
LEGENDS IN UROLOGY

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When Gabriel Haas asked me to contribute to “Legends in Urology”, I had just stepped off the podium after giving the Whitmore Lecture at the 2009 meeting of the Society of Urologic Oncology. Surprised at the honor, I thought why me, since I told the story of Al Morales and others whose work led to BCG as successful therapy for superficial bladder cancer. But, recalling words of another legendary Canadian, Sir William Osler, - “in science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs,” I thought why not. Lucky to be at the right place at the right time, I built my professional life in the laboratory, clinics and operating rooms on the triumphs of others, and whatever success I have achieved can be attributed to good people, good luck, hard work, focus, some talent and few brains, in that order. Recalling the journey allows me to highlight important individuals who have made my academic life so rewarding.

I was born in St. Louis, but raised in Northern California. From the deck of our home nestled at the foot of Mt. Tamalpais, I looked across the bay at the campanile on the Berkeley campus, and just to the left, San Quinton Federal Prison. Given the unrest and vagaries of youth in the 1960s, it was anyone’s guess where I would end up. My parents’ strong values prevailed, however, and I made it through the University of California, studying biology and history. Eager to broaden my horizons, I ventured south to attend medical school at the University of California at Irvine, a prescient decision, because I spent summer clerkships fortuitously working with Dr. Roger Barnes, unaware he was a legend in urology. In his own inimitable way, he taught me fundamentals, and seeing what he could do, I knew I would become a urologist. I completed residency at UC Irvine under Dr. Donald Martin, where I received solid urological training. As a chief resident, I had the privilege of operating with Donald Skinner, who taught me thoracoabdominal surgery, kindled my interest in oncology, and encouraged me to pursue a fellowship and an academic career. In 1975, the preeminent urologic oncology fellowship program was in New York at the Memorial Sloan-Kettering Cancer Center (MSKCC) under Dr. Willet Whitmore. During my interview, Dr. Whitmore said the fellowship was becoming so competitive that I was unlikely to be selected for the usual one clinical year, considering I would follow Paul Schellhammer (academic par excellence, later President of the AUA), and Winston Barzell (probably the finest surgeon I ever saw). But if I elected two years to include basic research, my chances would be much better. I became the first two-year Special Fellow in the newly expanded (now 3 years) MSKCC urologic oncology program (Whit knew what he was doing!).

Why urologic oncology? Because it embodies science, medicine, surgery, and intellectual pursuit (I knew someday surgery alone would not sustain my academic interests in urology). Above all, I thought I could make a difference, and I quickly learned at MSKCC that excellent care and clinical investigation go hand in hand; every patient can help answer relevant questions, resulting in changes in medical practice and improving outcomes.

My Fellowship began in the immunology laboratory of Dr. Lloyd Old, a renowned immunologist, with whom I established and maintain a lifelong collaboration. I also attended conferences across the street at Cornell. Dr. Victor Marshall, a giant in urology, conducted grand rounds and was fond of picking on Memorial Fellows. One day, a resident was describing a prostate case, displaying the IVP, when Dr. Marshall called out in his booming southern drawl, “Harry, what y’all think of this case?” (I still hadn’t met him formally, and never learned how he knew my name). Sitting in the back of the room, I answered that I wasn’t concerned about the prostate, but I would remove the cancer in the right kidney (it had been missed by the resident, attending, and radiologist). I must have impressed Dr. Marshall because he became a mentor, appointing me as a Urology Fellow at New York Hospital-Cornell Medical Center, which proved instrumental in support of my laboratory research in tumor immunology.

Working with Lloyd Old, Herb Oettgen, and Mike Bean, I studied immunologic mechanisms in urologic cancer patients, including early vaccine trials, and was exposed to some of the brightest minds in tumor immunology, who regularly visited us at the Sloan-Kettering Institute for Cancer Research to collaborate in experiments. More important, I learned scientific method, developing a sound foundation to design and conduct future clinical research. The high volume surgical experience under Drs. Whitmore, Harry Grabstald, and Pramod Sogani was superb, the very best in oncology. They painstakingly taught my co-Fellows, Rich Macchia (Chairman at SUNY-Downstate), Skip Holden (CaP SURE) and I curative operations for each urologic cancer. I also took time to scrub with general and pelvic oncologic surgeons, to learn their techniques. The multidisciplinary conferences, unique at the time, have never been equaled in depth or substance, as ideas, concepts and treatment strategies were freely questioned, devised and implemented. Each hour spent with each attending was an invaluable learning experience, but Dr. Whitmore provided the guiding principles and sage advice that kept us going, asking for more. Always with an open door and willing to talk, Whit taught me how to ask and answer questions, and to think. I'm sure other Fellows feel the same.

