
LEGENDS IN UROLOGY

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I am honored to be asked to join the impressive list of international experts who have advanced the science and practice of urology. Each experience is unique and yet universal. We are inspired, work hard, and with luck and the help of many, we are privileged to significantly improve the lives of our patients.

Reviewing the biographies, I note that many acknowledge the remarkable academic or scientific contributions of their parents. My parents and grandparents were bright, blue-collar workers and farmers who valued education. Both of my parents had the grades and wanted to go to college but did not have the resources. Dad worked two or more jobs most of the time. In high school on career day, I whimsically chose the medical doctor talk. I was impressed by his words “you don’t have to be that smart to be a doctor, but you do have to be willing to work hard.” I had always worked hard and had saved my \$1.10 an hour wages from the steel and pipe company for college. I had good grades, but bumped them up when my history teacher, Mr. Johnson, illustrated that you could be an egghead and still be cool.

Living in Culver City, I was within biking distance to UCLA. By chance an Alpha Phi Omega friend asked me what my GPA was. “You should apply for early admission” he said, so I did. I was worried after getting a “C” on my first organic chemistry test. The evening before the second exam Dad died suddenly from a pulmonary embolus. He was 40. Our GP came to the house to comfort the family. His kindness strengthened my decision to go into medicine. I was in a daze but took the chemistry exam anyway. I got lucky; the professor threw out our lowest exam grade. Avoiding a “C” let me start UCLA Medical School after 3 years and complete my BA after a year of med school. In retrospect I regret not taking the program that added the PhD with an extra year of research.

I was inspired by the UCLA medical faculty and fascinated by the research. We were able to receive paid summer research fellowships, and I immunized rabbits with melanoma to make antibodies. Willard Goodwin, chairman of Urology, was wise and creative. He brought steroid treatment to prevent kidney transplant rejection, percutaneous nephrostomy, and other innovations to urology, but what impressed me the most was not his brilliance, creativity and humor, but his kindness. During IVP conference at the VA he heard a woman in the hall who was lost and upset. He stopped the discussion and went out to help her. The faculty included the famous JJ Kaufman, Don Skinner, my future mentor and hero Ben Gittes- and Pat Walsh who was there as a resident.

After 7 years at UCLA, it was time for another perspective, so I took a rotating internship at Oregon Health Sciences University that included medicine, OB/GYN, surgery, ortho, neurosurgery, pediatrics, ER, etc. Rotations were 36 hours of in-house call and 12 hours off. One either woke in the hospital or had to go to the hospital. Those were the VietNam days so interns who did not have the Berry Plan were looking at spending the next 2 years in the military. Luck came again. Portland was headquarters for the Indian Health Service. My rotating internship and an NIH fellowship interview with Don Morton of melanoma immunotherapy fame gave me a leg up. I got an Indian Health Service commission and served as medical director of the Colville Indian Reservation. It was a joy to get to use my general practice, pediatrics, surgery and OB/GYN training. During my orientation visit I reduced a dislocated shoulder, using the stocking foot in the armpit method, and on my first workday a nurse came running to my car. “Come quickly, Dr. Lamm, Rosemary had a baby.” Rosemary had an elevated BMI, did not

realize she was pregnant and delivered in the toilet. The baby was successfully resuscitated but died of Sudden Infant Death Syndrome the following year. Times were hard. The reservation was good experience, fulfilled my desire to experience general practice, and convinced me that urology, with the mix of surgery, medicine, hospital and office practice, care of men, women and children was the future for me.

After the prerequisite general surgery year, I matched at UCSD where Ben Gittes was chief. Elwin Fraley, Chair of Urology at Minnesota, was visiting professor during my first year in San Diego. Fraley spoke of his and A.Y. Elliott's electron microscopic finding of C type RNA viral particles in transitional cell carcinoma cells. Gittes had an NIH training grant, and the residents spent the second year doing research. I decided to study bladder cancer and set up a special HEPA filtered room to give the bladder carcinogen FANFT. In 1973, the Western Section meeting was in Honolulu, and I got two papers accepted which paid my way. After the presentations, while relaxing on the beach with Ben Gittes, Dave McCullough, and our wives, Dave said "Don, you are going to study bladder cancer, so why don't you try BCG?" My first thought was that it would be unlikely that a single treatment would work, but it was certainly worth a try.

Lab work often didn't go as expected. I did dozens of parathyroid transplants in rats and never produced a renal stone but switched to a struvite model that demonstrated the efficacy of acetohydroxamic acid. Intralesional injection of the latest BCG cell wall preparation failed to reduce tumor growth. At the time we did not know that prior sensitization is required for non-living mycobacteria. Undaunted and unwilling to accept defeat, we randomized the groups again to repeat BCG and control. Hooray, the second treatment significantly reduced tumor growth. We submitted the work for the AUA resident research award but lost. The paper was rejected by a prestigious cancer journal, slowing its publication in *Investigative Urology* to 1977. The research year and many challenging cases at UCSD resulted in diverse publications: stone disease, transplantation, and pediatric urology with another hero, George Kaplan. I briefly considered private practice but hoped to emulate the professors and practitioners that I held in highest esteem. I gladly accepted an assistant professorship at the University of Texas Health Science Center at San Antonio (UTHSCSA).

