# LEGENDS IN UROLOGY

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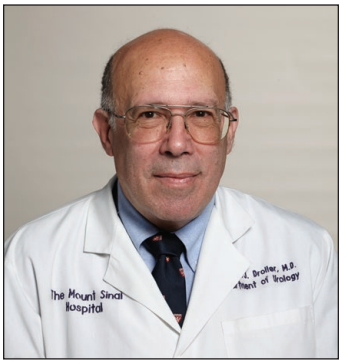


I am the son of immigrant parents from simple backgrounds in Germany who had escaped from the Holocaust in the late 1930s and settled in a middle-class neighborhood in Brooklyn, New York. They lived their everyday lives with honesty and integrity, engraining these values in my younger brother and me as they spoke of the importance of education, an appreciation of a simple, non-materialistic lifestyle, and the responsibility of "giving back" for whatever success we might achieve. Their encouragement that I go into medicine as the embodiment of these values seemed the logical outgrowth.

I attended Stuyvesant, a public high school where the curriculum focused on science. This prepared an early path for me to follow towards an academic medical career. My acceptance then at Harvard extended this path and impacted my life in several ways. It was here that I first met people with a true diversity of experiences, attitudes, concepts and ideas that prompted me to develop an openness and curiosity for new challenges and adventures different from any I had known or imagined. It was also here that I encountered instructors and professors who were not only knowledgeable and creative but highly accomplished and often iconic and therefore especially influential. In my freshman year, Professor George Wald, a future Nobel laureate, taught introductory biology and kindled my appreciation of the life sciences. When he appointed me a laboratory section man in his course during my senior year he inspired me to question basic biologic concepts in the pursuit of deeper knowledge and new ideas. In my junior year Professor Keith Porter taught a course on electron microscopy as applied to cell biology. Impressed with his extensive knowledge, biologic insights, and the fluidity of his lectures and writings, I asked him how he achieved this. His answer that "I think and write, then rethink and rewrite many times again" became a mantra for me in my own future scientific explorations, writing and editing. As I then learned the techniques of electron microscopy the following summer under Dr. Tom Roth, Porter's post-doctoral fellow, I embarked on a research project that would become the focus of my senior thesis. My intensive work on, enthusiasm for, and excitement with this project during my senior year were proximately and ultimately responsible for my commitment to a research career. In this, Tom and Professor Porter became strong role models for my understanding of the importance of honesty and integrity in any work I was later to do.

My acceptance at Harvard Medical School then offered new worlds to explore in which a robust faculty initiated my exposure to medical research and clinical medicine. As my 4 years came to a close, however, I could not decide which direction to pursue. Choosing a medical internship to keep all of my options open, I soon realized how much I preferred the more active life of a surgeon. I applied for a 1st year surgical residency at the Peter Bent Brigham Hospital, remembering how much I had enjoyed my rotation there during medical school. The faculty and my new fellow house officers at the Brigham provided me with a sense of having "returned home". Working under Dr. "Franny" Moore, Chief of Surgery and a truly legendary and inspiring figure, made my overall experience truly memorable. I especially liked my rotations in Transplantation and Urology. The former exposed me to Dr. Joseph Murray, a creative and dynamic surgeon who would go on to win the Nobel Prize in Medicine for his work in transplant immunology and who, in his reserved manner, became a role model as an insightful clinical investigator, a "giving" teacher and a charismatic but humble physician. My urology rotation exposed me to Dr. J. Hartwell Harrison, whose Southern charm and *joie de vivre* were infectious. Overall, the camaraderie between faculty and house staff and the clinical challenges I encountered on these two rotations prompted me to choose urology as the field through which to pursue my academic aspirations.

Looming before me, however, was the war in Vietnam. I was among the many who sought either to defer or avoid active military service. I obtained a position in the US Public Health Service as a Clinical Associate at the National Institutes of Health. My 2 year appointment gave me the opportunity to return to laboratory research during which I studied blood platelet aggregation using electron microscopy and biochemical assays to assess the roles of adenyl cyclase, prostaglandins and cyclic AMP in this process. The feeling of independence, the excitement of discovery, and numerous productive interactions with many creative colleagues provided the intellectual stimulus that cemented my commitment to research.

Now seeking this in a urology residency, I was directed to the urology program at Stanford and Professor Thomas Stamey, known for his groundbreaking work in hypertension and renal function and his tenacious focus on research. I drove across the country anticipating the new challenges and adventures that Stanford and the West Coast would present. However, I did not enjoy the department's new emphasis on urinary infection, did not adjust well in transitioning from the freedom I had enjoyed in my research at the NIH to a resident's restrictive work schedule, and did not acclimate to the West Coast as "home".

