
LEGENDS IN UROLOGY

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I am honored to be asked to write an article for *The Canadian Journal of Urology* about a Legend in Urology, but a bit intimidated about writing about myself. I was born in Brooklyn, NY in 1947 and lived there until I left for college shortly before my 18th birthday. My father was a dentist and my mother stayed at home raising my older brother and myself. I had a very warm and supportive upbringing, with a large extended family and frequent family gatherings. Being a true baby boomer, it is not surprising that I rarely wanted for companionship. There were always relatives or friends available for activities.

I am a product of the New York City public school system, with even my elementary school having 1,000 students and my high school almost 6 times as many. Classrooms were crowded, and occasionally students had to share a desk. Education was not exactly individualized, but like most of my fellow students, I learned how to “survive” in a crowd without withdrawing into anonymity. However this type of school experience also had its limitations, and while I enjoyed most classes, it wasn’t until I left for college at the University of Chicago (UC) that I realized how much pleasure I had in studying almost any subject.

UC was a serious institution with many more graduate, postdoctoral and professional students than undergrads, but professors were inspiring and seemed to take personal interest in every student. This may be a naïve impression, but it has stayed with me. Of course the mid-1960s was also a time of cultural and political change. This permeated UC, and I certainly participated in what might be considered “counter-culture” activities. But most of all, I loved studying almost any field. Debates about philosophers (a friend earnestly once told me that “Kierkegaard got down to the real ‘nitty-gritty’”), architecture’s influence on society, and James Madison’s view on government and society in the Federalist Papers were not only assigned topics for reading or for essays, but were the subjects of late evening conversations.

At UC, I was also exposed to research. I spent time with a Botany professor, Manfred Rudat, defining one of the steps in the endogenous synthesis of a plant growth hormone, gibberillic acid. The opportunity for discovery, even if it was a very small step, made it clear to me that I wanted to do molecular research, and both Professor Rudat and other advisors convinced me that I could do that with a medical career and always have a profession to fall back on if research progress slowed. For a variety of personal reasons, I limited my medical school applications to New York City schools and chose (and was chosen by) New York University (NYU).

Early in my clinical years (M-3) I realized that I really loved surgery – but I also greatly enjoyed patient care and having long-term relationships with patients. These factors, and a wonderful experience on my Urology rotation in my senior year, led me to choose Urology as a career. I did my first two years of general surgery training at NYU/ Bellevue Hospital – but by then I had already decided to enter Urology and had applied to, and been accepted by Stanford University for residency.

The 4 years in Tom Stamey’s program at Stanford were wonderful. It was not only the clinical and surgical experiences I had, but also trying to understand how someone as creative as Dr. Stamey viewed things. The great joy he took in patient care and detailed clinical studies was contagious. After a few brief case reports, my first longer article was written with Dr. Stamey on interstitial cystitis (IC) (an entity I still know little about). We

described the large bladder capacity form of this condition, which accounts for the overwhelming majority of patients with IC, and reported at least some success using a series of intravesical cloropactin instillations (which Dr. Stamey had heard about from a colleague in the United Kingdom) as treatment. Success was modest, but long-term remissions did occur – and we still have limited information about the pathogenesis of this entity or mechanisms of action of cloropactin.

Upon finishing residency, I had a two-year commitment in the Public Health Service (PHS) – which I spent as Chief of Urology at the New Orleans PHS Hospital and as an adjunct faculty member at Tulane University. Both Tulane and the city were very welcoming. My wife, Susan and I love rock ‘n’ roll music and jazz – and of course there’s no place superior to New Orleans for this type of music or for its very unique food.

While in New Orleans, I also met Jean DeKernion, a native Louisianan– during his brief tenure on the Tulane faculty. By then I knew I wanted to have an academic career, and it was Jean who both inspired and convinced me that it should be in Urologic Oncology. Although at that time even in the strongest academic programs, the subspecialization we have today was uncommon (most urologic oncologists treated all cancers), it was obvious that large volumes of patients were required to carry out clinical and translational research. Both of us agreed I also needed fellowship training – mostly to develop research skills, so I joined him at UCLA when my two years in the PHS were completed.

At UCLA, although I was welcomed by the entire department, Dr. DeKernion clearly was my mentor. Very quickly after arriving he had me meet John Fahey, a world renowned immunologist. Dr. Fahey had developed a clinical immunology and immuno-oncology program, which had numerous fellows, and post-doctoral and graduate students taking classes and discussing research projects together. Kohler’s and Milstein’s paper on “hybridomas” – the cells needed to make monoclonal antibodies, had only recently been published, and it was considered a project worthy of NIH funding to generate monoclonal antibodies to tumor associated antigens expressed by specific cancers (with the idea of improving tumor diagnosis, classification, staging, and therapy). Indeed with close mentoring from Drs. Fahey and DeKernion, I generated a few monoclonal antibodies to antigens on human bladder cancer cell lines, learned a host of immunological, molecular and histologic techniques, and wrote and got funded an R01 grant on this topic (appropriately awarded to Drs. Fahey and DeKernion). Moreover, I took a variety of graduate courses, and by the time I was leaving, had redirected my interest to growth factors in cancer. Professor Harvey Hershman’s lab welcomed me to work in this area and I gained enough experience to be able to direct technicians and present at scientific conferences.