UTHSCSA had Audie Murphy VA Hospital across the street, which offered opportunity for research support. I had a lab to continue bladder cancer research, residents, and supportive faculty. The NIH put out an RFA for a controlled randomized clinical trial to confirm Alvaro Morales' 9 patient study showing that intravesical and percutaneous BCG reduced urothelial carcinoma (UC) recurrence. Luckily, they approved two applications, mine and Carl Pinsky's from Memorial Sloan Kettering. Somehow, I got started first, and my paper was selected for presentation at the AUA. I will never forget Alvaro's call after the program came out: "Don, did it work?" Yes, it did, with statistical significance ($p < 0.03$) in 37 randomized patients! Of course, the MSK study with 86 patients was also positive, and later all 3 groups, Morales, Lamm and Herr confirmed the high response rate of BCG in CIS.

Success in the first randomized clinical trial of BCG versus resection alone in patients with stages CIS to T2 who had 3 or more completely-resected tumors within a year set the stage for our multicenter SWOG 8216 study of BCG immunotherapy versus doxorubicin chemotherapy in CIS, Ta and T1. The initial results were amazing. Only 21% of papillary tumors treated with BCG recurred at one year compared with 62% treated with doxorubicin. Long term efficacy was confirmed. As shown in our NEJM article graph, 5 year recurrence-free survival in CIS was 45% with BCG induction and quarterly single maintenance compared with 17% for doxorubicin using the same schedule. When presented to the FDA one reviewer said he was "unimpressed" by the graph, raising my concern that BCG might not be approved. The AUA met shortly thereafter, and many concerned urologists signed my petition for approval of BCG. "Taking time to respond to petitions only takes away time from the approval process," I was told. BCG was initially approved in 1990 for CIS, but not for papillary tumors.

Immunotherapy was new to urology; and optimal management of side effects was still being developed. BCG was understandably slow to gain acceptance. Most considered MMC to be at least as effective and less toxic than BCG. Previous studies failed to show that MMC was significantly better than other chemotherapies, so in SWOG 8795 we compared BCG and MMC using induction and monthly maintenance for both arms. The ethical oversight committee terminated the study early due to the clear superiority of BCG: 23% recurrence with BCG and 34% with

MMC, as published in the then-fledgling *Urologic Oncology*. Randomized studies in Europe that included more lower risk patients and used only 6 week induction BCG failed to show superiority of BCG over MMC.

In SWOG 8795 recurrence of high-grade UC was significantly reduced with BCG, but there were not enough patients with disease progression to show a difference. Studies by Badalament at MSK using monthly maintenance and Hudson at Washington University using quarterly maintenance found no advantage of maintenance over induction. Was maintenance BCG dead? The risk for recurrence of UC is lifelong. Immune stimulation induced by BCG wanes with time. Median time to progression or death in high risk patients is long, over 8 years in SWOG studies. Lymphocytic infiltration of the bladder post BCG decreases markedly by 6 months, and highest risk for recurrence is within the same time period. To reduce early recurrence and extend the duration of immune protection from recurrence in SWOG 8507 we compared induction and induction plus 3-week maintenance at 3 and 6 months, then every 6 months to 3 years. Three week maintenance increased recurrence free survival compared to induction alone by more than 20% ($p < 0.0001$). Disease worsening (T2 or above, cystectomy, systemic chemotherapy etc.) was reduced by 8% ($p < 0.04$) and survival increased by 6% ($p < 0.08$, NS). “Disease worsening” was used because urologists know the risk of persistent CIS and high grade T1 disease and remove the bladder before it is too late, but critics insisted that “BCG only delays and does not prevent progression.” Fortunately, if we consider metastasis and death as progression, the EORTC proved them wrong.

EORTC 30911 compared 3-week maintenance BCG with epirubicin using the same schedule. A total of 837 evaluable patients were followed for 9.2 years. In addition to reducing recurrence ($p < 0.0001$) metastasis was reduced ($p = 0.04$) as well as overall and disease specific mortality ($p = 0.023$). Unexpectedly, the 497 patients with intermediate risk disease had superior protection from progression (HR 0.42; $p = 0.023$ vs. high risk, $n = 332$, HR 0.66; $p = 0.42$) and death (intermediate: HR 0.35, $p = 0.02$ vs. high: HR 0.60, $p = 0.39$). One wonders if these data were considered when BCG shortage recommendations were made to limit BCG to high risk patients. No one asked, but I would recommend 1/3 dose BCG warmed (like a baby bottle) in 1/3 volume (15-17cc) saline for 3-week maintenance in both high and intermediate risk.

I could not have survived or succeeded without the care and support of Wanda, my wife of 57 years and mother of our son and 3 daughters who, despite their father’s neglect, are working to better the world in their own ways. Challenges in practice and research may have increased, but I am inspired by the students, residents and young men and women who bring promise of far greater accomplishments ahead. Now retired, what next? Have you heard that BCG is associated with an up to 80% reduction in Alzheimer’s?

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