My first decade as an Attending, from 1979 to 1990, can be regarded as a golden era in urology at MSKCC. There was just Dr. Whitmore, Pram and me, later Mike Morse (Saint John). I continued my lab work, but I was swamped with patients, transitioning quickly from Fellow to Attending. Whit and Pram were always there to support us, and owing to being in the right place at the right time, clinical research took off. In 1959, Dr. Old had discovered that BCG inhibited growth of experimental tumors and BCG became widely used against melanoma and other tumors at MSKCC when Morales reported in 1976 that BCG was active against bladder tumors. Poised to confirm Morales' monumental discovery, we conducted three NCI-funded prospective, randomized trials showing that intravesical BCG therapy reduced the frequency of tumor recurrences, delayed tumor progression, and improved survival, and we defined the variables predicting tumor recurrence and progression in patients with superficial bladder cancer. Following our patients for a decade, I noted that some who remained free of tumor in the bladder began to relapse at greater than expected frequency in extravesical urothelial sites, notably the distal ureters or prostate, such relapses increased over time and often proved lethal, negating the beneficial effects BCG had in the bladder. We showed that metachronous urothelial tumors were clonal, and we defined patterns of spread from the bladder into the prostate, changing practice how we followed and evaluated patients with positive urine cytology. BCG studies and salvage regimens against high risk bladder tumors continues unabated today.

Dr. Whitmore impressed upon me the value of doing my own TURs of bladder tumors, and in fact, it was always policy to base treatment on our own evaluations, and not those of others. I was able to document how a restaging TUR improved tumor staging. After two decades integrating restaging TUR into all of our bladder-preservation protocols for non-, minimal and muscle-invasive bladder cancers, restaging TUR, especially for pT1 tumors, has finally been incorporated into practice guidelines for superficial bladder tumors. I also adopted Dr. Whitmore's habit of fulgurating papillary tumors, common practice shortly after the cystoscope was first invented in 1877, but seemingly forgotten by most modern urologists. Control of recurrent papillary tumors using outpatient fulguration is now resurrected as part of mainstream practice.

Another of my mentors was Dr. Alan Yagoda, a genius among medical oncologists. I was still a Fellow, when Alan asked me to help write a long overdue chapter on GU malignancies for an oncology textbook. We holed up in his office one long week end, and with his secretary Isis taking notes, Alan talked, paced, yelled was more like it, but we wrote the chapter, and in the process, I learned the fundamentals of GU oncology and current state-of-the-art from a master. More important, I learned how to think like an oncologist. Alan developed MVAC, the first effective chemotherapy regimen against metastatic bladder cancers in 1983. Because half our patients were still dying of occult metastases, we began to study MVAC as neoadjuvant therapy before cystectomy, as well as to select patients for bladder-sparing surgery. MVAC extended our surgical boundaries, and we showed better survival in patients with unresectable or metastatic bladder cancer by post-chemotherapy surgery, standard practice then and today, but one that was met with considerable opposition when I first presented this concept at a national ASCO meeting.

Even as a Fellow, I never understood why radical nephrectomy was routine practice for small renal tumors, even when the opposite kidney was normal, when historically the rationale for local excision had been established. In 1976, I performed my first elective partial nephrectomy, and predicted detection of small renal tumors would increase owing to increased proliferation of CT scans. Indeed that happened, and partial nephrectomy, amongst considerable criticism, became the operation of choice in my hands for most incidentally discovered renal tumors, later establishing it as an effective alternative to radical nephrectomy, providing comparable local control and 10-year survival.

