LEGENDS IN UROLOGY

Derek Raghavan MBBS (Sydney), MD (Sydney), PhD (London), FRACP, FACP, FASCO, FAAAS
Levine Cancer Institute
Charlotte, North Carolina, USA

"LEGENDS OF UROLOGY WITH WHOM I HAVE WORKED"

I suspect that I probably consumed too much fine wine prior to agreeing to take on the onerous task of self-description for this series. It is gratifying to be included in the fine company of so many long-standing friends. One of the main points of this brief autobiography is that a key feature of my career in urological oncology is that it is predicated on strong personal friendships, and all of my key clinical and scientific outcomes have been associated with work carried out with pals, with those relationships having been maintained continuously for decades.

I was born in Buenos Aires, the son of a diplomat who was posted there at the time. My early days consisted of a series of moves around the world, and I suppose that gave me something of an international view of life and career, and perhaps an ability to create relationships swiftly and easily. Most of my early education was either in U.S. expat or Australian schools. My grandfather had been in medical school in the United Kingdom prior to World War I, served in the army during the war, and returned, believing that he had seen too much bloodshed, and changed careers. I mention it as I think he may have been the early influencer of my desire to be a physician. In addition, my mother was a diagnostic radiographer during WW2, and that may also have been part of the influence to this career. As far back as I can recall, medicine was a calling, intermittently populated with other career aspirations. I completed high school in Australia and completed my tertiary and graduate education at the University of Sydney. Despite my affection for Urology and its participants, I never seriously considered surgery as a career, and perhaps made the mistake of sharing that view with each of my surgical chiefs during my training (I have always been pretty candid, often to my detriment). Despite that, I did have something of a flair for medical politics, and thus was actively involved in the Sydney University Medical Students Society, ending up as its President, and also was the President of the Resident Medical Officers' Association at my training hospital, Royal Prince Alfred Hospital, in Sydney. I guess that taught me the art of negotiation, which is so important for a clinical trial leader. After training in Internal Medicine, I had planned a career in Clinical Immunology, hoping to fuse my interests in science and clinical medicine. However, it happened that the first Professor of Cancer Medicine at the University of Sydney, Martin Tattersall, was appointed at that time, relocating from the United Kingdom, and I was seconded to Oncology to "show him the ropes" at an Australian teaching hospital. It took very little time for me to recognize that this was the career that I had sought, allowing me to practice old-style patient-focused clinical medicine, while maintaining a commitment to clinical and experimental research. After initial clinical training with Martin Tattersall and Richard Fox (a scion of Australian translational oncology), I was awarded a traveling fellowship to the Royal Marsden Hospital and Ludwig Institute for Cancer Research. Under the tutelage of Professors Munro Neville and Sir Michael Peckham, I learned about radiation oncology, experimental pathology, genitourinary cancer, and moved on to complete a PhD with Munro and Dr. Eadie Heyderman in experimental pathology of germ cell tumors. At a conference in the UK, I met Paul Lange, then a young Turk and Associate Professor of Urology at the University of Minnesota, who invited me to a post-doctoral clinical and lab fellowship with Elwin Fraley, BJ Kennedy, Bob Vessela and him – with further exposure to sublime management of testicular cancer, as well as a shared office with Nick Vogelzang with whom I published on prognostic factors and therapy of germ cell tumors. I returned to the University of Sydney and Royal Prince Alfred Hospital, taking on roles as Staff Oncologist and Research Director of the Urological Cancer Research Unit, and came to know so many fine Aussie urologists – Bruce Pearson, John Rogers,

Bob Wines, and so many other legends of the Australian urology scene, and helped in the evolution of many of the leaders of current Australian Urology – in fact Mark Frydenberg (now Chairman at the University of Melbourne) spent a year in my lab. Clinically I was one of the first Australian medical oncologists to show formal interest in genitourinary oncology, and thus was viewed as something of an oddity by my medical oncology colleagues (not much has changed), but also with some affection by the Aussie urologists, who pretty much adopted me, accorded me membership in the Urological Society of Australasia, and supported me in my research and clinical trials. It was a great model that we developed together, largely through the influence of the afore-mentioned Pearson, Rogers, Wines and many others. One defining aspect was the recognition that a group of motivated urologists in private practice could work effectively with academic clinicians to complete important research projects – and these included some of the first studies of neoadjuvant therapy of bladder cancer, phase II and III trials of novel therapeutics in prostate cancer, and randomized clinical trials addressing optimal therapy of metastatic germ cell tumors. Two important studies that I helped to lead as Australian PI focused on validation of bleomycin (PVB vs. PV) for germ cell tumors, and we helped to complete the study that proved superiority of MVAC to cisplatin for metastatic bladder cancer. That was the time when the redoubtable Pat Loehrer and Larry Einhorn became life-long friends and colleagues. In parallel, I was fortunate also to be the Aussie on the writing committee for the international neoadjuvant CMV randomized trial, led by the EORTC, and first came to know Ian Tannock as a kindred spirit in rational investigation and treatment of genitourinary cancer. I felt lucky to be part of two major international studies that defined the role of neoadjuvant treatment of bladder cancer, having published one of the first neoadjuvant single agent platinum studies years earlier. Around that time, I hired Dr. Pam Russell to run my laboratory and we identified a bladder cancer stem cell, and completed some of the early molecular and novel preclinical therapeutic studies of bladder and prostate cancer, including the molecular characterization of small cell anaplastic prostate cancer. We showed activity of cisplatin and other platinum analogs against xenografts and cell lines of bladder cancer, publishing the data in *Cancer Research* in the early 1980s. Our neoadjuvant bladder cancer studies attracted attention after publication in *Journal of Urology* (1985), and at a series of bladder cancer meetings, I developed lasting relationships with Mark Soloway, Jerry Richie, Bill Shipley and Marc Garnick, often speaking together on panels in the days where a small number of us were recycled regularly at GU meetings. Perhaps one of our more impactful papers was published in *New England Journal of Medicine*, focusing on the biology and management of bladder cancer, and managing to get Richie and Shipley to sign off on a set of unifying concepts!

