching even less so, practitioners looked to so-called uroscopy ‘wheels’, in which flasks, or ‘matulas’, of urine are illustrated with gradations in color that indicated a supposed diseased state. The wheel on this month’s cover of IJUH appeared around 1506 in Nördlingen, Germany and was created by Ulrich Pindor for his *Epiphanie Medicorum*.(4) As these wheels required a defined ‘input’ to derive an ‘output’ function, they represent an early version of a medical nomogram. Unfortunately, the circle falls short of providing the practitioner with any tools to treat the supposed ailment. It seems fitting that uroscopy was popular in the ‘Dark Ages’ but its practice persisted well into the 19th century and decades of the cover of the *Journal of Urology* depicted an 18th century physician performing uroscopy in juxtaposition with a ‘modern’ urologist performing cystoscopy.

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# John Blair Deaver's War on the Prostate

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**Introduction:** John Blair Deaver was an iconic American surgeon who rose in prominence at the outset of the 20th century when the specialty of urology was in its infancy. By some accounts he was a difficult personality and made an enemy of J. William White, the then Chair of surgery at the University of Pennsylvania. Deaver was also known as a brilliant operative surgeon and educator, performed over 15,000 appendectomies, and invented his eponymous retractor very much in use today. Known more as an abdominal surgeon than a urologist, he still made contributions to the urologic literature and he himself became a revered expert in prostatectomy. We aimed to clarify the contemporary biography of Deaver and his influence in the creation of the modern urologic armamentarium.

**Sources and Methods:** We used primary source materials from the archives of the University of Pennsylvania, the National Library of Medicine, the Wellcome Fund, the Lancaster County Medical Society, the Medical History Library of the University of Pennsylvania, the Medical Society of the State of New Jersey, the American College of Surgeons, and published literature.

**Results:** Deaver was a general surgeon and proponent of early appendectomy and "preventative surgery". He devised the retractor that bears his name to allow surgical exposure through small incisions. He was particularly skilled at suprapubic prostatectomy for benign diseases, for the endoscopic management of urethral stricture, and of ureteral stone disease. His Saturday teaching clinics for practicing surgeons became a world-wide phenomenon in his lengthy career. He foresaw the rise of surgical specialists and recognized the need for surgeons of the future to embrace expertise in a precise field. At the same time, he called for increasing communication among medical and surgical fields and a dedication to lifelong excellence. Two quotations credited to Deaver, which encompassed his simple philosophy regarding surgical interventions were "Cut well, get well, stay well" and "Let the patient heal".

**Conclusions:** Deaver's death in 1931 ended the life of one of surgery's titans, an innovative force in surgical skill and education. His death while undergoing therapeutic radiation serves as an ironic metaphor that those who serve may not reap similar benefits.

**Keywords:** John B Deaver, Deaver retractor, prostatic surgery,



ohn Blair Deaver (1855-1931) was an American surgeon at the turn of the 20th century and a product of the highly competitive world of general surgery at the University of Pennsylvania.(1,2) He heralded from a line of physicians and Deaver dedicated his first book to his father Dr. Joshua Deaver, writing that his "character and sterling qualities as a physician have been the guiding influences of my professional life".(3) Deaver graduated from the University of Pennsylvania (Penn) in 1878 but matriculated to Philadelphia's German Hospital, in part, due to an apparent personal conflict with the proto-urologist J. William White (1850-1916), the 3<sup>rd</sup> John Rea Barton Professor at Penn. Deaver wrote a major textbook on genitourinary surgery with the 4<sup>th</sup> John Rea Barton Professor, Edward Martin (1859-1938).(4)

Deaver may have been regarded as an aggressive surgeon, having been referred to, in at least one biography, as one of "the great slashers" and was reported to have performed on some days more than 25 operations.(5) He was also an educator and held a popular Saturday afternoon clinic that attracted even foreign surgeons to attend. It was following the death of Dr. White that Deaver was called to the Chair of Surgery at the University of Pennsylvania in 1911. Deaver wrote nearly 250 articles and five major textbooks of surgery, was a busy clinician, historian, and an innovator of surgical instrumentation and positioning. By some accounts, however, he had a difficult personality. The details of the confrontation he may have had with White are unknown but they never overcame their mutual animosity towards one another.

Deaver's clinical work, bridging several specialties from head and neck, abdominal, and urologic surgery, was becoming increasingly rare and yet his attitudes towards specialists may have been more prescient than alleged.(6-8) Deaver's demise at the age of 76 was rumored to be due to prostate cancer yet all medical records of the case were instructed to be destroyed. (4) Thus, there are some paradoxes to Deaver's life and his accomplishments which we wished to clarify. Our objective was to explore his writings, lectures, and accomplishments, in his life and times, to better understand the impact he had on his community and future generations of patients and their surgeons.

### SOURCES AND METHODS

We accessed primary and secondary sources on Deaver from the archives of the University of Pennsylvania, the Lancaster City and Council Medical Society, the Medical Society of the State of New Jersey, Deaver's lectures, and his published works including Deaver's 1905 and 1922 editions of *Enlargement of the Prostate: Its History, Anatomy, Etiology, Pathology, Clinical Causes, Symptoms, Diagnosis, Prognosis, Treatment; Technique of Operations, and After-Treatment*.(9-18)

### RESULTS

#### Early Career

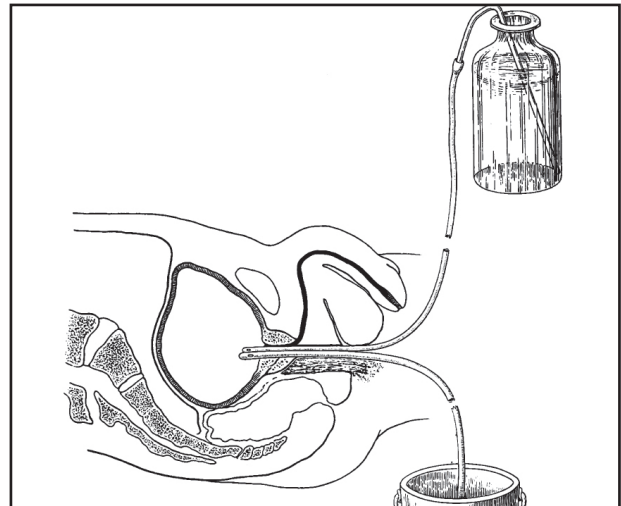
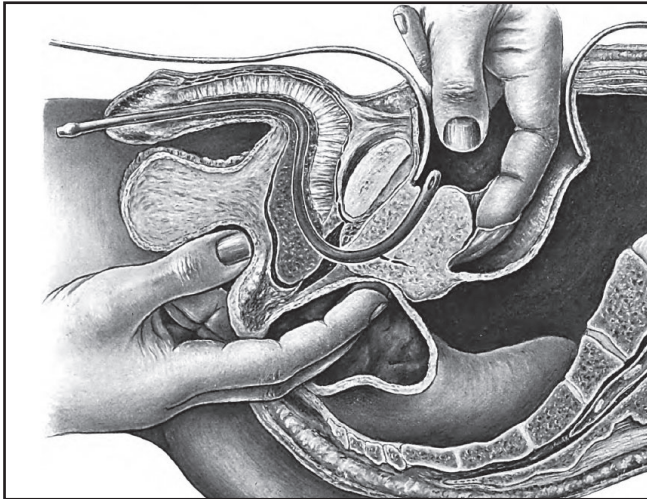
John Deaver received his M.D. from the University of Pennsylvania in 1878, became an intern at Germantown

Hospital, and thereafter entered private practice. From 1886 he became a surgeon at Lankenau (then German) Hospital where his surgical practice thrived. He was ambidextrous and would routinely perform six major surgeries a day. He was especially known for his appendectomies of which he performed, it was said, greater than 15,000.(19) He once asked of his students "Who does more surgery than John B. Deaver?" "The Mayo brothers," he would answer himself, "because there are two of them."(19) Deaver was a prolific writer and teacher. In 1911, he was called to the University of Pennsylvania as Professor of Surgery after both the 3<sup>rd</sup> Chair, JW White, died and then his protégé, the 4<sup>th</sup> Chair, Edward Martin retired. Deaver became the 5<sup>th</sup> John Rhea Barton Professor of Surgery in 1918 until he retired in 1922. He inspired many students in the medical school, so much so that Penn's John B. Deaver Surgical Society was established in 1897, serving as an honorary organization for students wishing to pursue surgical careers, and was active for 70 years. "Personally," he once wrote, "some of my pleasantest and most satisfying recollections are the hours spent in clinical work among my students. It has been my endeavor to (teach them) the sacredness of their calling and to impress them with the fact that it depends upon them to develop the surgery of the future."(20, p.105)



**Figure 1.** (Left) John Blair Deaver (JBD) (without cap) and his OR staff, at the German (later Lankenau) Hospital, outside Philadelphia, Pennsylvania, c 1900.(Courtesy, University of Pennsylvania) (Right) JBD, 1922, as President of the American College of Surgeons, (Image courtesy of the Archives of the American College of Surgeons, Chicago)





**Figure 2.** Deaver's illustration of open 'radical' prostatectomy for BPH, after the method of Peter Freyer, whereby transrectal counterpressure facilitated intravesical manipulation. The text specifies that the right hand is gloved. (Right) Deaver's then revolutionary concept of continuous bladder irrigation before the advent of 3-way 'bag', or now known as Foley, catheters.(9)

### Deaver and urology

The disorders and diseases of the prostate, particularly benign prostatic hyperplasia (BPH), were as much an issue in Deaver's lifetime as they are still today.(21-23) Deaver lived through the open surgical era when suprapubic and retropubic prostatectomies were in their infancy and the develop of more precision urological tools, such as the Foley catheter, did not yet exist.(24) Deaver once wrote that "it is a remarkable thing that any part of the human body liable to such important pathological changes as the prostate gland should have acquired a conspicuous place in surgery within such comparatively recent years."(9, p.13) He had an acute awareness of the details of urologic history and the discovery of the prostate and the myriad practitioners devoted to its management. "It seems a pity," he once lamented, "that so many controversies in regard to surgical priority are so constantly arising...It appears that prostatic surgery is particularly unfortunate in this respect. (The 17th century surgeon Johannes) Riolaus bitterly denounced his contemporaries for claiming as their own operations which had been employed before their grandfathers were born, and for a hundred years before even that time." (9, p.13)

It is undoubtedly true that the development of urology as a stand-alone subspecialty of surgery certainly occurred during the early half of the twentieth century, just as surgeons had discovered the prostate as noted by Deaver. There are many histories of the development of surgery for both benign and malignant prostate disease, and much activity occurred at the

dawn of surgical specialization in the late 1800s. Deaver practiced in Philadelphia just as American urology became formally organized as a separate specialty. The first President of the American Urological Association (AUA), Ramon Guiteras (1858-1917), often spoke of "urology" as a standalone field and that urologists would emerge as a distinct specialty from more general surgeons like John Deaver.(25) Still, Deaver often alluded to the many new technologies available to the budding field, including electricity, and to the need to embrace those procedures that had good results rather than those that appeared to be more novel. Deaver acknowledged some of the great names of early urology as true innovators include Robert Proust (1873-1935) of Paris, Peter Freyer (1851-1921) of the United Kingdom, and Enrico Botini (1837-1903) of Italy.(9) He devoted himself, rather, to suprapubic and perineal prostatectomy and wrote substantially on the safety and merits of proper pre-operative medical preparation and surgical technique. He was not enthusiastic to embrace the untested. "I think that this is the proper place to sound a note of conservatism," he once opined. "Many surgeons are rolling up long lists of successful (or unsuccessful) operations by either the suprapubic or the perineal route. But it appears to me that some such operators maybe a little hasty in resorting to operative interference...One death clearly caused or hastened by an ill-judged resort to operative treatment will demand an immense number of successes to blot out its remembrance. And I cannot but think that some surgeons are displaying more enthusiasm in adding ten



**Figure 4.** 'Mace Banquet' of the American College of Surgeons, 1921. Deaver, center with glasses and moustache, sits to the left of Charles Mayo (1865-1939) with bow tie and, in the front with handkerchief, William Mayo (1861-1939). Deaver was said, "Who operates more than John B. Deaver? The Mayo Brothers - because there are of two of them."(19) (Courtesy, Archives of the American College of Surgeons, Chicago)

or twenty operations every year to their tale of cases, than they are in seeking the best interest of their patients."(9, p.204)

There was, however, no distinction in Deaver's time of a simple versus radical prostatectomy the way it is known today. In contrast to the Halstedian definitions reserved for benign and malignant disease, respectively, Deaver and his colleagues viewed a "simple prostatectomy" as a resection of visually offending lobes and a "radical prostatectomy" merely a more aggressive resection of the entirety of the prostatic adenoma. Thus, Deaver's writing on "radical prostatectomy" was not an operation for cancer, as would be described by HH Young in his pioneering 1904 perineal approach for malignant disease.(26,27) Deaver's work was instead focused on the perineal and suprapubic approaches for clinically benign disease and often quoted and studied the techniques, patient positioning, and results of Freyer and Proust. In Deaver's time, the anatomic relationship of the prostatic adenoma, the prostatic urethra, and the prostatic capsule was not fully appreciated, especially in large prostate glands, even by surgeons like Freyer who many contemporaries claimed was "labouring (sic) under a grave misapprehension" that he was able to remove

the adenoma and leave the "urethra entirely intact."(9, p.13) Such operations, though, were performed in the early 20th century when methods to ensure anesthetic and surgical safety were at their infancy and self-retaining in-dwelling balloon catheters had not been developed. Deaver knew that many men undergoing surgery for prostate enlargement were frail and elderly and he was well aware of the narrow window of clinical safety for these men. "I do not think I can justly be accused of being a timid operator," Deaver wrote in 1904, "but I am free to confess that I am afraid to do too much to some of these old men: their tenure on life is slight, and pressing our manipulations too far may, at any moment, 'loose the silver cord', and instead of curing our patient by a brilliant operation, we shall have killed him by meddlesome surgery."(9, p.204). Deaver relied on statistics of the craft and published the mortality rates of all the known approaches to surgical resection of the prostate, and described in detail the two fatalities of his own (although he was unable to clinically explain the etiology for their post operative demise).

The physiologic risks to the patient, and the stress on the surgeon, was great, Deaver warned, and that far better time would be spent in an operation's preparation

than in its performance. "The shock of the operation is a strain on even a well-preserved heart; but it may be much lessened by getting the heart into training previous to the operation....and the routine administration of cathartics... is debilitating to the extreme." (9, p.216) Thus, there were efforts to explore non-operative methods of treating prostatic enlargement and Deaver was no exception.

J. William White was the first to advocate for castration as a method to treat the enlarged prostate and was embraced by several other practitioners including Deaver. The use of castration was, lamented Deaver, somewhat "indiscriminate" and often led to disastrous consequences and mortality rates of 10-15%. (9, p.196) "One of the chief dangers", he wrote was "the development of mania, which seems dependent on the removal of the sexual organs, and not upon the mere fact of there having been an operation of some kind performed, as has been claimed by a few writers." (9, p.197) Deaver shared his successes and failures on many occasions and on the subject of castration for BPH he admitted that "a number of years ago I myself adopted this form of treatment with...unsatisfactory results; but I do not think it too much to say that I shall never employ it again. I regard it as an operation absolutely indefensible at the present time." (9, p.199). In a premonition of prostatic arterial embolization for BPH, Deaver acknowledged that some advocated for the use of surgical ligation of the internal iliac artery in hopes of causing ischemic atrophy of the prostate. His quoting deaths after such procedures due to peritonitis, renal failure, and gangrene of the foot suggest that Deaver lacked enthusiasm for its consideration. (9)

Deaver was a prolific author and at the time of his textbook on prostatic enlargement he also published books on surgery of the upper abdomen, the head and neck, on appendicitis, and on surgical anatomy. (3,28,29) In addition to his six books, he authored about 250 papers. (1) His depictions of deep pelvic and prostatic anatomy included the course and derivation of Denonvillier's fascia, the somatic innervation of the prostate (and the description of referred pain to the penile meatus), and the smooth muscle surrounding the prostatic urethra preceded current models by 80 years. (9,10). His expertise also included textbooks on the management of male urethral strictural disease, management of bladder tumors, and the history of medicine. His textbook on prostatic surgery alone containing 200 historical citations. (30-32). Deaver's 1910 lecture "When and by whom should surgery be advised", delivered at the 144th annual meeting of the Medical Society of New Jersey, began a phase of his career where his experience and sagacity led to establishing evolving concepts of quality assurance and critical analysis. (7) His 1923 book, with SP Reimann, "Excursions into Surgical

Subjects", could now have far greater horizons upon which to write his opinions in contrast to the highly specific subject material of his earlier works. (20) The treatise touched on biliary surgery, a hagiography on Louis Pasteur, and thoughts to encourage younger surgeons through the "trials and tribulations" of a surgical life.