Since the second year in the urology program was a research year. I decided to seek a research position in immunology to complement my interest in transplantation and considered returning to Boston. In hearing about these plans, Dr. Stamey asked me to speak with Dr. Jack Remington before I made any decision. Jack Remington was a young, highly energetic, and dynamic investigator at the Palo Alto Medical Research Foundation who was doing immunologic research. Upon meeting him I was greatly impressed with him as an enthusiastic and imaginative investigator and was intrigued by his suggestion that I examine the role of activated macrophages on cell proliferation in bladder cancer. He thus convinced me to stay.

My research year turned out to be important in several ways. First, it directed me towards laboratory research in cancer immunology. Second, it stimulated my clinical interests in bladder cancer. Third, it confirmed my decision to pursue an academic career involving both laboratory and clinical research on urologic cancers. Fourth, the time I now had free of a resident's clinical responsibilities allowed me to expand my life outside of medicine. And fifth, Esther, whom I met at the beginning of this research year and whom I would later marry, introduced me to her Swiss background, the San Francisco Opera, the California wine country, and to her enthusiasm in exploring and appreciating life's opportunities.

My return to the program's final 2 clinical years was made bearable by Esther's encouragement and support. As the end of residency then approached, I mused about taking time off to travel rather than proceed directly to a faculty position. However, Esther suggested that I instead find a research opportunity overseas that would not only provide a base from which to travel but would also allow me to be academically productive. Luck was with me as I found a laboratory at the University of Stockholm that was pursuing studies in immunology and bladder cancer. That Esther had spent nearly 2 years in Stockholm before coming to the States, spoke Swedish fluently and had good friends there who could ease our way into this new adventure made this opportunity perfect for what I was seeking. Moreover, since the WHO Eleanor Roosevelt Cancer Fellowship I received would provide roundtrip travel for me and my "spouse", Esther and I decided to get married. At the time this seemed perfectly logical.

The Department of Immunology at the University of Stockholm was a leading center of immunologic research. Professor Peter Perlmann, Chair of the Department, had discovered antibody-dependent cellular cytotoxicity and led studies by his faculty of researchers and doctoral fellows in various areas in immunology. Nearby institutions were also pursuing immunologic studies in a variety of cancer and non-cancer models. I felt like a veritable sponge in absorbing cutting-edge knowledge in immunology and cancer biology. Immersed in this scientifically robust environment, I discovered the enhancing effects of interferons and the inhibitory effects of prostaglandins on natural killer and antibody-dependent lymphocyte cytotoxicity against bladder cancer cells in vitro.[1,2] I observed that tumor cells themselves produced prostaglandins when exposed to immune effector cells, effectively subverting the immune response being mounted against them. Inhibiting prostaglandin production could therefore enhance cellular cytotoxicity. This could be further enhanced by interferons. I thrilled at these discoveries and was incentivized to take full advantage of the short daylight hours and long winter darkness to spend many hours in the lab, interact closely with research colleagues, and become highly productive in accumulating an abundance of new data and information. Moreover, the location of the lab directly across Lake Brunnsviken in walking distance from the Karolinska Hospital allowed me to attend the weekly urology conferences. This not only kept me current

in clinical urology but was where I first met Professor Lennart Andersson, the then newly appointed Chair of Urology. We would subsequently work together under the auspices of the WHO on the organization of a number of conferences and preparation of several monographs on urologic cancers.

After 7 months of intensive laboratory work, Esther and I started the 6 weeks of travel we had originally planned. I also arranged to present research talks at medical institutions in several of the cities we visited. By the time we returned to Stockholm in mid-April, Spring had finally arrived. We could now take advantage of the better weather and longer daylight hours to explore the North and South of Sweden while I completed the last of my research studies before returning to the States. The year truly fulfilled what we had set out to do both academically and personally. We now were fully ready to begin our new academic life in the States.

Prior to having left Stanford I had accepted an offer by Dr. Patrick Walsh to join his faculty at Johns Hopkins. Pat had recently been appointed Chair of Urology and had already begun to pursue the awesome responsibility of building on the heritage of Hopkins urology. He had recruited Dr. Robert Jeffs and Dr. Fray Marshall, both of whom would become wonderful colleagues and friends. Professor W. W. Scott, the former Chair of the Department and now editor of The Journal of Urology, had created a research environment through his recruitment of Dr. Don Coffey to direct the department's laboratory investigations. Both he and Don were highly supportive as I began to pursue my own research program. Lastly, Dr. Hugh Jewett, known for his pioneering studies in the staging of prostate and bladder cancer, guided my clinical interests in bladder cancer.