After completing two years of fellowship, I finally got my first “real” job, on the faculty of the Urology Division at the University of Wisconsin. I quickly became a busy clinician, but also had my own lab – provided by Paul Carbone, head of the University’s Cancer Center. Additionally, Wisconsin was the epicenter of the Eastern Cooperative Oncology Group (ECOG), also led by Dr. Carbone, who quickly ushered me into the group. In ECOG I met and worked with real stars in Urologic Oncology such as Paul Lange and Dick Williams in Urology, and Larry Einhorn, Pat Loehrer, Donald “Skip” Trump and later George Wilding in Medical Oncology.

Three years after coming to Wisconsin and joining ECOG, I was given the opportunity to write a randomized phase III clinical trial, EST 3886. This study was designed to challenge or confirm the controversial policy (championed by the Mayo Clinic) of starting androgen deprivation therapy (ADT) immediately on men who underwent radical prostatectomy (RP) and had positive lymph nodes, rather than withholding ADT until distant metastases developed (the more widely accepted approach, which was based on the findings of VA studies conducted 15-20 years earlier which indicated that while ADT delayed disease progression, it did not prolong survival). While EST 3886 accrued slowly, survival of men with positive nodes receiving immediate ADT following RP, was far superior to that of men who had ADT withheld until distant metastases developed. The study was published in the *New England Journal of Medicine*, and while initially controversial, has been incorporated into standard care.

My UCLA growth factor mentor, Harvey Hirschman had taught me that the best experiment would answer a specific scientific question “yes or no” – and such is the case for randomized prospective clinical trials. I also learned that randomized phase III clinical trials in surgery with an oncologic endpoint (often survival) take a LONG time to conduct and complete. EST 3886 was approved by the NCI in 1986 and was not completed and published until 1999 (with a later follow up in 2006).

During this time, I maintained a very large surgical practice and continued lab work. I was fortunate enough to get NIH grants including a Program Project (P0-1) in selected methods in human bladder carcinogenesis. I frequently collaborated with Cathy Reznikoff, a cell biologist at Wisconsin who developed an *in vitro* carcinogenesis model using her immortalized “normal” human urothelial cell line, SV-HUC – which is still widely used as non-transformed human urothelial cells in many *in vitro* studies.

I also became convinced that early detection of bladder cancer, by detecting tumors destined to become muscle invading before they had actually done so, would reduce mortality and morbidity from this disease. I carried out large screening studies using home testing with chemical reagent strips for hematuria which strongly supported this hypothesis; but could never secure funding (or convince the NCI) to support a randomized prospective trial, which would be needed to confirm it.

By this time (1995) I had been at Wisconsin for 13 years and felt if I was to become a chairman – now was the time. The opportunity to replace Abraham Cockett at the University of Rochester was coming up (Dr. Cockett had just finished his term as president of the AUA) and I applied for and received the position, assuming the Chairmanship in mid-1995.

My 22 1/2 years as chairman at Rochester has been a continuous learning experience. Our department has grown from 4 full-time adult urologists (including myself), and 2 pediatric urologists to 14 and 3, respectively. We’ve gone from no basic science researchers to 3, and under my successor Jean Joseph’s guidance, growth is continuing in several subspecialties. We now cover 4 hospitals “exclusively” and “share” 2 others, while we only worked in 1 when I arrived. While I no longer do hands on lab work, I collaborate with those who do (Yi Fen Lee, Chawnshang Chang, ShuYuan Yeh, and Hiroshi Miyamoto) on projects related to renal, bladder and prostate cancer.

About 7 years after coming to Rochester, our institution left ECOG and joined the Southwest Oncology Group (SWOG). I was immediately welcomed by the leadership of the SWOG GU Cancer Committee, Dave Crawford and later Ian Thompson (Urology), Nick Vogelzang (Medical Oncology), and Cathy Tangen (Statistics) and was asked to become co-chair of the Renal Cancer subcommittee, a position I continue to hold. Also, I was given the opportunity to design and conduct S 0337, a randomized prospective clinical trial testing immediate post TURBT intravesical gemcitabine versus saline for suspected low-grade urothelial cancer. The impetus for this study was that while a single immediate post TURBT instillation of a variety of chemotherapy agents has been repeatedly shown to be effective, and is part of both AUA and EAU guidelines, very few urologists perform it. This study was strongly positive for patients receiving gemcitabine and has recently been published in the *Journal of the American Medical Association* (JAMA). We are now conducting molecular studies to predict response to gemcitabine, performing a formal cost analysis, and are exploring ways to increase usage of this treatment throughout the country. Because clinical and translational research not only requires insight, but also large clinical volume, I continue to be active in the clinic and the operating room. I also continue to teach residents, medical students and graduate students.

Of course, none of this would have been possible without the enormous love and support of my wife, Susan and our two sons, Ross and James. Their understanding and extreme patience with my activities has been instrumental in my career.

I recently had the great fortune of being named the recipient of the Ramon Guiteras Award by the AUA, which by its own description is its highest honor. At the awards banquet, I said something that I believe deeply, that “we are truly privileged to be able to do things we love to do: teaching, patient care, surgery and clinical and translational research”. As I have throughout my career I intend to do what I advise my residents and younger colleagues: keep asking questions, and utilize the resources and infrastructure available to work with your colleagues to best answer those questions.

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