### The Famous Retractor.

It is unknown when Deaver envisioned a narrow instrument with a long, curved, and blunt end to assist with deep pelvic retraction. He makes no mention beyond the "simple retractors" needed for appendectomy in his 1896 work on the subject. (3) There were no specifications of any retractors at all in his 1909 work *Surgery of the Upper Abdomen* although some illustrations in the work allude to an early form of one. (28) Newhook et al. believed that the first mention of Deaver's retractor was in Deaver's own article in a 1928 issue of the *Journal of the American Medical Association (JAMA)* on papillary cystadenocarcinoma of the ovary and its surgery. (33) However, the retractor had already been included in standard hospital surgical supply catalogues as early as 1915 when a 1-inch wide stainless steel device was priced at \$1.00. (34) AB Johnson's marvelous 1915 tome on abdominal surgery invoked the use of the Deaver in most deep abdominal operations and Norman Guiou of Ottawa favored a 1 inch Deaver in a 1923 article on transperitoneal Cesarean section to displace the bladder downward. (35,36) Deaver retractors had become standard military equipment by World War II appearing in the operating room set-up requirements for open stomach, liver, and kidney procedures. (37)

### The Deavers

Deaver had children well into his later years. He married Caroline Randall (1868-1945) in 1889 who gave birth to Elizabeth (Thomson) (1891-1968), Harriet (Alexander) (1895-1970), John Blaine Deaver, Jr. (1898-1921), and Joshua Montgomery Deaver (1901-1978), a noted physician in his own right, born when Professor Deaver was 43. The Deavers purchased a 44 acre plot of land in Wyncote, Pennsylvania in April 1898 for \$25,000 where they would build their home off Mill Road. (38) Deaver was particularly attached to his young son, John Jr., who appears to have died in Hot Springs, Arkansas at the age of 22 when his father was already 66. (38) The Deavers had John, Jr. interred at Laurel Hill Cemetery West in Bala Cynwyd, Pennsylvania and he chose to dedicate the 1922 edition of his textbook on prostate disease as follows: "To the memory of J.B.D., Jr., who departed this life at the threshold of manhood, and who I had hoped would travel in my footsteps, this book is affectionately dedicated." (39, 10) Deaver may have undergone an important personal



transformation, or sustained the beginning of serious medical problems, soon thereafter and retired from his academic obligations in June of 1922 much to the "regret" of the Board of Trustees of the University of Pennsylvania who accepted his resignation.(40)

### Demise

Deaver himself died on September 25, 1931, at the age of 76, presumably from prostate cancer, while being treated with pelvic X-ray therapy by his friend, the 'skiagrapher' (i.e. radiologist), Henry Khunrath Pancoast (1875-1939) at the University of Pennsylvania. The details of Deaver's disease, his therapy, and outcomes are unknown as Pancoast destroyed all evidence and X-rays at the request of his esteemed patient. He was interred next to his son John Jr in the Deaver family plot at Laurel Hill.(39) Franklin H. Martin (1857-1935) founded the *Journal Surgery, Gynecology and Obstetrics* in 1905 and served as the 1928-1929 President of the American College of Surgeons (1913). In his obituary of Deaver, Martin wrote that Deaver was an "enthusiastic statesman of surgery...a star operator, and early achieved international fame. He loved his chosen work which he pursued, with great industry and without signs of weakening, to the age of seventy-five. The surgeons of every land, when they visit Philadelphia in the future, will miss this genial host with his philosophy, his irrepressible humor, his diagnostic skill, and his marvelous technique."(1)

### DISCUSSION

On Tuesday, June 28, 1910, John Deaver rose to the dais at the Hotel Chalfonte, Atlantic City at a meeting of the Medical Society of the State of New Jersey and gave the invited lecture, "Why and By Whom Should Surgery be Advised".(7) At the age of 55, Deaver spoke not about the details of prostatic, gall bladder, or appendiceal surgery but rather surgery as a craft and rallied surgeons to be the patient's strongest advocate for timely surgical care.

"I have seen physicians felicitate themselves," he said, "upon finding a dangerous and difficult condition as indicating that their recourse to an operation was fully justified. The time has come when such a state of affairs constitutes a reproach, meaning that the best time has been allowed to pass and the patient brought by delay in jeopardy of is life. An easy operation means a safe and easy recovery." He coined the term "living pathology" as an invective to encourage pathologic

diagnoses to be made in the living patient and prevent subsequent disease.

It follows that he was also a strong proponent of "preventative surgery", as opposed to preventative medicine which, he felt, dealt with the mere prevention of disease in the "normal person". Preventative surgery, in contrast, Deaver felt was clinical care directed to those "who have already been seized with an affection... and aimed to prevent the disastrous consequences of a diseased process already set in motion." Deaver appears visionary when seeing surgery as an important component of a medical consortium of experts rather than as a pyramid with any one specialty at any tier. "To fight disease," he declared, "we must be brothers in arms. For every operation, there should be many consultations, instead of many operations for every consultation...I respectfully submit...that the physician alone is not a safe judge of the time or necessity for surgical treatment....The decision should be arrived at as the product of medical and surgical deliberation together...The best interest of the patient will be conserved, precipitate surgery will be checked, and likewise eleventh hour operations be relegated to the past".(7, p.63) Deaver's death at the age of 76 brought to close an unheralded legend in his own time, devoted to the teaching of his craft and its betterment, but in full acknowledgement of its limitations. He apprehensively saw a future world of sub-specialization in which surgeons would strive to excel in "healing one disease and not to be expert in curing many"; to suffer a kind of "detachment of interest...apt to exaggerate the importance of their particular functions."(7) Deaver's biography reminds us, therefore, of a prolific life beyond his innovative interests in modernizing abdominal, deep pelvic, and urologic surgery, but also in the responsibility of surgeons to better our craft in the interests of the patient.

In his 1922 American College of Surgeons Presidential Address, Deaver spoke of the continued need of self-improvement, especially in a rapidly evolving and complex medical world. "...We who are daily at work at the operating table and in the sick room, know full well the limitations of our science... (Our) practice and the lack of finality in the art in which we are 'looking for the high white star of Truth', (inspire us) to become masters, and the mastery of which today is beset with much greater difficulty than at any former time."(8 p.606)

## CONCLUSION

Deaver thus provides us with a compelling biography. He improved a physical aspect of the surgical world, with a device as simple as the retractor that bears his name, but his impact on others was complex. He expected much of others and set the bar of patient service exceedingly high which he viewed as an almost sacred calling. He also inspired the young and was deeply dedicated to the education of future generations to ensure continuously improving patient care.

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# Benjamin Franklin and the Debunking of Mesmerism

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**Introduction:** In 1784, Benjamin Franklin headed a Royal Commission in France to investigate animal magnetism and its then celebrated practitioner, Franz Anton Mesmer. Mesmer believed that a universal magnetic fluid flowed through every being on earth. Illness was caused by blockage or imbalance in the fluid's flow. Mesmer claimed he could manipulate the fluid to restore balance and health to the body. Our aim was to determine Franklin's role in the Commission and his use of scientific principles to question the validity of a popular medical regimen.

**Sources and Methods:** We used contemporary, primary literature pertaining to Franklin, Mesmer, animal magnetism, and mesmerism during the years 1778 to 1785 in Paris, France; archives of the National Library of France; and the Benjamin Franklin archives of the Library of Congress, USA.

**Results:** Franklin and his colleagues conducted placebo-controlled, 'blinded', sham and real experiments on themselves and patient volunteers. The investigators concluded that any positive effect from Mesmer and 'mesmerism' was due to the power of suggestion rather than the effect of any physical fluid or its manipulation. Franklin condemned mesmerism in public fearing its practice could lead to quackery but privately he saw no harm if it kept patients away from more dangerous medications.

**Conclusions:** The Royal Commission's report condemned mesmerism on scientific and moral grounds, but Franklin took a more nuanced view that psychological factors could favorably influence health. In fact, mesmerism, in some form called by other names, thrives today.

**Keywords:** Benjamin Franklin, Anton Mesmer, mesmerism, medical fraud, charlatanism, placebo-controlled trials



On August 11, 1784, a Royal Commission ordained by Louis XVI of France published the findings of its investigation of animal magnetism and mesmerism.(1,2) The members consisted of eight eminent physicians and scientists chosen from the Paris Faculty of Medicine and the Royal Academy of Sciences, headed by America's ambassador to France, Benjamin Franklin (Figure 1). The Commission was tasked specifically to determine the truth behind the supposedly miraculous medical cures claimed by the most celebrated practitioner, and namesake, of animal magnetism, Franz Anton Mesmer (Figure 1).

Mesmer believed that an invisible magnetic fluid emanated from the stars and planets and permeated all elements on earth, especially living organisms, to maintain balance and harmony in the body. Mesmer called his sensational new discovery 'animal magnetism'. (3) All illness, Mesmer conjectured, resulted from the fluid's imbalance or from the fluid's faulty distribution.

By manipulating a patient's magnetic fluid with an iron wand, or even his own hands, Mesmer claimed he could restore the fluid's equilibrium, thereby alleviating any number of contemporary medical conditions including rheumatism, headaches, scrofula, ague, gout, asthma, blindness, epilepsy, tumors, and even paralysis. Mesmer's idea of an 'invisible fluid' investing all objects may have been influenced by similar Age of Enlightenment discoveries including Newton's theories of gravitational forces, Franklin's theories of electricity, Lavoisier's measurements of 'energy' as a 'calorie', and the invisible hydrogen gases used by Jacques Charles in his pioneering balloon flight in and around Paris. (4) Franklin was colonial America's ambassador to France and his role in securing French support of the Continental Armies was critical to America's winning the Revolutionary War. Franklin was a polymath, a creative genius who applied scientific reasoning and empiricism in understanding electricity, and inventor of musical instruments, bifocals, and furniture, and

developed urinary catheters. He himself suffered from bladder stones but only accepted treatments that he felt were supported by sound scientific principles. It is likely that he accepted with eagerness, therefore, to serve on a Royal Commission that was to examine the scientific validity of Mesmer's claims. Our objective was to determine Franklin's role in the Commission and whether it served as a prototype for the methodical evaluation required of today's most popular medical and urologic regimens.

## SOURCES AND METHODS

Books, journals, papers, monographs, essays, and letters, published in the English and French literature relating to Franklin, Mesmer, mesmerism, the Report of the Commissioners charged by the King with Examination of Animal Magnetism, Yale University Sterling Memorial Library; the Bakkan Museum and Library, Minneapolis, Minnesota; the National Library of France ([www.gallica.fr](http://www.gallica.fr)); and the Library of Congress ([www.loc.gov](http://www.loc.gov)).<sup>(5,6)</sup>

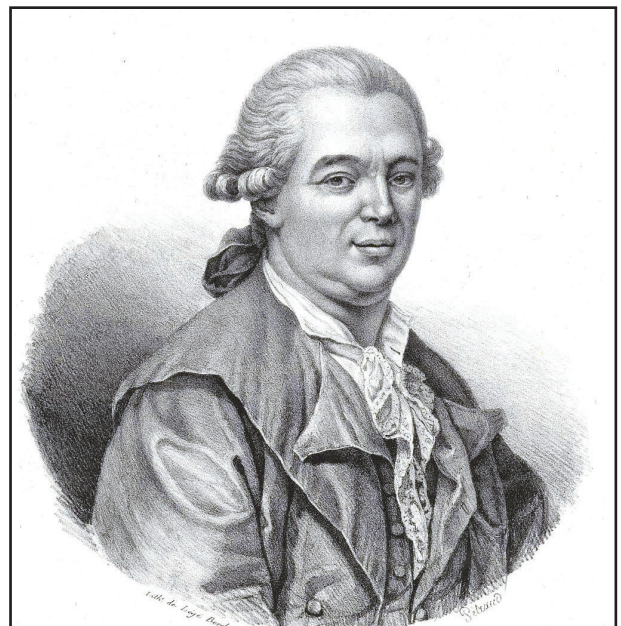
## RESULTS

### Franklin and Mesmer

In the late 1700s, Benjamin Franklin was in his 70s and Mesmer in his 40s. Franklin was taken out of school

at age 10 and self-educated; Mesmer was a graduate of the prestigious medical schools in Vienna and was known to be charismatic and beguilingly intelligent. Mesmer arrived in Paris in February 1778 and established a large and lucrative practice, taking care of the medical problems of Paris' wealthy elite. Mesmer and his methods became so popular, he was shunned by the physician establishment.<sup>(7)</sup> Established doctors not only doubted the science behind his methods but saw Mesmer's success as a threat to their income. Skepticism abounded. Shortly after Mesmer's arrival, Franklin received a letter from a good friend, in Vienna, who wrote:

*"I hear the Vienna conjuror Dr. Mesmer is at Paris, that he has been presented to the Royal Academy, that he still pretends a magnetical effluvium streams from his finger and enters the body of any person without being obstructed by walls or any other obstacles, and that such stuff, too insipid for to get belief by any old woman, is believed by your friend, Mr. (Jean Baptiste) LeRoy (President of the Academy of Sciences was later a member of the Commission)."*<sup>(8)</sup>



**Figure 1.** (Left) Benjamin Franklin (1706-1790) by the French portraitist Joseph Duplessis (1725-1802), 1778, which later appeared on the US \$100 bill (Public Domain). (Right) Franz Anton Mesmer (1734-1815), lithograph by the 18th century master Pétraud, (Bordeaux Municipal Library, France)





**Figure 2.** Left. "The Baquet of Monsieur Mesmer or Faithful Representation of the Operations of Animal Magnetism" (artist unknown, from the De Vinck Collection, National Library of France (Public Domain)); Right. Last remaining actual 'tub' of Mesmer now on display at the Museum of the History of Pharmacy, Lyon France. (Courtesy, Musée d'Histoire de la médecine et de la Pharmacie, Lyon, France)

Franklin first met Mesmer in 1779. Accompanied by a close lady friend, who was also an accomplished musician, Franklin visited Mesmer to watch him play the glass 'armonica' (an instrument invented by Franklin himself and used by Mesmer during his magnetic seances). However, Mesmer was more interested expounding on his theories of animal magnetism than playing the armonica. In late 1779, Mesmer invited Franklin to meet and observe him perform cures so that Franklin could "discover for himself the advantages of animal magnetism."<sup>(8)</sup> Franklin did not record whether he observed Mesmer work with patients, but after hearing testimony of patients who believed they were relieved of their aches and pains, or cured of their ills, he began to see an element of deception in Mesmer's operations.<sup>(6,9)</sup> Franklin felt that nature, 'left to her own devices', relieved many ills without any human intervention and wryly suspected that an "unintended boost to nature lay at the root of Mesmer's success."<sup>(6)</sup>

Franklin's views and skepticism about mesmerism emerged in a letter dated March 19, 1784, to a colleague who had requested Franklin's opinion of the value of animal magnetism:

*"As to the animal magnetism, so much talked of, I am totally unacquainted with it, and I must doubt its existence till I can see or feel some effect of it.*

*None of the cures said to be performed by it have fallen under my observation, and there being so many disorders which cure themselves, and such a disposition in mankind to deceive themselves and one another on these occasions, and living long has given me so frequent opportunities of seeing certain remedies cried up as curing everything, and yet soon after totally laid aside as useless, I cannot but fear that the expectation of great advantage from this new method of treating diseases will prove a delusion. That delusion may, however, and in some cases, be of use while it lasts. There are in every great, rich city, a number of persons, who are never in health, because they are fond of medicines, and always taking them whereby they derange the natural functions, hurt their constitution. If these people can be persuaded to forbear their drugs, in expectation of being cured by only the physician's finger, or an iron rod pointing at them, they may possibly find good effects, though they mistake the cause."<sup>(10)</sup>*

This letter is quoted in its entirety to illustrate that Franklin, although skeptical, was keeping an open mind, even admitting that animal magnetism may do some good, if for no other reason, than keeping patients away from existing malicious remedies (eg., bloodletting,



**Figure 3.** “The Potager of the Hôtel de Valentinois” showing the gardens of the palatial home where Franklin lived during his ‘French period’, in the Parisian suburb of Passy. It was in the home where the Commission did most of its work on animal magnetism and, in the gardens themselves, a careful analysis and debunking of ‘natural magnetism’ espoused by Mesmer and Desnos (by Alexis-Nicolas Pérignon (1726-1802), c1770, National Gallery of Art, Washington DC, Public Domain)

mercurials, etc.).