Within a relatively short time I was able to resume the work I had begun in Stockholm. I continued studying the enhancing effects of interferons and the inhibitory effects of prostaglandins on natural killer cell activity, but now in a chemically induced animal model of bladder cancer. I also began to develop my clinical understanding of bladder cancer through discussions I had with Dr. Jewett on the outcomes of his patients and through reviews of their pathology with Dr. Joseph Eggleston, a urologic pathologist with whom I correlated clinical outcomes with tumor histology. When Pat suggested that I write a monograph about bladder cancer, I explored the literature to better understand what was known of the disease. This led to the proverbial "eureka" moment.

By way of background, in the 1940s Dr. Jewett had described a staging system for bladder cancer that comprised its sequential development from mucosally confined papillary disease to invasion of the lamina propria, progressive invasion of the muscularis propria, and ultimately invasion into the peri-vesical soft tissue. Each succeeding stage was associated with an increased likelihood of metastasis. Although this model had been widely accepted for decades, it did not completely explain the biologic course and nuances of treatment outcomes I observed in Dr. Jewett's patients and what I discussed with Dr. Eggleston. Moreover, the entity known as carcinoma in situ had not been included in this schema. Originally described in association with muscle invasive disease in the early 1950s, carcinoma in situ had only been factored into the staging system by the WHO in 1974, according to which carcinoma in situ was presumed to initiate the stage-wise clinical progression of disease. To my mind, however, carcinoma in situ as a high-grade lesion could not logically lead to the development of low-grade mucosally confined papillary tumors, the most common form of bladder cancer. I thought it more likely that a low-grade form of carcinoma in situ, though perhaps not histologically recognizable, was the first step in neoplastic transformation in the pathogenesis of low grade papillary mucosally confined disease. In contrast, lamina propria invasive papillary disease and the more deeply muscle invasive papillo-nodular and nodular forms of bladder cancer, all of them high grade lesions, could indeed more logically be viewed as arising from high-grade carcinoma in situ. Moreover, the fact that muscle-invasive cancers often occurred without a prior clinical history of urothelial cancer suggested that they had likely originated from flat high-grade carcinoma in situ that had invaded silently before clinically declaring their presence. These considerations suggested to me the hypothetical existence of separate pathways in the development of these distinct forms of urothelial cancer. I constructed a schema to depict this. Dr. Eggleston thought it not unreasonable. Dr. Jewett simply smiled and said that this schema allowed him to understand the pathogenesis of bladder cancer in his patients more clearly. I am sure that he was only being kind. This schema became the nucleus for the monograph that I published in 1981.[3] Pat then invited me to incorporate these new ideas in the chapter on bladder cancer for the next edition of Cambell's Urology, of which he was editor.[4]

During the next decade, advances in molecular biology led to reports of specific genetic changes in association with different bladder cancer diatheses. I asked Dr. Peter Jones, a molecular biologist whose interests focused on

urothelial cancer, whether these changes might be superimposed on the clinical-pathologic schema of developmental pathways I had described. The correlations we observed seemingly validated this concept. Our publication on this was the forerunner of subsequent studies associating specific chromosomal changes with the development of various forms of bladder cancer.[5]

Meanwhile, Dr. George Prout, Chief of Urology at the Massachusetts General Hospital, and Dr. Gil Friedell, Chief of Pathology at the University of Massachusetts, founded the multidisciplinary "National Bladder Cancer Collaborative Group A" (NBCCGA) to study clinical issues in bladder cancer. I was invited to become a member of this group and participate in their studies. The discussions among group members and their insights undoubtedly influenced my additional thinking on the pathogenesis of different forms of bladder cancer. For example, distinctions in outcomes between superficial and deep muscle invasion could respectively be associated with their more papillary or nodular appearance, their invasion as either "broad front" or "tentacular", and whether or not lymphovascular invasion was present. Furthermore, variable outcomes following identical treatments in presumably identical stages and histologies of muscle invasive bladder cancer suggested heterogeneity in their intrinsic biologic behavior. Such observations allowed me to refine the biologic schema I had proposed.

It was at just about this time that I received an offer to become Chairman of Urology at the Mount Sinai Medical Center in New York. Because I felt myself ready for a change, I accepted Mount Sinai's offer. In part, this was because the recently appointed CEO and President at Mount Sinai was Dr. James Glenn whom I had first met during my residency when he was Visiting Professor at Stanford. I had already become impressed with his dynamism and charisma but became even more so when Jim expressed his vision of developing a more academic presence for Mount Sinai in New York.

The urology program, absent a fulltime faculty, lacked a rigorous educational foundation. Its residency was on probation and in danger of being terminated. In accepting the Chairmanship I assumed that Jim would be supportive and protective of me in instituting the departmental changes we both knew were needed. However, as I began to establish a clinical presence, recruit a fulltime faculty, and address issues in the department's clinical quality, antagonism and resistance from the voluntary attendings, who were a force in the institution, quickly emerged. Within 3 years of my arrival Jim Glenn was suddenly terminated. Without the protection I assumed through his presence, all of my initiatives were now openly challenged. This severely limited support for the Department and my efforts towards its development. Despite this, the clinical growth and academic productivity of the fulltime faculty I recruited allowed us to build an educational foundation for the department, achieve ACGME accreditation for the residency program, and somehow succeed in developing the department's academic reputation.

