LEGENDS IN UROLOGY

Herbert Lepor, MD
Professor and Martin Spatz Chair of Urology
Professor of Pharmacology
NYU Grossman School of Medicine
Chief, Urology NYU Langone Health
New York, NY, USA

My pathway to Urology began during my senior year at UCLA when applying for medical school. Due to financial constraints, I was interviewed for The Johns Hopkins School of Medicine by Dr. Willard Goodwin, the emeritus Chair of Urology at UCLA. I gained acceptance to many top tier medical schools including Hopkins. I sought guidance from Dr. Goodwin whether to matriculate at Hopkins. His response "definitely go to Hopkins and make it a high priority to meet Dr. Patrick C. Walsh who was just appointed Chair of Urology at the Brady Urological Institute. I knew nothing about Urology but followed Dr. Goodwin's advice.

During my introductory meeting with Dr. Walsh, he encouraged me to discuss summer research opportunities with Dr. Donald S. Coffey, known affectionately as The Chief. Dr. Coffey took me under his wing and summers throughout medical school were spent investigating the nuclear matrix and interacting with Urology residents. A requirement of the senior Osler medicine rotation was to write a detailed report on a medical condition. I sought Dr. Walsh's guidance for a urology related project that would fulfill the medical rotation assignment. At the time, Dr. Walsh was preparing a presentation for medical grand rounds on Idiopathic Retroperitoneal Fibrosis (IRPF) and so this became the topic of my project. I spent the entire winter vacation reviewing every paper published on IRPF and presented Dr. Walsh my comprehensive review of the topic. He was quite impressed with the first draft of the paper, which was subsequently revised, submitted and published as review article in the *Journal of Urology*.

During my senior year in medical school, I completed sub-internships at MGH and UCLA. Despite wonderful experiences at both institutions, Hopkins was #1 on my urology residency rank list. I was thrilled to match at Hopkins where the commitment to excellence and innovation was palpable. The opportunity to be further mentored and inspired by both Drs. Walsh and Coffey ultimately defined the trajectory of my academic career.

The major milestone of my two years as a Halstead general surgery resident was meeting the love of my life, Ellen Shapiro MD, who would become my wife and the first woman Brady Urology resident. Over the ensuing 41 years, we have been co-investigators, co-faculty, and co-surgeons while together raising two exceptional children, Abbey and Lauren.

I began my Urology residency research July 1992. Day #1 in the lab, Dr. Coffey inquired about my research goals. I expressed my interest to investigate the autonomic innervation of the human prostate in order to provide insights into the medical management of BPH. Dr. Coffey immediately contacted his colleagues in Pharmacology who were world renowned neuro-scientists. I quickly learned how to perform radioligand binding assays in the brain, a tissue that readily homogenized. No one had successfully measured neuro-receptors in GU tissues due to its abundance of connective tissue and the inability to prepare a uniform tissue homogenate. After many frustrating months with nothing to show for my efforts, I immersed human prostate tissue in liquid nitrogen and pulverized the frozen tissue into dust, which enabled successful generation of the illusive Scatchard plots. Characterizing the muscarinic cholinergic and alpha 1 adreno-receptors in the prostate were my first receptor successes. Prior in-vitro contractile studies by Marco Caine demonstrated human prostate smooth muscle contraction was mediated by adrenergic agonists. The specific adrenergic sub-type mediating prostate smooth muscle contraction was unknown. My research goal to provide insights into medical therapy was looking more promising.

In 1980, Dr. Walsh fortuitously had the opportunity to observe human fetal dissections illustrating the autonomic innervation of the lower urinary tract. He astutely noted that the autonomic innervation en route to the penis passed along the prostate and hypothesized that injury of these nerves during radical prostatectomy (RP) was the