### The Commission and its Establishment by the King

Franklin and the commissioners began their investigation in March 1784 using systematic methods of public observation, self-study, case by case analysis, and hypothesis testing.(11) They knew they could not see the ‘invisible fluid’ but they could measure its effects. They sought to test two variables influencing the effects of animal magnetism, whether patients were told (or aware) they were being treated, and whether they really were treated. Mesmer preferred to treat his subjects in a group setting, called ‘magnetic seances’. Patrons sat around a large wooden tub called a ‘baquet’ that had been filled with ‘magnetized’ water, shards of glass, and iron fillings (Figure 2). The patients were asked to grasp iron rods protruding through the lid of the tub to conduct the magnetic flux through their bodies. Mesmer walked among his patients, and using his finger and hands, gently probed sensitive areas on their bodies – face, breast, stomach, lower abdomen, inner thighs, even the ovary (most patients were women). Many reacted with sighs, drowsiness, hysterical laughter, twitching of limbs or ecstatic shrieks and, after an hour or two of such administrations, the subjects would faint, fall into a trance, or succumb to violent convulsions, called a ‘crisis’. Each ‘crisis’ was believed to be necessary to break the blockage of the fluid and restore magnetic harmony in

affected parts of the body. When patients recovered, they professed to be relieved of their ailments.

### The Commission Methods

The commissioners noted that when one patient fell into a crisis, others followed within several minutes. To avoid collective bias of this crowd effect, the Commission decided to conduct further experiments on themselves and individual patients in private, many held at Franklin’s residence, Hôtel de Valentinois in Passy, a suburban area of Paris (Figure 3). Mesmer refused to cooperate but his chief disciple, Charles Deslon, agreed to demonstrate Mesmer’s treatments at the Franklin residence.

Franklin set out to test the ‘magnetized’ water in the tub with an ‘electrometer’ but no magnetic activity was detected. Franklin allowed himself to be ‘magnetized’ over three consecutive days but experienced no effects, nor relief of his gout, or bladder stone ailments. The investigation then proceeded to test whether the ‘crises’ that mesmerists claimed to induce were caused by the psychological power of suggestion (referred to as ‘imagination’) versus the physical action of an invisible fluid. In a series of experiments designed and conducted by Antoine Lavoisier and Franklin, Deslon was asked to magnetize subjects (who were often blindfolded) without their knowledge (“magnetism without imagination”) or tell patients they were being magnetized by Deslon when they were not (“imagination without magnetism”).



### Mesmer and the Tree

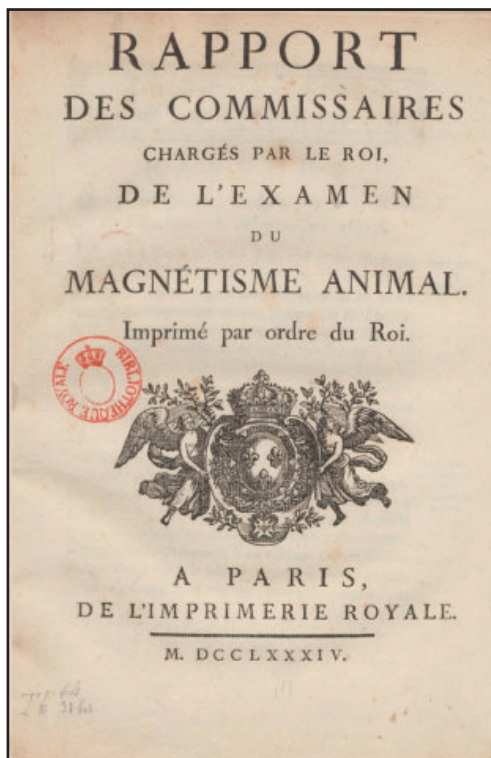
Mesmer believed that an inanimate object, such as a tree, could be as effective as communal tubs in conducting the magnetic fluid. "When a tree has been touched according to the principles and method of the magnetism, every person who stops under it, ought to experience in a greater or less degree the effects of this agent and there have even been some in this situation who have swooned, or experienced convulsions".(2) Franklin wished to witness such an event. He asked Deslon to magnetize one tree among five in his garden (Figure 3). A partially-paralyzed boy of 12 was blindfolded and told to hug each tree believing all were magnetized. At each tree, the boy became more and more animated until the fourth tree where he collapsed in a full-fledged crisis, 24 feet from the tree Deslon had magnetized. He was taken to a padded room to recover still paralyzed. Deslon explained that this contrary event illustrated 'natural' magnetism that was inherent in all of nature and affecting all the trees. Lavoisier and Franklin pointed out that would make it impossible for any sensitive soul even to walk in a garden without experiencing violent convulsions.(2)

### Telepathic Crises

A blindfolded woman was told that Deslon was magnetizing her and, in a different room, another woman was told Deslon was magnetizing her from behind a closed door. In reality, Deslon was not, in fact, attempting to magnetize them yet both women experienced crises. A third female subject sat in a room behind a paper partition, talking gaily and feeling nothing when, unbeknownst to her, Deslon was on the other side trying to magnetize her. When he emerged from behind the barrier and repeated the same provocative gestures, however, she had a crisis. On another occasion, a woman was given several cups of water to drink which she believed to be magnetized. She had a crisis then recovered and felt well while drinking a cup of water that had been 'magnetized'.

### Scientific Hypotheses

The Franklin Report concluded that animal magnetism, as a physical force, did not exist. The true causes of the effects observed in patients were, according to the Commission, phenomenon proposed as 'compression' (i.e. touch upon sensitive areas of the body), imagination (i.e. power of suggestion), and imitation (i.e. physical response of



**Figure 4.** (Left) The cover of the 1784 report of the "Commissaires Charged by the King to Examine Animal Magnetism" later referred to as the 'Franklin Report' as an homage to its *de facto* lead scientist. (Right) "Le magnétisme dévoilé" or 'Magnetism revealed'. Franklin holds a copy of the report emanating light. A baquet is shown breaking apart, releasing 'ignorance', as a blindfolded unclothed figure. Mesmer and Deslon are escorted away on broomsticks and donkeys, symbols of quackery. (Unknown artist, National Library of France).

individuals after witnessing a crisis in others). The last paragraph of the report concluded:

*"Therefore, having demonstrated by decisive experiments that the imagination without the magnetism produces convulsions, and that the magnetism without the imagination produces nothing, [we] have concluded with a unanimous voice...the existence of the fluid is absolutely destitute of proof, and that the fluid, having no existence, can consequently have no use."*(1)

They went even further to claim that animal magnetism was dangerous, concluding "when the imagination produces convulsions, the means it employs are violent, and such means are almost always destructive...The compressions and the repeated action of the imagination employed in producing the crisis may be hurtful ...and cannot fail in the end of producing the most pernicious effects."(2) The Commission also submitted a second report privately to the King, detailing the salacious nature of animal magnetism and condemning it on moral grounds as a threat to women (Figure 4).(5)

### **Effects of the Report in Popular Culture**

Reaction to mesmerism changed from one of enthusiastic support to one of scorn, depicted in an engraving of the time, 'Le Magnetisme dévoile' (Figure 4). Abbe Faria, an Indo-Portuguese monk and contemporary of Mesmer, wrote "nothing comes from the magnetizer, everything comes from the subject and take place in his imagination."(12)

All of this posed a dilemma for Franklin. He recognized privately that belief and hope (even misguided) was a powerful remedy for some patients but realized that publicly endorsing the curative effects of a technique that had no basis in science could lead to medical quackery.(9)

### **Mesmerism in history and modern times**

The Franklin Report put an end to Mesmer (he died in obscurity in 1815), but not to mesmerism. In a letter to his grandson, Franklin wrote, "The Mesmer Report is publish'd and makes a great deal of Talk....Some think it will put an end to mesmerism. But there is a wonderful deal of Credulity in the World, and Deceptions as absurd have supported themselves for the Ages."(6)

In fact, mesmerism, or something like it, had been practiced long before Mesmer. The noted physician, Michel-Augustin Thourer, remarked that many faith

healers had accomplished cures resembling Mesmer's, mentioning Paracelsus and the notorious Valentine Greatrakes (the 'Irish stroker'), as examples from the 17th century. Even the term 'animal magnetism' had been coined and "now, as was then, an old falsehood". (13) Just recently, a mesmerism-like practice returned in the form of 'therapeutic touch (TT)', rooted in mysticism but alleged to have a scientific basis, that involves no actual touching. Practitioners wave their hands above the skin, allegedly realigning patients' energy fields. Restoring energy balance allows the patient's body to heal itself. In 1998, TT was debunked when 21 experienced practitioners were unable to detect any 'human-energy field' around subjects in repeated blinded experiments.(14) Mesmerism is still being taught by a certain Marco Paret in Nice, France at the so-called International Institute for Neuro-Linguistic Programming (NLP), Hypnosis, and Communication. (15) Paret trademarked the word "Mesmerismus" to mean "connecting the forces of nature to one's work and influence" and that "having these forces available, in creating the plan of his life, everyone can aim for the top." Mesmer is currently being resurrected as a precursor to hypnosis and Freund's psychotherapy.

### **DISCUSSION**

Frankling had been stricken with bladder stones and gout at the time of the Commission's work and he was largely confined to his Passy residence.(16) In the past, Franklin was regarded only as a titular head of the Commission, who approved and signed the report but had little to do with the actual investigation. On the contrary, we found that Franklin was familiar with Mesmer and mesmerism long before the Commission was formed, that many experiments took place in Franklin's presence in Passy and his garden, and that he was involved much more in the concepts and conduct of the experiments than previously thought.(9)

The Commission was revolutionary in the way it used scientific methods we would recognize today in the objective evaluation of even the most popular medical remedies. In their five months of work, the commissioners witnessed public magnetism of patients and conducted private sham and genuine experiments with a variety of individuals, where both the patient and mesmerist were literally blindfolded and 'blinded' to the treatment and its visible effects (i.e. double-blind, placebo-controlled clinical trials). The blinded nature of the placebo-controlled work (patients did not always know when the magnetic operation was being performed) marks the Commission's most innovative



contribution to science. The work also established the influence of belief on the unwitting practitioner as many 'mesmerists' like Deslon were not 'frauds' *per se* but misguided believers in their methods.

The Franklin Commission, and later in what became known as the 'Franklin Report', was also pioneering for its sharply worded and unambiguous terms declaring animal magnetism a farce, Mesmer a charlatan, and that Mesmer was nothing more than a master of deceit. The late paleontologist Steven Jay Gould (1941-2002) wrote that the report "should be rescued from its obscurity, translated into all languages, and reprinted by organizations dedicated to the unmasking of quackery and the defense of rational thought." (17) Thomas Jefferson also felt the Commission's report was irrefutable, writing in 1790 that "the animal magnetism, too, of the maniac Mesmer...received its death-wound from his hand, in conjunction with his brethren of the learned committee appointed to unveil the compound of fraud and folly." (18)

The major conclusion of the Commission's report was that touch, imagination, and imitation were the true causes of the effects of animal magnetism, and imagination was the principle of the three causes (the power of psychological suggestion to influence behavior in excitable and sensitive individuals). Although this was the collective view, it was not entirely Franklin's private view, and his personal observations on the powerful therapeutic impact of non-specific treatment factors remain compelling. (19,20) Indeed, Franklin personally arrived at a more nuanced denouement of mesmerism than the harsh sentence published in the 'Report.' (6) He came to realize that the exercise of reason was a harder sell than the supernatural, and persistence of delusion and the power of charisma was a lucrative and alluring business. He did not doubt the sincerity of patients' belief in magnetism or the physical responses he observed to Deslon's manipulations. Some patients, he concluded, may indeed have felt better after even undergoing bogus treatments. Franklin came to balance the need for scientific acumen with an appreciation of the psychological factors that can contribute both to the severity and relief of illness.

A perplexing question is why such snake-oil quackery and claims of mysterious medical cures continue to thrive today without any scientific basis. In his report, Franklin speculates on an answer for our times:

*"Perhaps the history of the errors of mankind, all things considered, is more valuable and interesting than that of their discoveries. Truth is uniform and*

*narrow; it constantly exists, and does not seem to require so much an active energy, as a passive aptitude of soul in order to encounter it. But error is endlessly diversified; it has no reality, but is the pure and simple creation of the mind that invents it. In this field the soul has room enough to expand herself, to display all her boundless faculties, and all her beautiful and interesting extravagancies and absurdities."* (10,21)

## CONCLUSIONS

Franklin had an active and major role in the Commission which used double blinded, placebo-controlled trials to reveal the fraud of mesmerism. The full Franklin report should be read by all, especially urologists, who must weigh often uncontrolled and subjective benefits claimed by technology-driven new devices and treatments. (1,2)

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# Hernias, Healing, Hagiography: Faith and Medicine in the Era of St. Artemios

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**Introduction:** Artemios of Antioch was a Roman general and imperial prefect in the 4th century CE who was subsequently martyred under the reign of Emperor Julian and canonized in the Orthodox Church. Based on a 7th century account of miracles, St. Artemios figured prominently in early Christian incubation rituals in which individuals afflicted with specific maladies would travel to and reside within the Church of St. John the Forerunner in Oxeia waiting to be healed. Many of the healing encounters attributed to St. Artemios concerned genital maladies. We aimed to explore the circumstances surrounding the treatment of these ailments and contextualize our findings within the relationship of faith and medicine during that time.

**Sources and Methods:** Primary source material was drawn from the 7th century *The Miracles of St. Artemios*. A database of miraculous encounters was created including demographics of the supplicant(s), complaint(s), the medium in which the saint had manifested, and his manner of treatment. Additional secondary sources regarding St. Artemios and Byzantine incubation rituals were identified via PubMed and Google scholar and examined.

**Results:** A total of 43/45 (90%) of healing encounters compiled in *The Miracles* involved a urologic issue ranging from inguinal hernias and testicular pain to penile sores. Most supplicants were male, age range infant to 70 years. St. Artemios most commonly manifested himself in a dream to the afflicted or their loved one – sometimes as himself, other times in disguise. In several encounters, St. Artemios appeared as a physician. Treatments of genital maladies included medical interventions (e.g. hernia reduction) and nonmedical interventions (e.g. making a sign of the cross, votive offering). Several supplicants sought St. Artemios after failing medical treatment elsewhere. *The Miracles* contain commentary against contemporary medical practitioners in favor of faith-based healing. Nearly all examples of healing took place within or near the Church of St. John the Forerunner in Oxeia, Constantinople.

**Conclusions:** *The Miracles of St. Artemios* offer a view into the genital maladies of classical Byzantine peoples who sought relief from the divine when contemporary medical practices showed no perceived or actual benefit.

**Key words:** St. Artemios, miracles, hagiography, genital maladies



Medical practitioners throughout the ages and across various cultures have sought the help of the divine in their quest for healing. The early Christian church was no different. Practitioners such as the Apostle Luke, the brothers Cosmas and Damian, and Panteleimon were canonized on account of their miraculous healing encounters and martyrdom and were often venerated as role models by aspiring physicians and surgeons.(1,2) The fourth century CE saw churches, dedicated to specific saints in eastern and western Europe, becoming popular sites for people

seeking physical healing, giving rise to the 'incubation' ritual of early Christendom.