Moreover, my increasing involvement in regional, national, and international urologic organizations such as The New York Section AUA, the Urology Section of the New York Academy of Medicine, the Urologic Research Society, the Society of Urologic Oncology, and several committees, courses and lectures at the AUA effectively buffered many of the issues and difficulties that I encountered at Mount Sinai in moving the Department forward. In addition, several colleagues offered opportunities that furthered the department's visibility and contributions I was able to make. Dr. Martin Resnick asked me to serve as an Associate Editor of The Journal of Urology, focusing on bladder and kidney cancer. Dr. Darracott Vaughan asked if I would be co-Chair with Dr. Alan Wein of the Bladder Health Council for the newly formed American Foundation for Urologic Diseases (AFUD) and be responsible for its focus on bladder cancer. Dr. Andrew Novick actively supported my election to the Board of Trustees of the American Board of Urology. In addition, Dr. George Prout invited me to be a founding editor of a new journal focused on urologic oncology. When he decided to step down after 5 years as editor, the Publisher asked me to take over the editorship. Each of these responsibilities was challenging, exciting, and ultimately greatly fulfilling. Moreover, I thoroughly enjoyed the stimulating interactions with colleagues that each of these opportunities afforded and the friendships they created.

My life was suddenly disrupted when I was asked to step down as Chair of Urology at Mount Sinai. An attempted merger between Mount Sinai and the NYU School of Medicine had led to significant financial commitments. The merger's breakdown converted these into liabilities. Outside consultants advised a corporate restructuring, part of which involved replacement of sitting Chairs by new Chairs appointed from within, all without a formal search. I was caught in this net.

I could only be grateful that my many outside activities during this difficult time distracted me from the frustration and disappointment I felt and allowed me to maintain a sense of self-worth. In addition, the support of many academic colleagues encouraged my ongoing academic productivity and was critical in sustaining my personal strength.

Among the many events and experiences that have influenced my career, I have generally credited my research fellowship year in Stockholm as instrumental in leading to many of the opportunities I subsequently had. Therefore, when I became President of the New York Section it seemed only natural to choose Stockholm as host city for our annual meeting. Then, 6 weeks before the meeting was to be held 9/11 happened. There were many calls to cancel the meeting. I decided not to.

Thanks to the support of our Swedish colleagues, whose scientific and clinical stature was so strong, and the courage and commitment of those from New York who decided to attend, the meeting was a success. Moreover, holding the meeting in Stockholm allowed for several very meaningful and emotional events: a Swedish children's chorus greeted us with American patriotic songs at the welcoming reception; the Karolinska Hospital raised the American flag at its entrance for the first time in its history as it welcomed us to our scientific meetings; Professor Lennart Andersson hosted a special reception in our honor at the Nobel Museum; and, we received special access to venues that symbolized solidarity with America during this uncertain time. All in all, the affirmation of the professional relationships and friendships we experienced and from which I had personally benefited frequently through the years allowed us not only to bring wonderful memories back with us to the States but to see these grow increasingly strong in the years that followed.

In now looking back on the privilege of having served in leadership positions for several of our organizations, societies, Boards and journals, I am deeply appreciative of the experiences I have enjoyed and the opportunities each has offered me to contribute in some way to their success. My gratitude is deepened for having been able to work with colleagues with many of whom I have developed enduring friendships. Any honors I may have received along the way, which have included Honorary Memberships in the German Urological Society, the Swedish Urological Society, and the International Bladder Cancer Network, an Honorary Degree from the University of Athens, Lifetime Achievement awards and Distinguished Service awards from the International Society of Urology and the AUA, were to some extent likely by-products of the friendships that I shared with so many colleagues in these various groups.

I am also grateful for opportunities to have mentored others in the development of their own academic careers. The significance of being designated a "legend" may ultimately be based on the ability to pass on to others one's ideas and concepts, and then to smooth their path in support of their own career development. Being able to witness the success they may then achieve can become highly gratifying in developing and establishing one's own legacy. I have been fortunate in experiencing this many times.

Lastly, I am grateful to my wife and children for having consistently been so supportive. My wife Esther was my "rock", especially during disappointments I experienced at intervals along the way. My children Miriam and Daniel tolerated my not being there for them as much as they might have wanted. All of these underscore my appreciation for what they sacrificed and what they accepted in my behalf. My gratitude to them knows no bounds.

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