I focused on uro-oncology but still maintained a clinical and research presence in general oncology, and published on thoracic malignancy and experimental therapeutics. In my spare time, I was active in the Royal Australian College of Physicians, and took on several interesting roles including Chairmanship of the Specialist Advisory Committee in Medical Oncology (the professional standards and training committee in medical oncology). One of my more interesting roles was as RACP representative on the Medical Tribunal, which gave me a relatively unique view of the failings of attorneys and the law. I always retained some interest in medical politics, and was active in the Medical Oncology Group of Australia, finishing up as Chairman.

In my mid-thirties, I was commuting between the Australia and the USA too often, and decided that it would be a good time to expand my research funding and opportunities with a sojourn in the USA, and reluctantly left my family, base and friends to take up a new role as Chair of Solid Tumor Oncology and Investigational Therapeutics at Roswell Park Cancer Institute in 1991. I had been offered a role as replacement for Alan Yagoda at MSKI, but did not wish to live in NYC, and an acquaintance from Minnesota, Clara Bloomfield, recruited me to the new role in Buffalo, NY. I had the chance to work with Bob Huben, Chair of Urology, but failed to convince him to stop smoking, with a very sad outcome some years later. That was the time when I first collaborated with Gabe Haas, then Chair of Urology at Syracuse. I re-established my lab program, with Dorothy Glaves Rapp as senior scientist, focusing again on novel therapies of bladder cancer in preclinical models, helping to develop some of the current agents in use for noninvasive bladder cancer. I spent some time leading the medical oncology arm of the GU committee of RTOG and was able to work more closely with Bill Shipley and participate in some innovative chemoradiation trials. That was also the time when we developed a large genitourinary cancer practice and were able to join Walt Stadler, Don Kaufman and Mike Carducci in developing gemcitabine for advanced bladder cancer. I was also President of the Medical Staff at Roswell Park, and in that role became involved in a complicated tug of war between the Administration and the Department of Medicine, which eventually led to the departure of many key clinical and translational leaders from the Institute, including Clara Bloomfield and me.

Just at that time, Peter Jones, director of the Norris Cancer Center, another good friend from the bladder cancer lecture circuit, and his team recruited me to lead Medical Oncology at the University of Southern California, giving me arguably one of the best opportunities of my uro-oncology life – viz. the chance to work with Don Skinner, John Stein, Eila Skinner, Gary Lieskovsky, Stu Boyd, Richard Cote, Ron Ross, Oscar Streeter, Peter Nichols, Bill Boswell, Dave Quinn and Peter Jones. What an amazing team and time – Skinner remains a close pal, and as a surprisingly shy chap, would often sneak off with me to a quiet dinner during AUA and other meetings and scheme on our next set of studies together. Having worked with so many fabulous surgical and intellectual talents, Don is still on my pedestal as the best urological surgeon in the world at that time. I still believe that John Stein, but for his tragically early death, would eventually have taken on that mantle. Don isn't playing golf these days, but still reads voraciously, adjacent to the Riviera Golf Club, and we are still in touch from time to time. We held weekly Grand Rounds together, and I still marvel at the memory of the extraordinary clinical outcomes that our teams achieved together – the *Journal of Clinical Oncology* paper on radical cystectomy outcomes, with John Stein as lead author, remains a classic more than 20 years later. While at USC, I joined the SWOG GU Committee, ending up as "Crusty" (or E. David…. what did the E stand for?) Crawford's Vice Chair, and we really did some extraordinary work as a team. One of the best conceptual studies that didn't actually work out was designed by Richard Cote, based on work done at USC, that led to the randomized P53 trial – with the hypothesis that P53 mutation predicted for outcome in the natural history of bladder cancer but also connoted for responsiveness to the MVAC regimen. The GU Committee had modern luminaries like Bart Grossman, Ian Thompson, Danny Petrylak, Maha Hussain (who still has extraordinary earrings), and the work of that time truly changed multiple paradigms of genitourinary cancer treatment. I worked a great deal with the g-u crew at the U of Michigan, and they were kind enough to accord me the university's Frank Moran Award, which meant a great deal to me. We also developed an international steering committee focused on advanced bladder cancer and did the heavy lifting to convince the US government to allow collaboration of SWOG with the EORTC, generating the MVAC versus gemcitabine-cisplatin-paclitaxel in cahoots with Joaquim Bellmunt and Cora Sternberg; a cool concept that didn't really provide any big advance. That was also a time when I was invited to serve on the Oncology Drug Advisory Committee of the FDA, and really came to understand their great work, but also the strengths and limitations of various pharmaceutical companies. I always thought it a bit unfair that my nickname on that committee was "Dr. No"!!!