Tracing their origins to the earliest Babylonian and Egyptian civilizations, incubation rituals in the contemporaneous Greco-Roman era (epitomized by that of the god Asclepius) were thought to have influenced the Christian incubation ritual which centered on sainthood.(3) The Christian incubation ritual involved a supplicant who sought healing for an affliction from a particular saint via a dream encounter. In order to attain a physical sense of 'closeness' to the saint for such an

encounter, the supplicant either resided or slept in a sacred location associated with the respective saint, which often was a church consecrated to that saint.(3)

One such incubation ritual of the early Byzantine Empire was centered around St. Artemios. According to historical accounts, Artemios of Antioch was a Roman general and imperial prefect of Roman Egypt (*dux aegyptii*) during the reign of Constantius II in the fourth century (Figure 1).(4) During the reign of Julian the Apostate (331-363 CE), Artemios was martyred after refusing to recant his faith and was subsequently canonized by the Church. In turn, Artemios' bones were brought to Constantinople and laid as relics in the church of St John the Forerunner in the hilly neighborhood of the Oxeia (Figure 2). Based on an anonymous seventh century account of healing miracles attributed to him, St. Artemios was often invoked by sufferers of hernias and testicular maladies who lived in or came to the Oxeia. Given that many of these accounts concern genital maladies, we aim to examine the circumstances surrounding the treatment of these ailments and to further explore the complex relationship of medicine and faith during that time.

## SOURCES AND METHODS

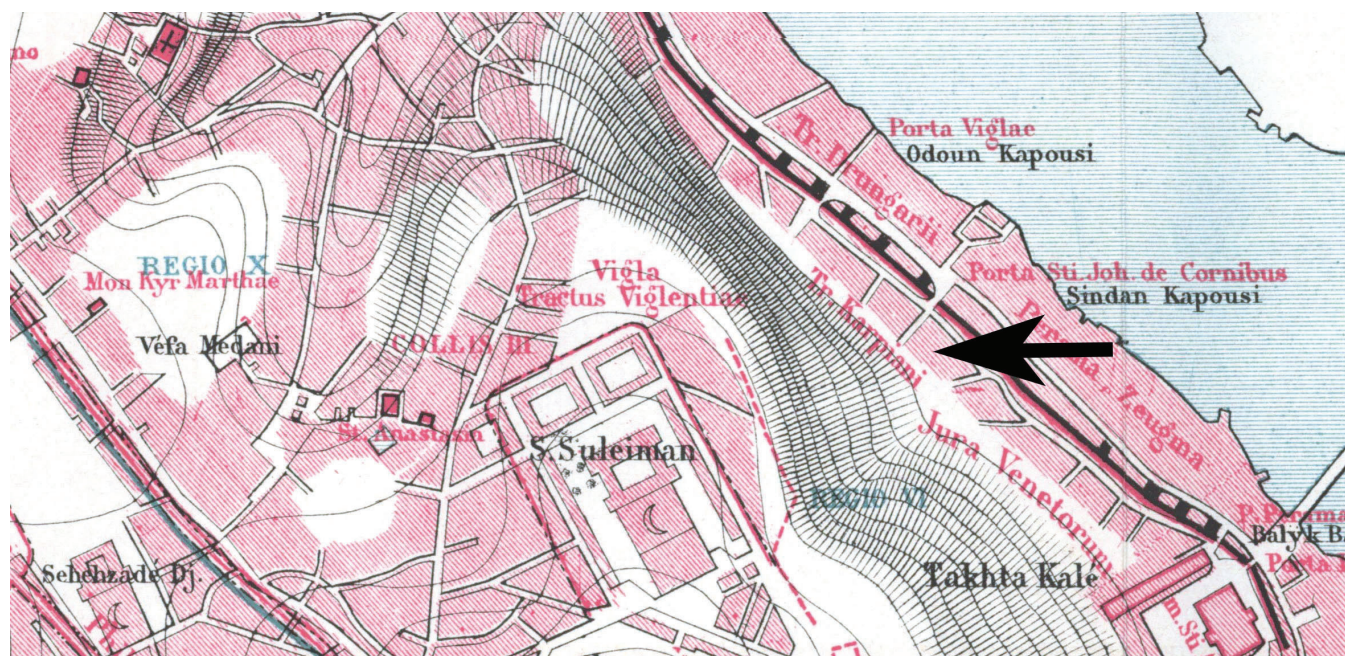
An online search engine was initially used to identify existing digital and written source material regarding St. Artemios. Translated hagiographical primary source material from the *Miracles of St. Artemios* was then used to compile a database of each miraculous encounter.(4) The database included demographic information regarding the afflicted person(s), their respective complaint, the medium in which the saint was manifested, and the method of healing (Table 1).

Physical affliction was broadly categorized in a manner to best minimize the subjectivity of assigning retroactive diagnoses of medical issues. For example, any affliction describing hernias, including hernias related to scrotal pain, genital discomfort, or coexisting with a described testicular malady, was categorized broadly under "hernia" and were not counted in another category. Afflictions that described testicular pain and boils were categorized under "testicular malady." Online software at WordClouds.com was used to build an aggregate frequency image, with size of the word in the image corresponding to frequency of appearance in the table.



**Figure 1.** (Left) The megalomartyr St. Artemios (d 362 CE) was originally a Syrian officer who was given the title of '*dux Aegyptii*' and, in 361 CE, was dispatched to Antioch to retrieve the bones of St. Andrew and Luke. (Image, WikiCommons, Public Domain) There, he was summoned by Emperor Julian the Apostate (right) who demanded Artemios recant Christianity. (Roman Coin, British Museum, Public Domain) Artemios refused, was allegedly tortured and beheaded, and his bones brought as relics themselves to the Church of St. John the Forerunner in the Oxeia neighborhood of Constantinople.





**Figure 2.** The 'Oxeia', the streets and neighborhood of the *Miracles of St Artemios*. The striking elevation lines show the steep heights of the Oxeia where the bones and relics of St Artemios were brought and stored in the Church of St. John the Forerunner in the 4th century CE. Seen to the right, facing the harbor, is the "Porta St John de Cornibus" (the Latin version of 'Forerunner'), leading into the narrow alleys, that would take the supplicant to the church itself which, according to a 1898 map by A Van Millingen, was just inside and to the east of the gates (black arrow). Now dominating the peak is the 16th century Süleymaniye Mosque, ("S. Suleiman"); the original Church of St. John the Forerunner has long vanished. (Above map by J. Mordtmann, 1891, Public Domain)

## RESULTS

According to our database, 41 out of 45 healing encounters involved a urologic issue, including hernias, testicular maladies, and penile sores (Figure 3). In terms of demographic information from these encounters, 97% of afflicted persons were male, with their ages ranging from infancy to 70 years old (Table 1).

The most common manifestation of St. Artemios was in a dream to the supplicant or to their loved one. In a few encounters, Artemios appears to the supplicant when the latter was in an awakened state in the guise of a "stranger" (Miracles #14 and 35). Three encounters notably do not feature any appearance of the saint (Miracles #4,17,21). With regards to dream manifestations, the saint predominantly appears as himself (39%) or in various guises as a family member, friend, or member of the nobility or clergy. In six encounters, St. Artemios notably appears in the guise of a physician (Miracles # 2, 6, 23, 40, 42, 44).

Treatments of genital maladies included "physical" interventions such as "forceful squeezing of testicles", "incision and drainage" (in so far as how they were described in the dream encounter), and faith-based

interventions (e.g. votive offering, making a sign of the cross). Described treatments by the saint are delineated via a 'word cloud' image comparing the frequency of such treatments in aggregate (Figure 4).

All but one of the healing encounters took place within the vicinity of the Church of St. John the Forerunner in Oxeia, a neighborhood of Constantinople (present day Istanbul)(Figure 2). The one exception occurs in Miracle #4, in which the 'young African's son' was healed at sea while the father was *en route* to the aforementioned Church.

## DISCUSSION

From the miraculous encounters attributed to St. Artemios, approximately 90% concern a urologic issue. Hagiography of miraculous cures was far from unusual during the Byzantine era, with works including *Life and Miracles of Thecla* arising in the fifth century and a compilation of the miracles of Cosmas and Damian dating to the sixth century. However, the miracles of St. Artemios remain distinct in that there is a predominant focus on a particular anatomic region—specifically male genitalia.(5) Only a few of the miracles of St. Thecla, for

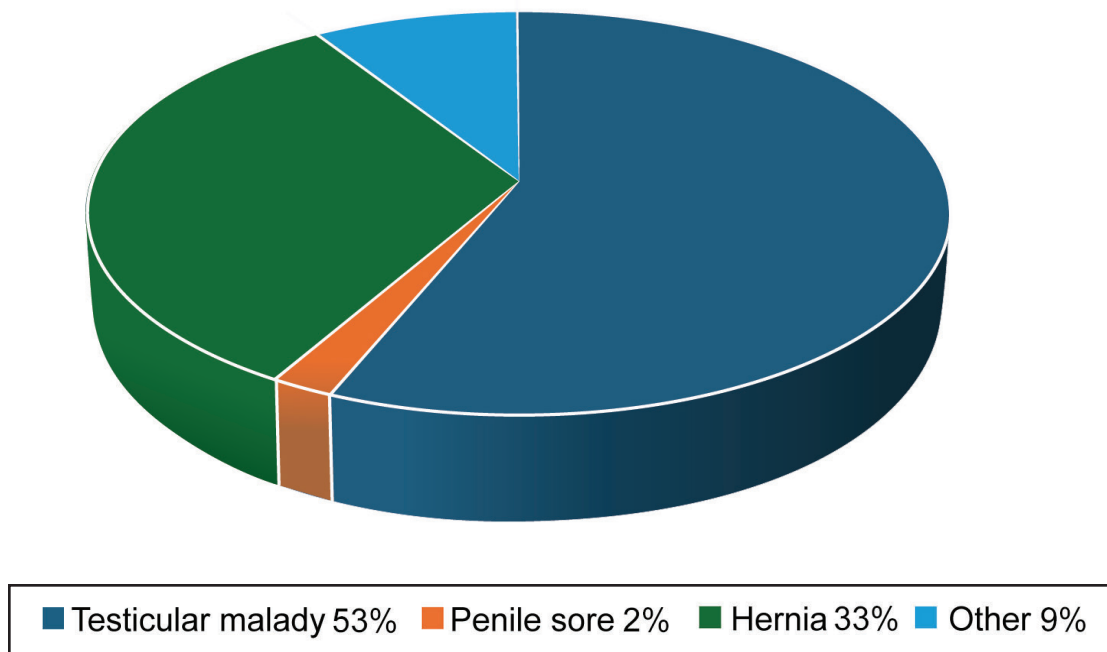
#	Miracle Name	Supplicant Info	Physical Affliction	Treatment	Manner of Appearance
1	Son of Anhimos, the chief physician	20 y/o male	diseased testicles, not able to use lathires	forceful squeezing of testicles	appeared in dream in semblance of patient's father
2	The man with three diseased testicles	45 y/o male	"three testicles"	forceful squeezing of testicles	appeared in dream in semblance of physician
3	The lancing of the Amasriean's boil	u/k age, male	testicular boil	incision and drainage of boil, poultice of the saint's wax	holy servant of God
4	The recovery of the African's son	child, male	testicular pain	creation of votive lamp with wine and oil	no appearance
5	The healing of Euporos, the Chilan merchant	u/k age, male, "young"	longstanding hernia, "diseased testicles"	examination and touch	appeared in dream as himself
6	Isidore and the exorcism of the black crow	53 y/o male	testicles possessed by "evil spirit"	examination and touch, exorcism in the form of a black crow	apparition in the guise of a chief physician
7	Plato, the young wogerer	u/k age, male	groin hernia from heavy lifting	trampling on stomach	appeared in dream as himself
8	George, the Phrygian babbler	u/k age, male	swollen testicles	forceful silencing	appeared in dream as himself
9	Theodore, the impatient Rhodian	u/k age, male	hernia	examination and touch, making sign of cross	appearance in dream as servant of God
10	The healing of the silver dealer Akakos' son	7 y/o male	hernia from "evil demon"	faith by response from the boy, making sign of cross	appearance in dream as himself to patient's mother
11	The lady of the double bath of Paschenios	infant, male	hernia	votive offering	appearance in dream to patient's mother as a palace nobleman
12	From the church of the Theotokos to St. John's	infant, male	hernia	examination and touch	appearance in dream as himself to patient's mother
13	From the bath of Dagsithkos to St. John's	50 y/o male	disease of testicles	incision and drainage of abscess, application of plaster of wax to ruptured spot	appeared in dream as disguised figure who pricked patient's testicles
14	A miraculous cure performed at sea	u/k age, male, sailor	disease of testicles	trampling on testicles	disguised stranger on a ship
15	Nases' blasphemy	u/k age, male	swollen genitals	repentance, slaying dove across sick man's testicles	appearance in dream as a nobleman
16	Sergios, the granary guard from Alexandria	60 y/o male	hernia	application of salve to genitals	appearance in dream as Administrator of Granaries
17	Sergios' relative and the Alexandrian actor	40 y/o male	hernia	displacement of condition to another person	no appearance
20	George, the Chartulary - follow up problems	20 y/o male	sore on tip of penis	white vinegar, salt, moistening to the sores	appearance in dream as himself
21	Stephen, deacon of the Great Church	u/k age, male church deacon	"rupture of testicles"	votive offering, prayer, healed after a bath	no appearance
22	The burglary victim	62 y/o male	water in chest, dropsy, "genitals that sank down to his knees"	incision and drainage of right testicle	appearance in dream as himself
23	The priest of the church of the Forerunner and the Persian doctor	u/k age, male priest	sudden hernia	attending church, "customary healing"	appearance in dream in the guise of Persian doctor
24	The betrothed woman	u/k age, female	sudden hernia	wax-salve plaster applied to genitals	Dream urged patient's mother to seek St. Febronia; attractive woman in monastic garb.
25	St. Artemios, as butcher	u/k age, male	longstanding disease of testicles	piercing lower abdomen with life, cleaning and replacing the intestines	appearance in dream as form of a butcher

**Table 1.** Miraculous encounters of St. Artemios (#1-25), including known supplicant demographic information, their respective complaint, the medium in which the saint was manifested, and the method of healing.(4) Miracles # 18 and 19 were deemed non-urolgic and were not included.



#	Miracle Name	Supplicant Info	Physical Affliction	Treatment	Manner of Appearance
26	Theodore the blacksmith	60 y/o male	longstanding hernia >30 years	inciting fear of castration	appearance in dream, told to go to the blacksmith three times
27	Theoetokos, the shipbuilder	50 y/o male, shipbuilder	diseased, swollen testicles >25 years	examination and touch in dream	appearance in dream in form of sailing master
28	The child who fell out of bed	child, male	ruptured intestines, traumatic scrotal injury ("testes flapping in the breeze")	dangling upside down	appearance in dream to patient's mother
29	The healing of the bowmaker	70 y/o male	hernia, unilateral swollen testicle	forceful pushing of testicle "up to intestines"	appearance in dream as someone of the illustrious
30	The tamer, Zonkos, and the church warden, Theodore	55 y/o male	ruptured intestines, swollen testicles while running	drinking flasks of olive oil - also led to healing of 4 other men with testicular ailments	appearance in dream as himself
31	Sergia, the highborn woman and her child	child, male	disease of testicles	making sign of the cross over testicles	appearance to patient's mother in guise of her friend
32	Menas, the stevedore	20 y/o male, stevedore	trauma to testicles	prayer, customary offering, examination and touch	appearance in dream as himself
33	Theognos' diseased chest	u/k age, young male	acute pain from hernia	anointing wax-salve ointment to testes of child	appeared as himself in dream to Theognos, the patient's family friend
35	George the Rhodian's encounter in the latrines	u/k age, male shipowner	longstanding hernia in both testicles	forceful gripping of testicles	guise as a stranger in the latrines
36	Sophia's son, Alexander	9 y/o male	sudden hernia	examination and touch in dream	appearance in dream to patient's mother
37	Andrew's hernia	40 y/o male	sudden hernia	examination and touch in dream	appearance in dream as himself
38	The moneylender's son, George	9 y/o male	swollen genitals	making sign of cross over genitals	appearance in dream as himself and with St. Febronia and St. John
40	George of Prateis's injury and his visit to Constantinople	18 y/o male (refer to miracle #38)	swollen left testicle from trauma	pushed testicle upward, making sign of cross over abdomen	guise of "handsome newly-appointed doctor"
41	The healing of Polychronios with the mark of the Holy Trinity	18 y/o male	sudden pain in left testicle	lancet to trace area over afflicted testicle	appearance in dream as himself
42	Artemios' appearance as a physician	infant, male	bilateral testicular disease	surgical intervention	appearance in dream to patient's mother as a physician/surgeon
43	Another child cured	infant, male	pain in testicle	eating cake and applying a cake poultice to afflicted testicle	appearance in dream to patient's mother as himself
44	George, the coppersmith and the imagined operation	30 y/o male	swollen right testicle	binding ligament of L testicle with a cord and feeling of "amputation" of the R testicle. Woke up to find both testicles normal and a cord attached to L testicle.	appearance in dream in guise of a physician
45	The jubbe berries	infant, male	swollen right testicle	spontaneously healing after mother consumed 2 jubbe berries given to her in a dream (she woke up to find a third berry in her hand)	appearance in the form of St. Febronia via dream to patient's mother

**Table 1 (continued).** Miraculous encounters of St. Artemios (#26-45).(4) Miracles # 34 and 39 were deemed non-urologic and were not included.