Although bladder cancer has been my primary focus, I have always been excited about the challenges posed by the other urologic neoplasms. For example, although patients lived for years on antiandrogen therapy for metastatic prostate cancer, they didn't look happy, and Dr. Whitmore had observed that after some had stopped estrogens, they regained their energy (and potency), and their disease did not rapidly progress. With Laurie Klotz (then a Fellow), aiming to preserve survival with better quality of life, we published the first report using intermittent androgen therapy, a novel concept validated in the lab. We were also able to regulate growth of prostate cancer by intermittently inhibiting polyamine biosynthesis, which led to a clinical trial in patients with metastatic prostate cancer. Although it didn't work, it shows that we were trying to bring the lab to the patient; today we call it translational medicine. My interest in the overall well being of prostate cancer patients drove me to team up with psychiatrists Jimmie Holland and Alice Kornblith, founders of the new field of psycho-oncology, and we produced the first quality of life studies in prostate cancer now a fundamentally important field in cancer research worldwide.

MSKCC is known for excellence in testis tumors. Dr. Whitmore pioneered RPLND and Dr. Grabstald was instrumental in the first adjuvant chemotherapy trials. However, the mantra was to treat those patients who need it, and avoid treatment in those who don't. Such thinking led to the first surveillance study for stage I tumors, and in advanced disease, we showed we could surgically salvage selected patients after chemotherapy, even with elevated tumor markers. Both of these advances were initially rejected by the urological community, despite being widely embraced by oncologists. We also made contributions to flow cytometry, cytology, and tumor markers in bladder cancer, fertility in testis tumor, pediatric GU tumors, urachal carcinoma, multimodal treatment of urethral cancer in males and females, epidemiology of urothelial neoplasms, and introduced concepts of earlier cystectomy in BCG-refractory patients and lymph node density applied to bladder cancer. Recent, I became interested in how quality of radical cystectomy and pelvic lymph node dissection impacts outcome of invasive bladder cancer, and showed in analysis of a prospective, multicenter randomized trial involving many surgeons that quality of surgery matters. Measuring surgical quality has now become a subject of intense interest and research, including the lost art –TUR of bladder tumors.

During my early years at MSKCC, urologic oncology was in its infancy, but it emerged and evolved, as a legitimate subspecialty in urology requiring specialized multidisciplinary training. At first there were few of us dedicated to oncology, but by 1984, there were enough of us to found the Society of Urologic Oncology. Although we started small, the SUO flourishes today with 18 recognized fellowship programs (and more to come), and is the recognized source of leadership in urologic oncology. I am proud to be part of it all and privileged to have helped train so many current leaders in urologic oncology, including Jim Montie, Jay Smith, Bart Grossman, Yves Fradet, Laurie Klotz, Peter Carroll, Eric Klein, Ian Thompson, Dave Wood, Joe Presti, Armen Aprikian, Dan Theodorescu, Neil Fleshner, Steve Campbell, Mike Cookson, Sam Chang, Cheryl Lee, Badri Konety, Jim McKiernan, and others, as well as current colleagues Paul Russo, Joel Sheinfeld, Guido Dalbagni, Machele Donat, and Farhang Rabbani. Many other outstanding individuals followed - a virtual who's who for the future of urologic oncology. Each brings unique gifts, they question concepts and decisions, they keep me honest, and I have learned something valuable from each one. Jeff Huffman, for example, taught me ureteroscopy. Fellows are investments for the future, and I pride myself on never refusing to visit them at their institutions, to offer continuing support and see first-hand how well they are doing. Having the privilege of knowing them in their formative years, I can better appreciate and take pleasure in their subsequent triumphs.

I have worked more than 30 years at MSKCC, and I plan to keep at it, one foot rooted in the lab, and the other at patients' bedsides, conducting prospective clinical studies, within context of providing what I hope is optimal individualized cancer care, not an easy task, but one that offers the continued excitement of discovery. I maintain my passion for history, writing articles trying to understand the present and glimpse the future by learning the lessons of the past. Fellows often ask me, what are the keys to academic success? As one who teaches by doing, it is difficult to answer in ideological context, so I resort to quips by the philosopher humorist, Will Rodgers: 'A man learns in two ways, one by reading, and the other by associating with smarter people; Get someone else to blow your horn and the sound will go twice as far; Even if you are on the right tract, you'll get run over if you just sit there.' Taking Mr. Rodgers guiding principles to heart, I keep thinking, reading, expanding my horizons, caring for patients, teaching Fellows, and doing my research. I don't think about stopping, because I'm having too much fun. Maybe that's the real key to success!

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