The next key event in my anthology is that Fred Loop MD, an amazing thoracic surgeon and CEO of the Cleveland Clinic, flew to Los Angeles to recruit me to lead the Taussig Cancer Institute. A compelling and visionary cardiac surgeon, Fred led me to see the opportunities, and I felt it was a good time to use my experience to shape a translational research center at this extraordinary medical facility. I recruited many faculty, was able to take the center to NCI designation by incorporating it with the Case Comprehensive Cancer Center, and moved it up to single digit ranking in *US News and World Report*. Our clinical medicine and science were strong, and I had the chance to work with Andy Novick, Eric Klein, Ron Bukowski, Rob Dreicer, Skip Heston and another set of gifted contributors to the GU oncology world. As an institute director, this was the first time that I had to learn to take a large step back from trying to lead trials and initiatives, and instead to take on a role that provided institutional support and resources, with advice and oversight, and it took a while to learn to retire from the lecturing "circuit". I hope that my experience was helpful in encouraging a broad volume of work and publication on the various genitourinary (and other) cancers, and irrespective of that, it was a highly productive time for concept development and trial accrual in all these domains. That said, I still managed to find time to explore the prognostic and predictive significance circulating tumor cells in prostate cancer with Howie Scher, and published our data in *Clinical Cancer Research*.

In the most recent phase of my career, I accepted an offer to create a new institute from ground zero in 2011 at Carolinas HealthCare System (now Atrium Health) in Charlotte, NC. Since then, we have recruited 150 clinicians and scientists who work at around 25 sites in North Carolina and South Carolina, and have built more than 500,000 square feet of cancer center space in Charlotte, and added space at many new office- and hospital- based centers. Each year, we enter between 1000-2000 patients into clinical and translational trials, and serve more than 60,000 people in outreach, education and screening studies. Drs. Pete Clark (Chair of Urology and a former Skinner protege) and Earle Burgess (a Bruce Roth trained medical oncologist) lead our genitourinary program and have innovated in molecular prognostication and prediction and new drug development. Both Earle and Pete are established and rising stars of the future, and their work on defining the importance of molecular profiling of metastatic bladder

cancer deposits (rather than relying only on the primary tumor) will eventually be paradigm shifting when the rest of the world catches up with their published data. Earle's ENZADA study, a complex chemo-hormonal regimen for advanced prostate cancer, has produced some of the best clinical data that I have seen in my career. Although this script is for a Urology journal, I still dabble occasionally in thoracic oncology, and developed the first mobile low dose CT body scanning unit in the USA, and have shown it to be a highly effective tool for finding early, and potentially curable, lung cancers in lower socio-economic populations in the smoking belt.

As I look back on my career, I sometimes wonder about legacy. Certainly the work on neoadjuvant treatment of bladder cancer, helping with the development of gemcitabine for metastatic bladder cancer, trials that may have changed the treatment of locally advanced and metastatic prostate cancer and the development of mobile screening for lung cancer for under-served populations have been of benefit to our patients and have led to altered paradigms of treatment. However, I think my training programs, focusing on maintaining careful clinical care interspersed with science, may have the most long-term impact, in that I have had a role in the training or faculty evolution of so many superb current luminaries in oncology and uro-oncology. I have watched them developing programs of even stronger caliber for the future. With that legacy, such as it is, medicine remains in safe hands.

When I eventually cease my professional career, the essence of who I am will remain unchanged – its fundamental structure is predicated on my family. I have been married twice, to Patricia for 25 years (a move to Cleveland was a final deal-breaker), and to Judy for the past 13, and both have made all the sacrifices so well known to characterize the lives of the partners of academic clinicians, while often being gracious hosts to the friends described above. My daughters, sons-in-law, and grandchildren have had less time with me than perhaps was optimal, but have never been ignored and (I believe) have always been taught, supported and appreciated to the maximum, and they all have respected and understood why those who read this journal do what they do.

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