**Figure 3.** Physical complaints of supplicants in the 45 Miracles of St Artemios illustrating the predominance of urologic problems. When canonized in the St. Artemios later became known as a Patron Saint of Hernias and his feast day is October 20, the date of his execution in 361 CE.

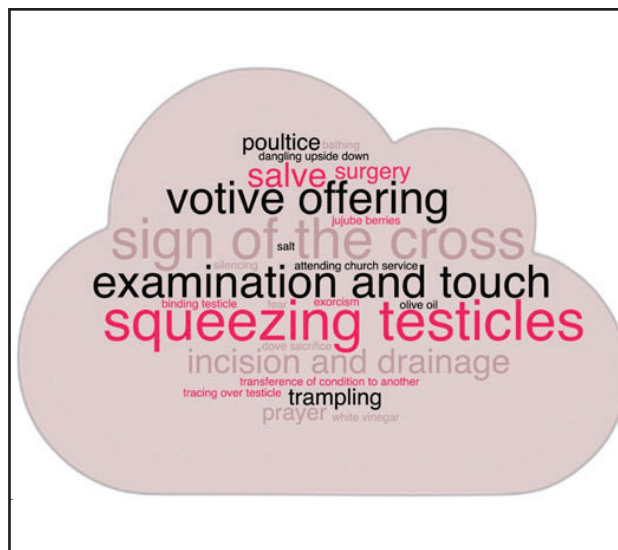
example, concerned physical healing, while the healing miracles attributed to Cosmas and Damian reflect a range of expertise from curing diarrhea to paralysis.(5–7)

While 78% of Artemios' encounters took place in a dream, all his miraculous encounters involve the afflicted person(s) or a family member on behalf of the supplicant undertaking a journey to the Church of St. John the Forerunner in Oxeia. The spatial relationship between miraculous healing and a particular locale thus epitomizes the nature of the incubation ritual and is consistent with incubation practices attributed to other saints of the era such as the second century's Cyrus and John (both d. 310 CE) and St. Therapon of Cyprus (284-305 CE).(6)

With regards to Artemios' appearances, one theory suggests that his method of manifestation may be to mollify anxiety and build familiarity with the supplicant. (5) Alwi argues that a "familiar" disguise—such as a family member, friend, or other respected person(s)—could exist to dispel any "sexual impropriety" between two Christian men, especially given the sensitive nature of many of the ascribed afflictions.(5) It is interesting that Artemios' three appearances as a female figure (including that of St. Febronia) are to mothers incubating their young children, lending credence to the theory of the saint building familiarity with the afflicted (Miracles #24, 31, 45). In that regard, Artemios as a healer is not unlike the

modern-day urologist who, in lieu of disguises, perhaps may use disarming humor and light conversation to build rapport with their patients.

In his encounters, Artemios is depicted as a very "physical" healer, often examining the afflicted body part(s). In seven instances concerning a urologic ailment, Artemios heals his supplicant solely by examining and touching the afflicted area, be it a young infant with a hernia (Miracle #36) or a 50-year old shipbuilder with "swollen testicles" (Miracle #27). In four instances, Artemios cures his supplicant with forceful "squeezing" or manipulation of the testicle. While most of these therapies take place in the context of a dream, the vividness with which the treatment is described and experienced by the afflicted makes the encounter very real to the supplicant. Artemios' physicality with respect to examination of healing is very reminiscent of the healing described in the texts of Paul of Aegina, a seventh century Byzantine Greek physician best known for his *Medical Compendium in Seven Books*. Considered the 'father of early medical writing', Paul built upon the foundation of Hippocratic and Galenic medicine and was among the first to describe surgical anatomy of the abdominal wall.(8) For example, Paul's vivid description of fixing an enterocoele, which he defined as bowel herniating into the scrotum, echoes Miracle #29 in which Artemios places his finger "on the



**Figure 4.** Word frequency map of terms invoked in the English translation of the *Miracles of St. Artemios*, illustrating the prevalence of the urologic nature of the complaints of the supplicants.

very spot of the testicle where it was diseased" to forcefully push the testicle "all the way up into the intestines."(4,5) That being said, it is often difficult to infer the exact medical issue from a descriptive nonmedical text via assigning a retroactive diagnosis. However, despite the limitations of seventh century medical vocabulary as well as the potential pitfall of translation, the description of the healing of the bowmaker's hernia in Miracle #29 seems analogous to a modern-day manual reduction of an inguinal hernia. That, and other vivid, medical-like descriptions in other encounters suggest that the anonymous author(s) to the *Miracles of St. Artemios* was familiar with and influenced by Paul and other contemporary medical texts of the time.

On the other hand, certain encounters with Artemios also reflect a guarded even hostile attitude towards nascent Western medicine practiced in contemporary Constantinople. Miracle #20 tells of a certain George's penile lesion, which had worsened despite seeking the opinion of several doctors and was ultimately cured by Artemios with a mixture of white vinegar and salt to "moisten the sores." In Miracle #36, a mother named Sophia seeks Artemios to heal her son's hernia because the doctors she had originally seen had "charged too much money" for a potential cure. Miracles #23 to 32 contain the most notable invective against doctors and surgeons. In Miracle #24, a betrothed woman with a hernia was healed after her mother offered a votive candle to St. Febronia (the female analog of St. Artemios). The cure prompted the author of the *Miracles* to ponder "where (now) are the fine-sounding Hippocrates and Galen and the other countless quacks?"(4,9) The contrast in language and heterogeneity of treatments thus not only reflect the diverse opinions of authorship behind the *Miracles* but also the complex relationship

between faith-based and Hippocratic-influenced healing in the Byzantine era.

## CONCLUSION

The miraculous encounters attributed to St. Artemios have given him the reputation as the patron saint of genital maladies. The *Miracles* also serve to highlight the importance of the physicality of the Saint's church and its Oxeia environs for incubation rituals to occur. The complex interplay of person, place, and time illustrate the multifaceted dynamic between Western medicine and faith-based healing in medieval Byzantium. St. Artemios still holds a place of importance in the Orthodox Church and he continues to be invoked by sufferers of hernias.

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# A History of Renal Cell Carcinoma through the pages of Robbins' *Pathology* and Campbell's *Urology*

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**Introduction:** The understanding of renal neoplasia, carcinogenesis, and the classification of kidney tumors has been a journey of misadventure. Struggles included identifying the cell of origin, differentiating benign from malignant tumors, and subclassification. We investigated how the changing landscape of renal neoplasia was incorporated into medical textbooks with a focus on Robbins Pathology and Campbell's Urology.

**Sources and Methods:** A PubMed search was performed using the terms "renal cell carcinoma" and "hypernephroma". Articles highlighting landmark discoveries of renal tumors were evaluated. A review of medical texts including Robbins Pathology and Campbell's Urology was conducted to establish the incorporation of scientific discoveries into the popular medical literature.

**Results:** The first mention of a tumor of the kidney occurred in 1613 but medical texts lagged for scientific discoveries by years, both in pathology and urology. Case reports of renal tumors were described sporadically in the 1800s but are not mentioned in the 1889 *Pathology and Morbid Anatomy*. Young's *Practice of Urology* (1926) illustrated the uncertainty as to the unknown origin of kidney cancers. Definitive evidence of RCC arising from renal parenchyma occurred in 1959. The adrenal origin theory was finally rejected by Campbell in 1963 and by Robbins in 1979. Papillary RCC was recognized as a separate entity from clear cell RCC in 1976 but detailed histopathologic subclassification of RCC did not occur until the late 1990s.

**Conclusions:** Renal tumors progressed from one category to more than a dozen established entities. As we continue the ongoing quest to understand renal tumors, Dr. Young's comment from 1926 holds true. Competent pathologists will continue to describe renal tumors under many different names.

**Key Words:** hypernephroma; renal cell carcinoma; History; Medicine; Grawitz tumor



he understanding and subclassification of renal neoplasia have been a journey of misadventure and course correction that continues today, from debates about cell of origin to the biologic behavior of tumors. What was understood as benign versus malignant could depend on the year. Furthermore, in the classic teaching, tumors presented at a late stage with a palpable flank mass, flank pain, and hematuria. It was challenging to establish the natural history of malignancy from small renal tumors discovered incidentally at autopsy.

The progression from gross examination and light microscopy to molecular techniques revolutionized our understanding of kidney tumors, while revealing uncertainty about what was known. As discoveries made their way into the medical journals, the medical textbooks reflected the ever-changing landscape of

renal neoplasia. Herein, we investigate the history of renal tumor classification through all editions of Robbins' *Pathology* and Campbell's *Urology* textbooks.

## SOURCES AND METHODS

PubMed was searched using the terms "renal cell carcinoma", "renal adenoma", and "hypernephroma", and sorted by publication date. Articles of landmark discoveries in the understanding and subclassification of renal tumors utilizing light microscopy, special chemical stains, electron microscopy, immunohistochemistry, and molecular diagnostics were reviewed. Medical textbooks were extensively reviewed to establish their progression and incorporation of scientific discoveries. Specific attention was turned to Robbins' *Pathology*, originally written by Stanley Robbins in 1957, and Campbell's *Urology*, originally written by Meredith Campbell in

1954. Subsequent editions were analyzed for their descriptions of renal cell carcinoma as cited in the text.

## RESULTS

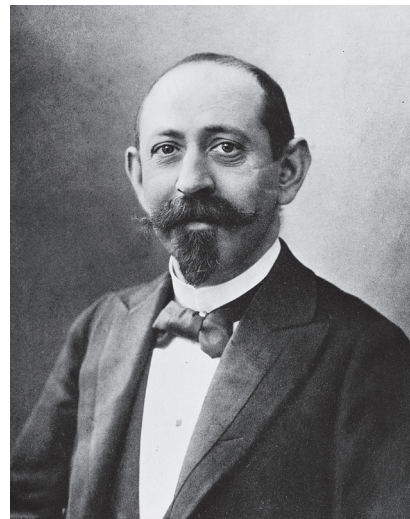
### Scientific Discoveries in Renal Neoplasia

A timeline of critical historic discoveries is presented, starting in 1613 with the first mention of a kidney tumor in Daniel Sennert's *Practicae medicinae*. In 1826, König proposed the first classification system of renal tumors based on gross features.(1) Paul Grawitz first described malignant kidney tumors in 1883 as "struma lipomatodes aberrata renia", proposing its origination from adrenal rests based on the gross and microscopic similarities to adrenal cortex (Figure 1).(2,3) Several case series in the late 1800's classified renal tumors based on clinical and morphologic features without addressing the cell of origin.(4-6) Supporting the adrenal origin hypothesis, in 1894 Otto Lubarsch coined the term "hypernephroid tumor" i.e. "Grawitz tumor" implying adrenal origin. In the early 1900's, however, Oskar Stoerk instead proposed renal cysts as the origin of renal tumors (Figure 1).(7) By 1936, scientific literature generally favored a renal origin.(8,9) In 1959 Oberling used electron microscopy to definitively prove the renal convoluted tubule as the origin of clear cell renal cell carcinoma (CCRCC).(10,11) In 1976, the Armed Forces Institute of Pathology (AFIP) discouraged the term

"hypernephroma". The same year, Mancilla-Jimenez distinguished papillary RCC (PRCC) from clear cell RCC (CCRCC).(12) In 1983, loss of chromosome 3p was identified as a hallmark of CCRCC.(13) Thoenes et al. described a chromophobe RCC in 1985.(14) In 1995, Störkle et al. used cytogenetics to show trisomies 3, 7, and 17, and loss of Y in PRCC, which was then divided into PRCC types 1 and 2.(15) In 2001, Argani et al. described 'Xp11 translocation' RCC and in 2002 Parwani described mucinous, tubular, and spindle RCC.(16,17) In 2013, the ISUP Vancouver classification of renal neoplasia recognized tubulocystic RCC, acquired cystic disease associated RCC, clear cell papillary renal cell carcinoma (CCPRCC), t(6:11) translocation RCC, and hereditary leiomyomatosis RCC.(18) In 2016, types 1 and 2 PRCC were found by molecular studies to be several different tumors; six years later, the types 1 vs 2 classifications were discontinued.(19, 20) In 2022, CCPRCC was renamed from "carcinoma" to "tumor" to reflect the often indolent biologic behavior of low stage neoplasia.

### Developments in Renal Neoplasia in Medical Textbooks

In the 1800s to early 1900s, many types of tumors were recognized, with the exception being renal neoplasms.(21) Young's *Practice of Urology*, published in 1926, discussed the paucity of knowledge regarding renal



**Figure 1.** Paul Grawitz (left) (1850-1932) first described renal cell carcinomas in 1883 as "struma lipomatodes aberrata renia." It was Otto Stoerk (1870-1926) (right) who named hypernephroid tumors as "Grawitz tumor" in an era of medical eponyms to honor scientific pioneers. It would be more than 100 years, however, before the correct origin, nomenclature, and etiology of renal cell carcinomas would be correctly understood. (Both, WikiCommons, Public Domain)



**Figure 2.** Titans of Urologic Education. Meredith F. Campbell (1894-1969)(left) was a founding father of pediatric urology but his work in establishing Campbell's *Urology* has influenced all fields of urology for generations (Courtesy, WP Didusch Museum, Linthicum). (Right) Stanley Robbins (1915-2003), creative genius behind the seminal pathologic text, Robbins' *Pathology*, was the chair of pathology of Boston University School of Medicine from 1965-1980 (National Library of Medicine, Public Domain)

tumors, questioning the adrenal origin theory and mentioning the disagreement among pathologists. "Indeed, the greatest uncertainty reigns as to the histogenesis of these tumors, and competent pathologists have described them as sarcoma, hypernephroma, angiosarcoma, endothelioma, and carcinoma."(22)

### Robbins Pathology

The first edition of Robbins *Textbook of Pathology* (1957) discussed malignant kidney tumors, stating "the great preponderance of these malignant tumors are primary renal cell carcinomas"(Figure 2).(23) Robbins acknowledged that RCCs were once thought to arise from adrenal cells based on the clear cytoplasm seen in CCRCC and the adrenal cortex. They concluded, "this origin is now considered as untenable", and recommended that malignant tumors of the kidney be referred to as renal cell carcinomas or hypernephroid carcinomas.(23) However, they added "...the possibility that such tumors may on occasion arise from an adrenal rest within the kidney cannot be totally excluded." There was no mention of the different histologic subtypes of RCC, rather it was considered a single tumor type.(23)

In the 2nd edition (1979), the authors refuted the adrenal rest theory in favor of tubular epithelial origin, reflecting the work of Oberling.(24) The authors discourage classifying tumors by histologic subtypes,