etiology for post-prostatectomy erectile dysfunction. Dr. Walsh challenged me to identify a histologic specimen showing the peri-prostatic autonomic nerves. That day, my colleagues in pathology were performing an autopsy on a young man who sustained lethal trauma. Because the prostate was small, a single transverse histological section demonstrated the autonomic nerves coursing along the prostate en route to the penis were extra-prostatic and therefore amenable to a "nerve sparing" RP. No good deed goes unpunished. My next assignment was to identify a human specimen that would enable delineating the precise pathway of the autonomic innervation to the penis and its relationship to the prostate. I identified a cadaver at the Maryland Anatomy Board that had been perfused with Bouin's solution and removed en bloc the bladder, prostate penis and rectum. The Armed Forces Institute of Pathology prepared 7000 whole mount step sections, and stained every tenth section with Hematoxylin and Eosin. In collaboration with the Hopkins Department of Medical Illustration, a three dimensional model was constructed illustrating the precise pathway of the autonomic nerves to the penis which validated the anatomic foundation for the nerve sparing RRP. Dr. Walsh generously assigned me "first" author on the anatomical paper, and included me as a co-author on the first description of the anatomic nerve sparing RRP.

My first faculty appointment upon completing residency was Chief of Urology at Jewish Hospital of St Louis and Assistant Professor of Surgery (Urology) at Washington University School of Medicine. I established a laboratory investigating lower urinary tract autonomic pharmacology and successfully competed for RO1 funding. In 1987, Abbott Pharmaceuticals invited me to lead a program investigating terazosin, a long acting selective alpha-1 adrenergic blocker for treatment of symptomatic BPH. Since the drug was approved for hypertension, the FDA mandated a 3-day admission to an in-patient observation unit which severely curtained enrollment. Due to these enrollment challenges, Abbott decided to cancel the BPH drug development program. I suggested we appeal the 3-day admission requirement to the FDA based on the safety of the first 100 subjects enrolled. The FDA agreed to a 1-day admission to an observation unit and soon thereafter study enrollment was completed. Terazosin was approved by the FDA for the treatment of symptomatic BPH in 1993 and became Abbott Pharmaceutical first billion-dollar drug. I was subsequently directly involved in the drug development of doxazosin, tamsulosin and silodosin for the treatment of symptomatic BPH.

In 1993, Ellen and I moved to the Medical College of Wisconsin (MCOW) where we maintained an active lab and characterized calcium channel, endothelin and nitric oxide receptors in the prostate. While at MCOW, I organized a multi-center randomized placebo controlled trail comparing an alpha-1 blocker (terazosin), a 5-alpha reductase inhibitor (5-ARI) (finasteride), combination of these two drugs, and placebo through the Veterans Administration Cooperative Studies Program (VACSP). A major challenge was convincing Abbott Pharma (terazosin) and Merck (finasteride) to fund a third of the trial without direct involvement in study design, data acquisition, data analysis and manuscript preparation. The VACSP #357 confirmed the clinical benefit of the alpha-1 blocker over placebo, however the 5-ARI was equivalent to a placebo and the combination of the alpha-blocker and 5-ARI were equivalent to alpha-blocker monotherapy. How was this possible that the FDA approved a placebo for the treatment of BPH?? The registration studies for finasteride enrolled men with very large prostate glands. A sub-set analysis of VACSP #357 showed that the 5-ARI provided symptomatic clinical benefit only in men with large prostates. While at MCOW, I also conducted the first sham BPH device study showing balloon dilation was equivalent to cystoscopy. This study showed the feasibility and importance of sham controlled BPH device studies. My contributions during the first 10 years of my academic career in BPH were recognized in 1996 by the AUA when awarded the Gold Cystoscope.

In 1993 at the young age of 37, I accepted the position as Chair of Urology at New York University School of Medicine. At the time, there was no fellowship trained urologists on faculty, none of the clinical faculty in the prior year co-authored a peer reviewed manuscript, no clinical trials were enrolling subjects, there were no fellowship training programs, the Urology endowment was less than $500,000, and all of the "full-time" faculty were independent corporations. Today, our full-time faculty is comprised of over 30 fellowship trained urologists. The majority of our senior faculty who started their academic careers at NYU are internationally recognized leaders in Urology. The Department of Urology at NYU Grossman School of Medicine has consistently ranked amongst the top 10 by USNWR and #5 by Blueridge for NIH funding.