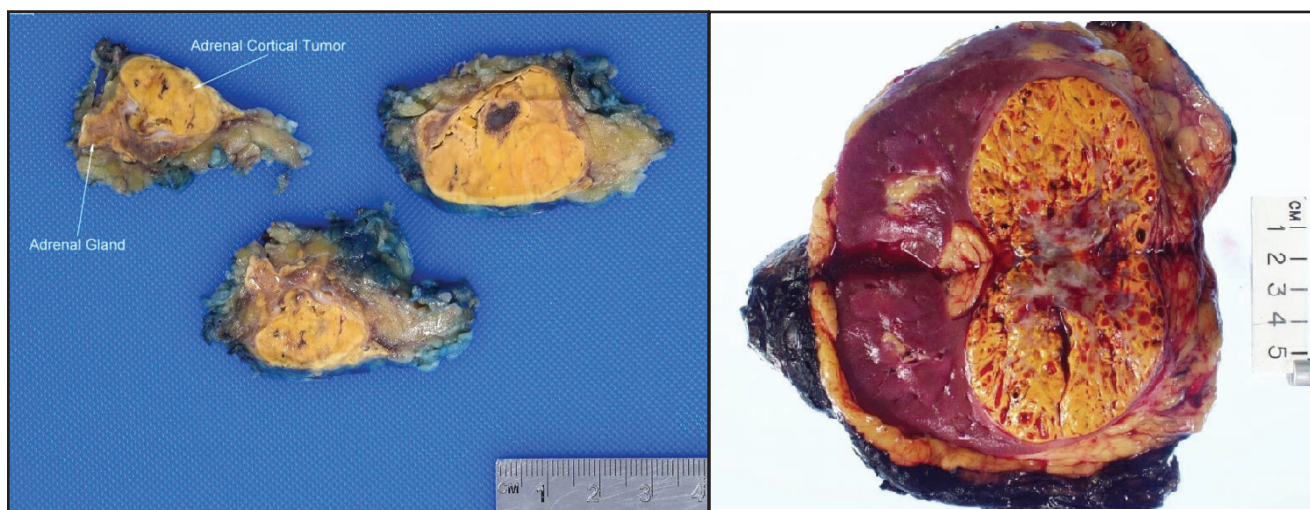
stating, "in any single tumor, all variations in cytologic patterns of growth may be present." They argue dividing tumors into histologic subtypes would be arbitrary and they had equal clinical significance. Thus, all RCCs were lumped into one category.(24)

The 3rd edition (1984) included renal oncocytoma for the first time as a benign tumor and recommended they be separated from the malignant RCCs.(25) The authors claimed the most common tumor cell was the clear cell.(26) Although all RCCs were still grouped into one category, the authors did discuss that some RCCs showed aggressive behavior, while others were indolent. (25) This marked the first edition that described the relationship among RCC, von Hippel Lindau syndrome (VHL), and aberrations in chromosomes 3, 8, and 11.(25) In the 4th edition (1989), the understanding of RCCs was unchanged from the prior version.(26)

The 5th edition (1994) subclassified oncocytoma into three grades. Grade 3 tumors were thought to have metastatic potential.(26) The authors also described the genetic aberrations of RCC in greater detail, concluding "current studies thus implicate the VHL gene, or a gene related to VHL on chromosome 3, in renal carcinogenesis," further noting that different chromosomal abnormalities underlie tumors with papillary morphology.(27)

In the 6th edition (1999), oncocytoma grading was eliminated, although metastases were reported,





**Figure 3.** Gross image of an adrenal cortical adenoma (left) versus a bivalved clear cell renal cell carcinoma (right). Both tumors are well circumscribed with a classic golden-yellow appearance. The origin of renal cell carcinomas (RCCs) was controversial well into the 20th century until electron microscopy definitively proved that RCCs were of renal parenchymal origin and not from adrenal embryonic remnants in the kidney. (Images courtesy of Jennifer B. Gordetsky, Vanderbilt University Medical Center).

oncocytomas were considered benign.(28) Collecting duct carcinoma was included for the first time.(28) The most significant change was the division of RCC into three major categories: clear cell (non-papillary) carcinoma, papillary carcinoma, and chromophobe carcinoma. (28) Emphasis was placed on the cytogenetic and histopathologic features as the driving forces behind the subclassification of tumor types.(28)

The 7th edition (2005) was largely unchanged from the prior edition, except for subclassifying collecting duct carcinoma.(29) The 8th edition (2010) was like the 7th with an elaboration on cancer syndromes, emphasizing VHL, hereditary leiomyomatosis, and hereditary papillary carcinoma.(30) The 9th (2015) and 10th editions (2021) provided a more elaborate description of the cell of origin for individual tumors.(31,32) Cancer syndromes were outlined in greater detail, and Birt-Hogg-Dube syndrome was described.(31,32) Translocation carcinoma (Xp11) was added as a new RCC subtype, bringing the total number of kidney tumor types in the most recent edition to five.(31,32)

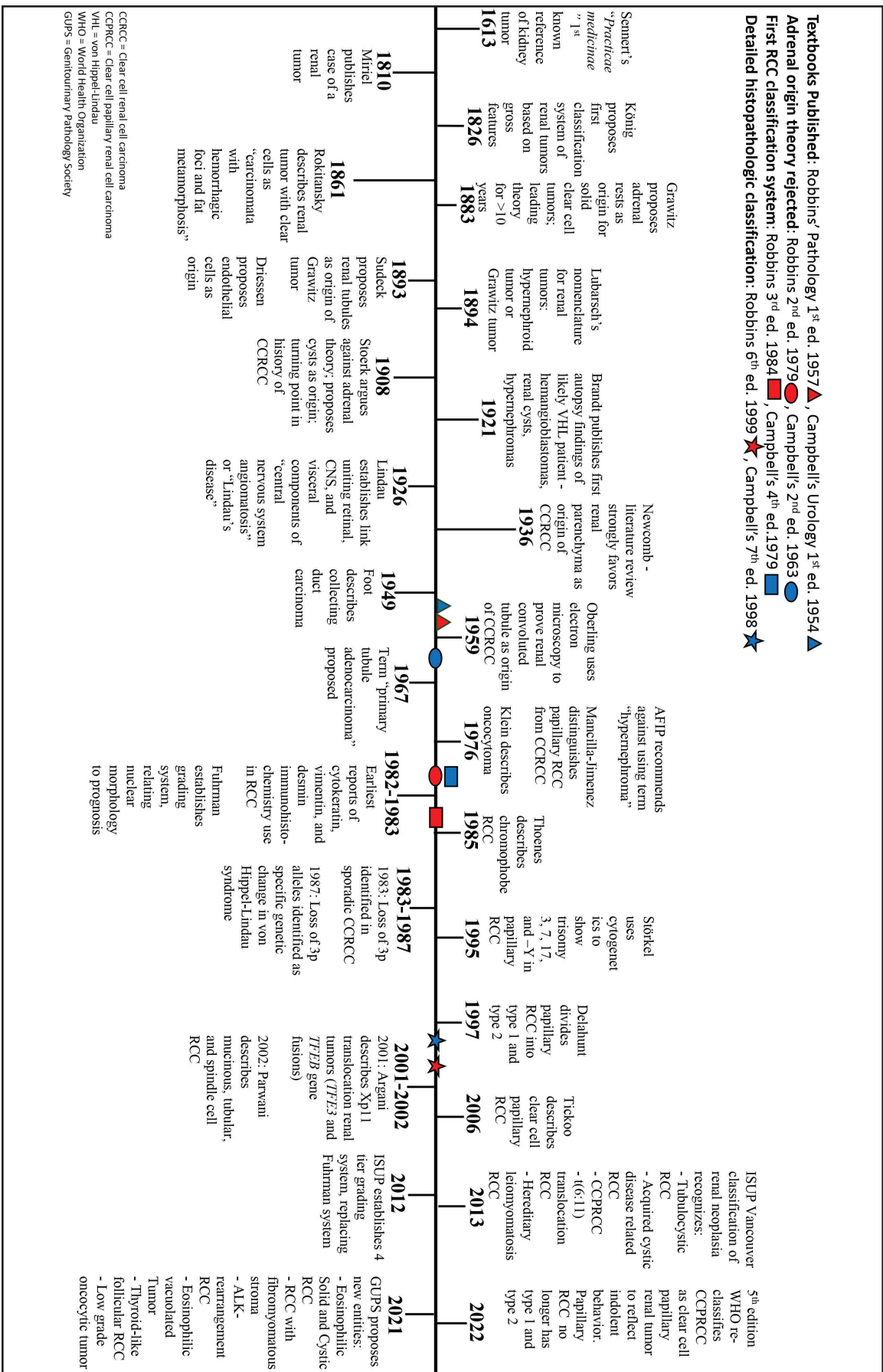
### Campbell's Urology

The 1st edition of Campbell's *Urology* (1954) classified renal tumors as adenoma (benign tumors) or hypernephroma (malignant epithelial tumors).(33) Malignant epithelial tumors were acknowledged to have created "much confusion" and RCC was thought

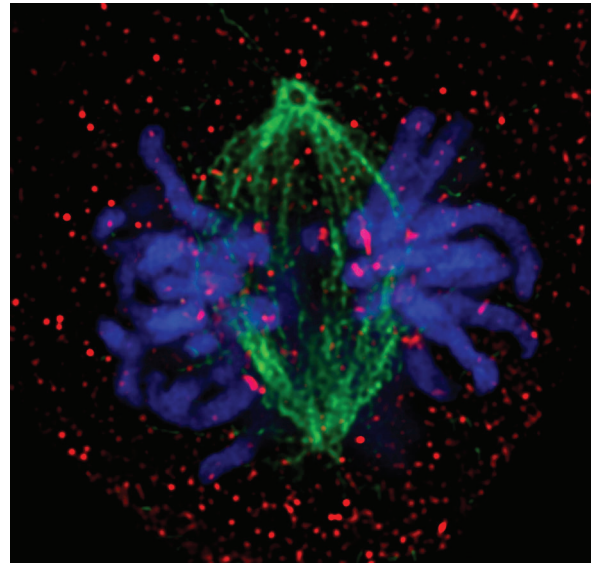
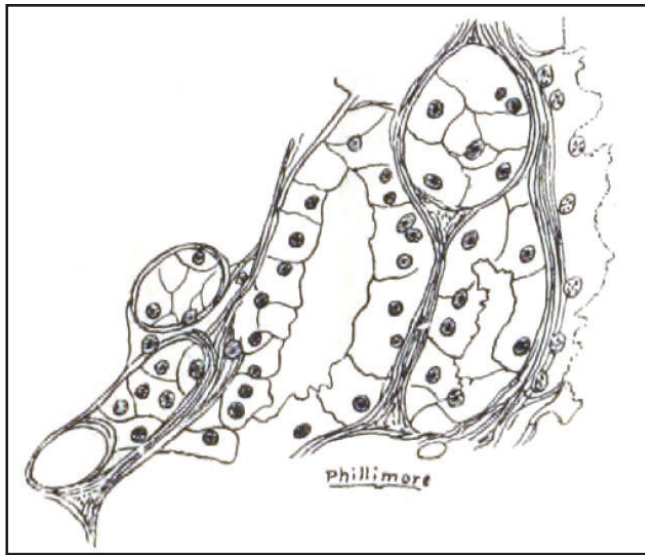
to come from "epithelial elements in the cortex and medulla and from embryonic components transplanted into and onto any part of the parenchymatous tissue". (33) Therefore, two tissues of origin were presented: embryonic adrenal rests and renal epithelium.(33) The text described hypernephromas microscopically as resembling the adrenal cortex but noted they did not contain "epinephrine or sex hormone factor". (33) They also described both "granular and clear cell types" but concluded that "since both cause death their differentiation is of little significance."(33)

In the 2nd edition (1963), malignant renal epithelial tumors were referred to as "adenocarcinoma (hypernephromas)."(34) The authors began the section on adenocarcinoma by stating, "probably no tumor has caused as much confusion histologically and histogenetically as the malignant epithelial tumors of the kidney parenchyma."(34) The authors commented that regardless of whether they are called hypernephroma, renal cell carcinoma, or renal cancers, they are all adenocarcinomas, have a variety of histologic features, and all metastasize to the lungs, bones, and adrenal glands.(34)

The 3rd edition (1970) contained more information on carcinogenesis.(35) "Great confusion" was mentioned regarding the "cellular structure of some of the malignant tumors."(35) Epithelial tumors had multiple names including adenocarcinoma, Grawitz



**Figure 4.** Notable moments in the understanding and pathologic classification of renal cell carcinomas over the past 150 years.



**Figure 5.** Evolution of pathologic evaluation of kidney cancer. (Left) 1890 rendering of clear cell carcinoma of the kidney by RH Phillimore, "a medical student", in "A Rare form of Kidney Tumor", Bell J and Johnston WG, *Mont Med J*, 1891. (National Library of Medicine). (Right) 2020 wide-field triple fluorescent stacked image of kidney cancer in prometaphase by P. Andrews, University of Dundee (Wellcome Collection).

tumor, hypernephroma, hypernephroid carcinoma, renal cell carcinoma, and alveolar cancer.(35) This edition divided tumors of the renal parenchyma into adenoma and adenocarcinoma, of which there were three types: hypernephroma, renal cell carcinoma, and alveolar carcinoma. (35)

The 4th edition (1979) stated that "an appropriate, simple, and all-inclusive classification of renal tumors has eluded pathologists and urologic surgeons alike over the past century."(36) This edition attempted to create a classification system that was "both complete and uncomplicated."(36) "Nephrocarcinoma" became the term of choice to encompass adult malignant renal parenchymal tumors, which included "classic hypernephroma and papillary adenocarcinoma". (36) The classification of adenoma and adenocarcinoma remained. (36) The authors also acknowledged the different histology of malignant tumors and believed tumors with predominant clear cell pattern had a better prognosis compared to those that with "granular or spindle cell" histology.(36)

The 5th edition (1986) changed the section previously titled "nephrocarcinoma" to "renal cell carcinoma" but kept "nephrocarcinoma" as a generic category for adult renal parenchymal malignant tumors that included "the classic hypernephroma and papillary adenocarcinoma." (37) "Nephrocarcinoma" would not be removed from Campbell's textbook until the 10th edition (2012).(42) For the first time in Campbell's, the importance of familial RCC was highlighted, specifically von Hippel-Lindau disease.(37)

Electron microscopic studies were cited as identifying the proximal tubule as the cell of origin for RCC.(37) Oncocytoma appeared as a new possibly benign entity, though there was "uncertainty in diagnosis and the occasional documentation of metastases."(37)

In the 6th edition (1992), DeKernion and Belldegrun considered oncocytoma a unique benign kidney tumor and chromophobe RCC first appeared.(38) A new section on cytogenetics, molecular biology, and immunology was established.(38) Deletions and translocations involving the short arm of chromosome 3 were stated to be associated with most RCCs. Under "pathology" RCCs were listed as clear cell, granular cell, tubulopapillary, and sarcomatoid.(38)

In the beginning of the chapter on kidney pathology in the 7th edition (1998), DeKernion and coauthors opined that "the evolution of knowledge about renal tumors is in actuality the history of surgical daring in a microcosm."(39) It was this chapter in the 7th edition that was the first to include a table titled "renal masses classified by pathology", which listed three main categories: benign, malignant, and inflammatory. (39) Clear cell RCC (both hereditary and sporadic) was noted to be associated with mutations in chromosome 3p and papillary neoplasms were noted to have trisomies of chromosomes 7, 17, and loss of the Y chromosome. (39) Renal cell neoplasms were classified as oncocytoma, chromophobe carcinoma, adenocarcinoma, NOS (clear/granular), collecting duct carcinoma, and neuroendocrine tumors. Immunohistochemistry was also added.(39)



In the 8th edition (2002), the section on clear cell RCC was expanded and a new section was added titled “familial papillary renal cell carcinoma and genetics of papillary renal cell carcinoma” that discussed mutations in the MET oncogene and hereditary forms of papillary RCC.(40) Major changes in the classification of RCC included addition of chromophobe RCC, elimination of the “granular” subtype, and recognition that sarcomatoid features were a poorly differentiated component of other tumors.(40) The “classification of renal cell carcinoma” listed conventional (clear cell), papillary, chromophobe, collecting duct, medullary, and oncocytoma.(40)

In the 9th edition (2007), RCCs were classified as conventional (subtypes clear cell, granular, mixed), chromophilic/papillary RCC (types 1 and types 2), chromophobic (type 1 classic and type 2 eosinophilic), collecting duct (included medullary), and unclassified.(41) Medullary carcinoma was recognized to be associated with sickle cell trait.(42) Familial RCC syndromes expanded to include VHL, HPRCC, familial leiomyomatosis and RCC and Birt-Hogg-Dube.(41)

In the 10th edition (2012), RCC associated with XP11.2 translocations/TFE3 gene fusions, mucinous tubular and spindle RCC, and multilocular cystic clear cell RCC were added as new entities.(42) Chromophobe RCC stopped being listed as having two “types” and the term “chromophilic” was dropped from papillary RCC.(43) The classification of renal tumors was stated to be in evolution “with changes stimulated by basic science advances and astute clinical observation”. In the 12th edition (2020), there are 16 subtypes of RCC mentioned and numerous other renal tumors.(44) Though, in keeping with tradition, one RCC has recently been changed back to a benign entity by pathologists. (19,44)

## DISCUSSION

Pathologists have historically relied on the human eye to understand the nature of disease. Applying the logic that things that look similar by gross examination or by light microscopy should be similar on a cellular level can lead to error, as it did in the original classification of RCC. As the authors of Campbell’s *Urology* remarked quite succinctly in the 2nd edition (1963), “probably no tumor has caused as much confusion histologically and histogenetically as the malignant epithelial tumors of the kidney parenchyma.” The original theory that RCCs

arose from adrenal rests was reasonable at the time. The adrenal cortex, and many adrenal cortical tumors, have a golden-yellow appearance grossly like the color of clear cell RCCs. Also, the proximity of the two organs, and the fact that historically RCCs presented at an advanced stage, made it difficult to grossly determine from where a large mass originated. Microscopic examination also added to the confusion as there are cells containing abundant clear cytoplasm in both the adrenal cortex and clear cell RCC. Our understanding of malignancy has benefited greatly from improvements in technology and diagnostic techniques (Figure 5). Electron microscopy put to rest the question of the cell of origin for RCC, but it has also been used to distinguish different types of renal tumors.(45) Special chemical stains also helped in the differentiation of renal masses and immunohistochemistry has become one of the most utilized tools in the diagnosis and differentiation of renal tumors.(46-49)

The history of renal tumors demonstrates the lag between scientific discoveries and publication of that data into medical textbooks. Gains in our understanding of renal neoplasia were reflected slowly in the successive editions of Robbins’ *Pathology* and Campbell’s *Urology*. The 1st edition of both textbooks presents the possibility of RCC arising from adrenal tissue, though Robbins makes a more forceful counterargument. No attempt at subclassification was made by either text in the 2nd edition. The 3rd edition is where we start to see Robbins and Campbell diverge, with Robbins (1984) including oncocytoma, highlighting that most tumors had “clear cell” features, and discussing an association with VHL syndrome. Oncocytoma shows up in Campbell’s *Urology* in the 5th edition (1986) and VHL in the 6th edition (1992). In addition, Campbell’s *Urology* was disinclined to abandon the old terminology of “nephrocarcinoma” and “hypernephroma”. Both terms were present through the 9th edition (2007).

Subclassification based on histology occurs around the same time in both texts in the late 1990s, with Robbins separating the different subtypes into clear cell, papillary, and chromophobe, and Campbell’s describing chromophobe carcinoma, adenocarcinoma NOS (clear/granular), and collecting duct carcinoma. Interestingly, as time goes on, Campbell’s become more inclusive of subclassification, molecular analysis, and takes on lengthier, detailed chapters on renal tumors while Robbins takes a more simplified approach. This may reflect differences in the intended audiences, with

Robbins' *Pathology* directed towards medical students and Campbell's *Urology* becoming the book of choice for urology residents, fellows, and attendings.

## CONCLUSION

Today, debate over the classification of renal tumors continues as intensely as it did in the past. Subclassification by IHC and molecular studies may lead to the development of novel therapies and create an individualistic approach to managing cancer. Yet as we continue in this ongoing quest to understand renal tumors, as Hugh Hampton Young stated in 1926, "competent pathologists" will continue to describe renal tumors under many different names.(22)

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# The Historical Origins and Contemporary Role of the Endoscopic Treatment for Urethral Stricture Disease

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**Introduction:** Stricture of the urethra has plagued humans likely longer than the historical record. Modern approaches to urethral stricture disease (USD) include excision and primary anastomosis, buccal mucosal onlay repair, and the emerging potential of tissue regeneration. Those who managed patients with USD benefits form a compelling narrative shaped by centuries of medical advancements, societal attitudes, and evolving treatment techniques. Urethral dilation and urethrotomy remain important tools in general urology, especially for those with short, benign appearing strictures. We explore the historical origins and developments of dilation and urethrotomy for the treatment of urethral stricture disease (USD).

**Sources and Methods:** Primary and secondary sources related to USD were reviewed and put into perspective within current practices.

**Results:** The earliest known treatment for USD is from the Ayurveda, in which its author(s) used urethral dilators lubricated with *ghee*. Erasistratus of Greece was said to have developed S-shaped metal catheters around 200 BCE, adapted and modernized by the Romans who used lead and bronze dilators. A renewed focus on USD arose in the 16th century during the first recorded gonorrhea epidemic and a primitive form of internal urethrotomy was developed. The introduction of the lanceolate-shaped catheter in 1795 allowed for successful internal urethrotomy. In the 1990s, Freid and Smith described a Seldinger technique for dilation over a wire and Steenkamp et al. demonstrated equivalent outcomes between filiform dilation and direct visual internal urethrotomy. In 2007, Herschorn of Canada introduced S-shaped coaxial urethral dilators. In 2011, Gelman et al. described direct vision balloon dilation. Recently, drug-coated balloon dilation is being investigated.

**Conclusions:** The origins of the endoscopic treatment of USD can be traced back to over 26 centuries ago and are dependent on corresponding advances in microchip development, fiber optics, and tissue regeneration.

**Keywords:** Urethral Stricture Disease, Dilation, Urethrotomy

**U**rethral stricture disease (USD) is a common urological condition defined by narrowing of the urethral lumen secondary to fibrosis of the urothelium and associated corpus spongiosum. The etiology of USD may be idiopathic, or due to trauma, infection, or instrumentation. Symptoms of bladder outlet obstruction are often associated with USD. Further complications such as urinary tract infections, ejaculatory dysfunction, and renal failure may occur in cases of unrecognized and unrelieved obstruction.

USD was identified early in the history of medicine and our current treatments share similarities with many of surgery's predecessors. Most modern initial approaches to USD are endoscopic, and often

repeatedly so due to patient preference, ease of access, less perceived invasiveness, and the training required for formal urethroplasty.(1)

This study aims to summarize the historical roots, evolution, and contemporary role of the endoscopic treatment in USD. We hope to demonstrate how previous developments have impacted our current treatment options.

## SOURCES AND METHODS

We identified secondary source materials on the history of urethral strictural disease and urethrotomy by consulting online resources through PubMed and the National Library of Medicine (www.nlm.gov); the National Library of France (gallica.bnf.fr);

and artefacts and archives at specified museums and resources including the William P. Didusch museum of the American Urological Association (AUA), Linthicum, Maryland (<http://urologichistory.museum>).

## RESULTS AND DISCUSSION

### 600 BCE – 1000 BCE: Sushruta

Prominent historical figures in medicine have tackled the treatment of USD. The earliest written documentation of USD began over 26 centuries ago in Ayurvedic medicine, indicating that USD has not only been an issue in the present day but also one that plagued our ancestors. Sushruta was said to be the founder of Ayurveda medicine. Known as the ‘Father of Surgery’, and of Indian Medicine, He was the first to describe a treatment of urethral strictures.(2) Sushruta is given credit as the source of the *Sushruta Samhita*, a veritable compendium of ancient Indian medical care. In the *Samhita*, he describes the use of bamboo and reed catheters lubricated with a clarified butter called *ghee*. Other cultures, including the Chinese, used bamboo catheters for strictural disease. The ancient Egyptians have long

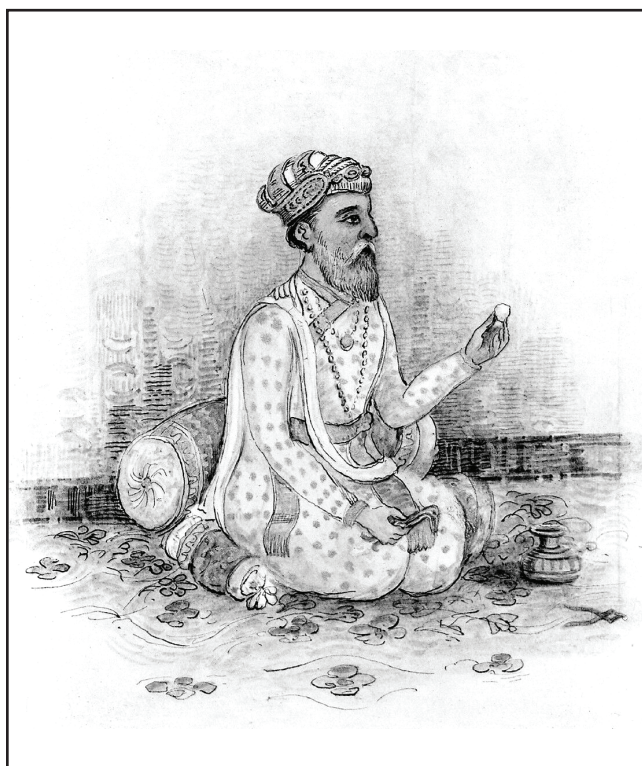
been credited with fashioning urethral dilating catheters from stiffened reeds but a reading of the Ebers Papyrus, the major surviving text from 1500 BCE of this period, mentions nothing of them and its translator, Cyril P Bryan pointed out that “it is to the credit of Egypt’s surgeons that they did not practice urethral dilation in cases of stricture.”(3)

### 460 BCE – 370 BCE: Hippocrates

Hippocrates (c. 450-c.380 BCE) spoke of urinary retention caused by urethral strictures, calculi, and abscesses but never directly referenced catheters or dilators.(4) In addition to his work on urethral pathologies, he was one of the first to reference sub-specialization in medicine in the famed Hippocratic oath that spoke of leaving lithotomy to experts in that art. During this time, lithotomy was being performed in Greek, Byzantine, and Islamic Civilizations.(5)

### 25 BCE – 50 CE: Cornelius Celsus

Cornelius Celsus (c. 25 BCE – c. 50 CE) authored *De Medicina*, known as one of the best sources of medical literature in the Roman Empire.(6) *De Medicina* described S-shaped catheters that are reminiscent of modern



**Figure 1.** (Left) Watercolour drawing of Sushruta by H. Solomon, from an Indian original. (Wellcome Collection, Public Domain) (Right) Fragment of a 12th -13th century copy of the *Sushruta Samhita*, from Nepal, in Sanskrit using ink and watercolor on a palm leaf. (Los Angeles County Museum of Art, Public Domain)



**Figure 2.** Reproduction of an S-shaped male catheter that was found buried in the Roman city of Pompeii following the eruption of Mount Vesuvius in 79 AD. (Courtesy of the Claude Moore Health Sciences Library, University of Virginia).

S-curve dilators:

*"For this purpose bronze tubes are made, and the surgeon must have three ready for males and two ready for females, in order that they may be suitable for everybody, large and small ... They ought to be a little curved, but more so for men, and they should be very smooth."*

Fitting his description, an S-shaped male catheter was found, buried in the Roman city of Pompeii following the eruption of Mount Vesuvius in 79 CE (Figure 2).(7) Additionally, Cornelius Celsus described a perineal lithotomy method that remained largely unchanged for 1400 years. Celsus was a proponent of prescribing diet as first-line treatment for bladder calculi, then perineal lithotomy if non-surgical interventions failed.(8,9)

#### **169 CE – 216 CE: Galen**

Galen (c.130 CE-c.210 CE) was a Greek surgeon and philosopher who lived in the Roman Empire.(10) He described a case in which a young boy in acute urinary retention due to urolithiasis required probing of the urolith away from the bladder neck with a catheter to allow urine flow.(8,11) Similar tactics for blood clots, as well as "some flesh growing out from an ulceration ... obstructing the neck of the bladder" were also described.(8,11) Like Hippocrates, Galen was also a proponent of sub-specialization:

*"In truth it is often necessary to deliver cures through the penis into the bladder. I need not say anything further on the catheter, except that it should only be used by those who are very familiar with the entire*

*bladder system."* (8,12)

Paul of Aegina (c. 625 CE- c. 690 CE) was an active surgeon in the Byzantine era whose descriptions of short- and long-term catheterization point to a recognition that urethral strictures may be a result of benign, malignant, or traumatic causes. According to Moog et al, Paul was the first to propose a metal quasi-permanent catheter. "If the whole glans be consumed," Paul was said to write, "a leaden tube is introduced into the urethra, and we direct the patients to make water through it." (8)

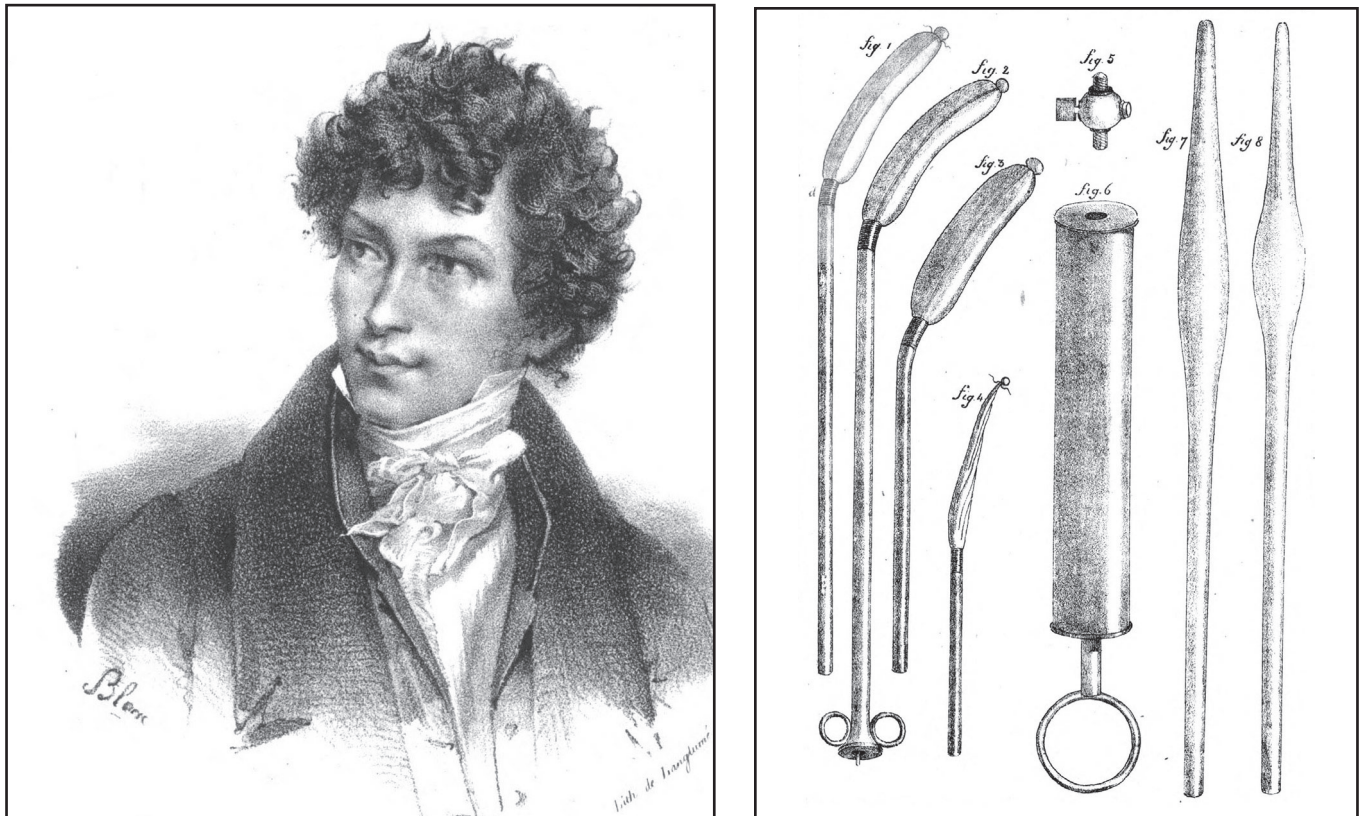
#### **Middle Ages**

The American surgeon John B. Deaver once wrote that "there was a time in the history of medicine when the surgeon simply furnished hands for the physician to whom any form of manual treatment was barred as beneath his dignity."(13) During the Middle Ages, urethral strictures and genitourinary problems were no longer deemed worthy of physicians. The treatment of these conditions fell to charlatans, quacks, and those following beliefs of witchcraft and religious superstition, resulting in the stagnation of urethral stricture management.(14)

#### **1520 CE: The First Gonorrhoeal Epidemic**

During the early 16th century, the first gonorrhoeal epidemic sparked a change in how urethral strictures were viewed.(14) USD began to be described as obstructing growths instead of urethral luminal constrictions. Thierry de Hery (1505 – 1599) was a French barber and surgeon who coined the term "carnosities" to describe flesh protuberances in the urethra, also





**Figure 4.** (Left) Theodore Ducamp (1793-1823), the brilliant author of the posthumously published text *A Treatise on Retention of Urine* (1827) in which he described wax casting to calibrate urethral stricture length and ballon dilation (right) as early as the 1820s. (Wellcome Library, Public Domian)

known as strictures.(15) De Hery recommended the use of lead sounds to perform “progressive dilation” of these strictures and viewed the resultant hemorrhage as therapeutic.(15,16) A classmate of de Hery from the Surgical School of Saint Louis, in Paris, was the famed surgeon Ambroise Paré (1510-1590). Paré aimed to improve de Hery’s methods using a safer alternative in which wax candles and lead sounds were also lubricated with ointments or caustics before the procedure was performed.(16)

### Modern Period

The Modern Period can be further divided into both Early and Late periods, with present-day included in the latter. Collectively, these were times of gradual improvement in both technology and procedural techniques used in urological procedures, some of which remain in practice today. Given the vast differences in technology accessible between time periods, the authors would like to note historic documentation is almost certainly limited in diagnostic accuracy and reporting. With the advent and improvement of modern-day cystoscopes, diagnosis of urethral stricture disease may be quite accurate, but we

must recognize limitations of tools available during each time period.