Upon arriving at NYU, I recognized an opportunity to re-focus my clinical practice on the surgical management of prostate cancer. In the year 2000, I began enrolling men into a prospective longitudinal outcomes registry. Over the years, I have leveraged this database of approximately 2500 cases to publish on early, intermediate and long

term LUTS, urinary continence, sexual function, disease recurrence and prostate cancer free survival following open RRP. I have also reported on early catheter removal, diagnosing and treating co-existing inguinal hernias, etiology and strategies to decrease rates of bladder neck contracture, and utilization of erythropoietin stimulating proteins as an alternative to autologous blood donation. I have debated on virtually every continent the merits of open vs. robotic RP. Based on the evidence from randomized studies, the robotic approach lost the debates but ultimately won the war based on marketing pressure and public demand.

NYU was one of the first centers in the country adopting MR fusion targeted biopsy (MRFTB). The ability to reliably localize the site(s) of clinically significant disease (CSD) by MRFTB and the recognition that men with low risk disease are excellent candidates for active surveillance served as the foundation for my interest in exploring focal ablation of prostate cancer. I began my foray into focal therapy of prostate cancer using laser ablation in 2013. Because of limitations achieving in-field confluence of energy using a single laser fiber, cryo-ablation became my ablative energy of choice. Beginning in 2017, my colleague Jim Wysock and I began enrolling all men undergoing partial gland cryo-ablationPGCA into an IRB approved a prospective registry which to date has enrolled over 400 cases. We felt compelled to demonstrate good oncological control by mandating protocol biopsies at 6 and 24 months. Our two year functional and oncological outcomes have been presented at AUA and published in peer reviewed journals and has set the standard for investigating focal therapy. No men following PGCA developed urinary incontinence or rectal injury and none received pre-treatment ADT. Of the men with no pre-treatment ED, erectile function returned to baseline in 80% and 95% have regained functional erections at two years. No men developed penile shortening, penile curvature or climacturia. Of men with intermediate risk disease, the rates of in-field and out of field CSD recurrence defined as any Gleason pattern 4 is 3% and 14%, respectively. Over a third of these CSD recurrences detected by extensive protocol biopsy were < 0.1 mm of Gleason pattern 4 and are on active surveillance. We hope to provide a 5-year oncological update at AUA 2024. My prediction, focal therapy is here to stay and will be the preferred treatment for selected cases of intermediate risk disease.

To date, I have been a contributing author on 436 peer-reviewed publications. A medical student, resident, fellow or junior faculty are co-authors on the overwhelming majority of these publications. I pursued research at the bench and bedside not for academic advancement but out of curiosity instilled by my mentors Drs. Walsh and Coffey. Today, I am working on the following projects with medical students and residents examining natural history of HGPIN in the modern era of biomarkers and MRFTB; PSA and MRI as a predictor or disease recurrence following PGCA; regret following PGCA, and the 5-year outcomes following PGCA. I hope these projects will inspire the next generation of urologists to contribute to advancing our field.

I will soon celebrate my 30th year as Chair of Urology at NYU Grossman School of Medicine. I am the longest serving Chair at NYU and the longest serving active Chair of Urology in the country. I am truly humbled to have been selected by the CJUI as a legend in urology. Google defines the term living legend as someone who is famous or admired and has done something very well. I presume my contributions over the past 40 years highlighted in this article serves as the basis for my coveted legendary status which is sincerely appreciated and hardly deserved. I am indebted to my mentors, colleagues, trainees, patients and family who contributed to my successes in Urology. It's an honor to share this legendary status with pioneers in Urology who I genuinely admire.

As I enter the twilight of my career, I find myself reflecting on my legacy which will be realized thru the lives I have impacted. The most important contributors to my legacy will be my two children, the 100 urology residents who are my urological progeny and many talented NYU urology faculty whose careers have thrived in a collegial and collaborative environment that valorizes excellence and innovation in patient care, research and education. Like myself, most physicians pursue careers in medicine to serve as healers. I take comfort knowing my legacy will endure thru tens of thousands of men with prostate diseases who entrusted me when they were vulnerable and whose lives were favorably influenced by genuine empathy, astute judgment and surgical skills.

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