### Early Modern Period

Progress in the early modern period began, like many things, with the Scottish surgeon John Hunter (1728 – 1793). With Hunter’s extensive work on USD and urolithic stone disease, he was able to classify urethral strictures to be either permanent, spasmodic (due to pathologic contraction of muscles around the urethra), or mixed. (3,14) In his practice, much like Paré, Hunter used dilators with caustics, such as silver nitrate or soda but in addition, used wax dilators he referred to as “bougies.” The term bougie comes from Bujyah, the name of an Algerian town where the best wax for French candles was said to originate.(14,17,18) Hunter advocated for the use of such bougies due to their ability to become malleable when heated. That property allowed him to model the stricture with the bougie and measure the distance to the stricture from the opening of the urethra.(17,18) Hunter was also able to treat bladder stones using bougies and used them for identification of the stones through a sounding technique. His advancements in medicine led

to The Hunterian Society of London, which was named in his honor.

Following in John Hunter's footsteps, several advancements in urologic surgery arrived in succession. In 1795, silver lanceolate-shaped catheters were invented for internal urethrotomy and quickly gained popularity due to their superior ability in cutting through strictures.(3,14) Later, in 1822, Theodore Ducamp (1793-1823) began using the first balloon dilation tool to treat strictures (Figure 4).(14,19) Thomas Jefferson (1743-1826) wrote to his personal physician, Robert Dunglison, in May 1825 that "a chronical complaint which has been troublesome for some time has within a few days become too much so to be longer unattended to. I must ask your advice in it (and) as soon as you can come with convenience. It disables me from going out either on horseback or in a carriage."(20) The "chronical complaint" was urinary retention and Dunglison arrived in Monticello to catheterize the former President several times well into 1826. In 1836, Leroy d'Etiolles (1798-1860) introduced the use of filiform guides and catheters to increase the success of the dilation of strictures, termed "bougie a boule," which allowed for easier passage through the urethra.(13,21)

#### Late Modern Period (Including Present Day)

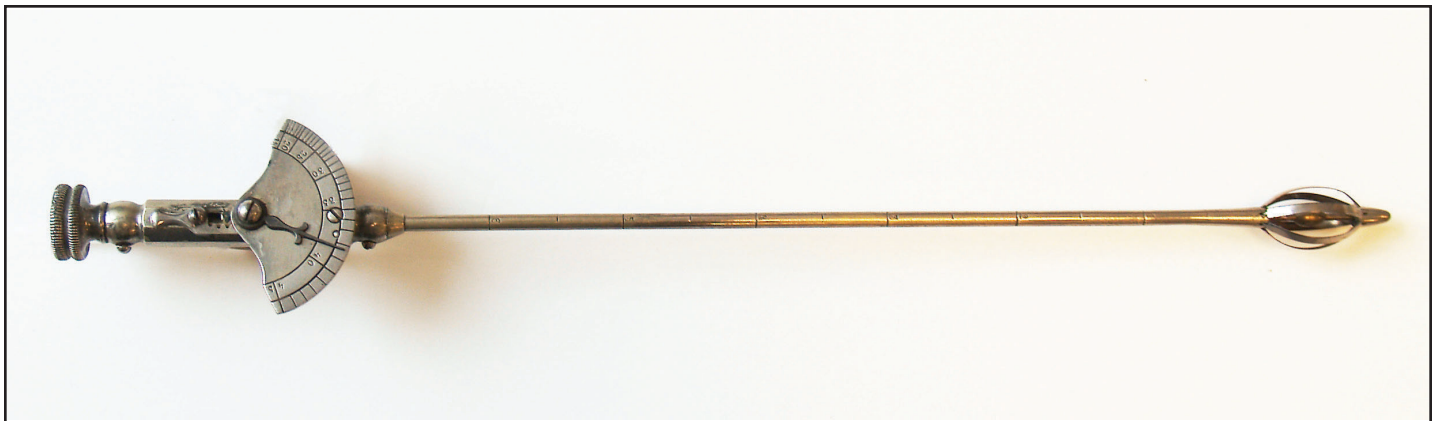
To begin the Late Modern Period, in 1848, Jules Francois Maisonneuve (1809-1897) began to use the urethrotome, an instrument able to cut through strictures in the urethra. (14) He built on d'Etiolles use of filiform guides by using them to guide his urethrotome, allowing for directed internal urethromies. Soon after, in the 1870s, Fessenden Nott Otis (1825-1900), began to use his invention which he called the "urethra-meter," more commonly known as a urethrometer,

to measure the appropriate caliber of the sounding tool required for urethral dilation (Figure 5).(14,21) Otis also created different mechanical dilators as well as a two-bladed dilating urethrotome which remains in use today.(14,22)

Leading up to the present day, the endoscopic dilator has progressed through many iterations. Notably, in 1979 the addition of a 30-degree angled lens was introduced.(23) Then, in 1984, a balloon was joined to the apparatus to aid in the dilation of targeted strictures.(24) In 1996, Russel Freid and Arthur Smith replaced filiform guides with "glide wires" that would extend fully into the bladder and allow for the improved direction of the catheter.(25) The glide wires would cannulate the urethra allowing for dilation to be subsequently performed using a Seldinger technique.(25)

In 2007, S-curved dilators were introduced by Herschorn of Canada who demonstrated their superiority over rigid, straight dilators, some 1500 years after the Roman design. The S-curve copied the curve of a normal male urethra, allowing for an easier passage over the guide wire.(26) These dilators are also covered with a hydrophilic coating, allowing for smoother entry through the urethra. Prototypes ranging in size from 8Fr to 20Fr were used to perform the procedure in thirty patients. After each procedure, a physician would complete an evaluation form with a rating scale between one and four, to describe excellent to unsatisfactory, for the design, hydrophilic coating, and ease of passage. It was concluded that S-shaped dilators were safe, effective, and retained specific advantages over rigid dilators, such as the ability to drain the bladder for patient comfort. (26)

Four years after the introduction of S-shaped dilators, direct vision balloon dilation was introduced. The addition of a camera into the urethra allowed for direct visualization



**Figure 5.** "Urethra-meter," more commonly known as a urethrometer, developed by Fessenden Nott Otis (1825-1900), to measure the appropriate caliber of the sounding tool required for urethral dilation. (Courtesy, WP Ddidusch Museum, Linthicum, Maryland)

of the stricture before dilation was performed.(27) Once the stricture was located, a balloon would be inflated with sterile water for five to ten minutes in duration, causing a constant radial force on the stricture. Further studies demonstrated that balloon dilatation under direct visualization lead to significant improvements in IPSS as well as uroflowmetric parameters.(28) In 2020, balloon dilation was improved further by the addition of paclitaxel, an antiproliferative chemotherapeutic that stops cell proliferation in an effort to decrease fibrotic scarring and therefore prevent stricture formation. Its addition to the surface of the balloon promoted better long-term outcomes after the initial dilation.(29) Drug-coated balloons may be associated with multiple benefits over local injection of the medication such as easy absorption due to hydrophobic properties, a prolonged half-life in the tissue with decreased risk of overdosing due to low serum concentrations when compared to injection into the same space, and circumferential delivery over the entire stricture while avoiding the spread of medication to unintended periurethral tissue.(30,31) The ROBUST I trial on this method showed good safety and excellent success, with no significant treatment-related severe adverse events such as urethral rupture and urethral fistula formation at 24 months post-procedure.(31) The ROBUST III trial, a randomized single-blind trial of drug-coated balloon dilation in comparison to either classic dilation or urethrotomy, showed a higher stricture-free rate at six months (76% vs 27%), less need for repeat intervention, and greater durability of symptom improvement in the drug-coated balloon dilation group.(32) The drug-coated group retained a side-effect profile in keeping with the classic dilation group.

### **Dilation or Direct Visual Internal Urethrotomy**

Direct visual internal urethrotomy (DVIU) is usually done in the operating room and uses either a Sachse urethrotome (i.e. 'cold knife'), developed in 1974 by Hans Sachse (1926-2018), or laser to incise through the scar formed by the stricture. Both DVIU and balloon dilation are currently used as first-line procedures to manage urethral strictures. However, there is no evidence that DVIU is superior to balloon dilation, or that any specific technique within DVIU - for example, laser in comparison to cold knife - is superior.(33) There may be weak support for using DVIU over dilation in the bulbar urethra, as visually-controlled dilation might reduce complications secondary to false passage

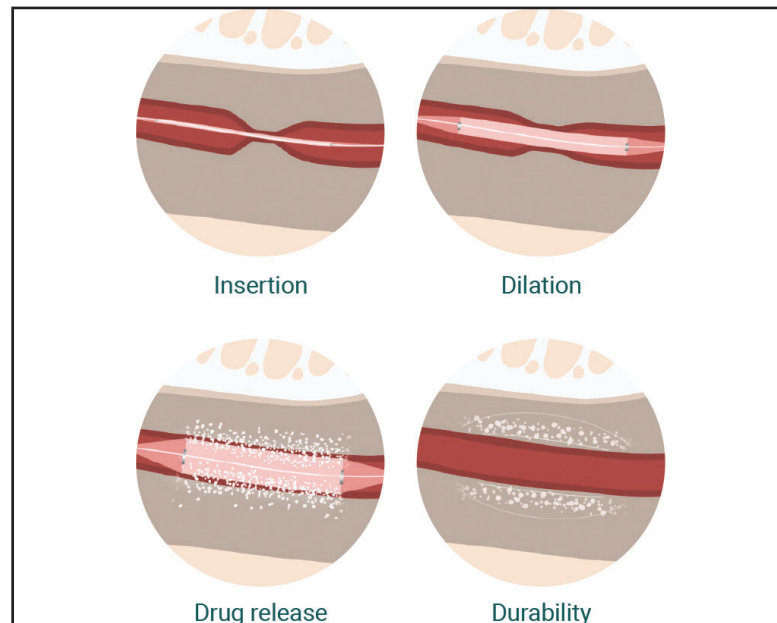
of the endoscopic apparatus, such as spongiosum tissue perforation and urethral bleeding.(33) Another important consideration is the potential increased risk of erectile dysfunction when DVIU is performed for penile urethral strictures.(33)

The main study that compared balloon dilation with DVIU was done by Steenkamp et al. who randomized 210 patients with seemingly comparable non-obliterative strictures at all locations of the urethra to receive either filiform dilation or DVIU. The study showed that DVIU and balloon dilation are equally effective, both with a recurrence rate of approximately 40% at 12 months for strictures less than two centimeters and 80% for strictures longer than four centimeters.(33) As such, the indications for DVIU and dilation at the anterior urethra are the same, with the most suitable indication being previously untreated patients with a single, short (one centimeter or less) bulbar urethral stricture. For this selection of patients, a 5-year patency rate of 77% has been reported.(34)

In cases of recurrent strictures, repeat DVIU or dilation are acceptable in certain conditions, according to the Canadian Urological Association (CUA), Société Internationale d'Urologie (SIU), and the American Urological Association (AUA).(35–39) Scenarios in which a solitary stricture or bulbar urethral stricture, with a length less than two centimeters, has recurred more than three to six months after the previous treatment are suitable for a repeat procedure. Strictures that have recurred at three months or less after the initial DVIU or dilation procedure have a poor success rate with a repeat procedure and are found to have no value after 48 months. In contrast to this, strictures that recur more than six months after the initial procedure have a 40% stricture-free rate at the 48-month mark after a repeat procedure. The CUA and SIU, however, do not recommend a third DVIU or dilation procedure after further recurrence unless in special situations involving patient comorbidities or resource availability, and in these cases a more invasive urethroplasty is indicated. (35–37)

The American Urological Association's (AUA) guideline originally did not fall in line with the CUA and SIU recommendations for recurrent strictures, stating that a second DVIU or dilation should not be performed as it is cost-ineffective and rather suggest a urethroplasty to manage the obstruction.(37) The AUA's reasoning for this recommendation was that repeated endoscopic procedures are unlikely to be successful





**Figure 5.** Mechanism of Optilume®, the intraurethral balloon designed to be inserted and dilated within a urethral stricture, allowing for drug release of paclitaxel. (Courtesy, Laborie Medical Technologies, Portsmouth)

and carry the risk of exacerbating spongiofibrosis, complicating definitive reconstruction. The AUA based these guidelines on the premise that prior endoscopic treatment for urethral stricture is an independent risk factor for stricture recurrence after urethroplasty. (33,37) In a 2023 addendum, the AUA changed their stance stating surgeons may perform urethral dilation or DVIU for recurrent urethral strictures if they are < 3 cm. Changes were made in light of new evidence as well as consideration for patient preferences. Updated AUA guidelines suggest endoluminal treatment for recurrent strictures < 3 cm may be considered as a palliative option for patients not interested in, or unable to undergo urethroplasty.(36) Furthermore, the ROBUST III RCT showed that 83.2% of patients treated endoscopically combined with paclitaxel-coated urethral balloon for recurrent anterior urethral strictures < 3 cm in length were intervention free at 1 year. ROBUST III participants also showed promising results with 67% of patients showing functional success at 3 years with use of the drug-coated balloon.(40)

Many strategies have been implemented to combat the high recurrence rates of strictures after DVIU and dilation procedures. Intralesional injection with steroids or mitomycin C (MMC), a chemotherapeutic agent, have been shown to have decreased stricture recurrence rates and remain a possible option.(41) While intralesional MMC injection paired with urethrotomy has shown a decrease in stricture recurrence rates when compared

to urethrotomy alone in a randomized clinical trial by Mazdak et al., its use in the urethra remains off-label.(39) Intermittent self-dilations, with or without the adjunctive use of intraurethral corticosteroids, have evidence to support their benefits in stabilizing the stricture and prolonging the time to recurrence, rather than reducing the recurrence rate.(42) Temporary urethral stents have also shown benefits but must be used with caution because a history of failed stenting is a predictor of increased stricture complexity and the need for more complex urethroplasty.(43)

In settings of acute urinary retention, in which more definitive reconstructive repair will be required, DVIU, balloon dilation, or suprapubic cystostomy can be used as temporizing interventions before a definitive procedure. These methods, paired with clean intermittent catheterization, can also be used when a patient is unfit for major urethral reconstruction, such as in the palliative setting.(39)

## CONCLUSION

The origins of endoscopic treatment of USD can be traced back to over twenty-six centuries ago in ancient Ayurvedic medicine.(3) Though significant advances have been made, there remains a lack of research and consensus in deciding the appropriate first-line procedure for USD in addition to the treatment of recurrent urethral strictures.(35) With some of the most prominent urological associations in North America

having differing recommendations for recurring strictures, room for future studies to dictate changes in guidelines for the treatment USD is abundant.(35–37) Drug-coated balloon dilation has shown promising preliminary results to be the gold standard for endoscopic treatment of USD, but further investigation and long-term follow-up are required to conclude its efficacy and safety.(30–32)

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