LEGENDS IN UROLOGY

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When asked by The Canadian Journal of Urology to tell "my story" for the Legends in Urology section of this journal, I was of course flattered, surprised, and reminded that though I am seemingly the same person I was years ago, I am trapped in a still well-functioning body that nevertheless is 70 years old according to my birth certificate. I echo many of the "old" (and more qualified) "legends" that have preceded me: I am by almost every definition not a "legend." Yet this mistaken selection does give me an opportunity to say a little about my career, in order to convey what I think I have learned during this long tenure in academia, and then end with some speculations about urology's future.

I have chosen not to recount the details of my professional journey; they have been previously published.[1] Briefly, I began my post medical school laboratory and clinical training at NIH and Duke, intent on a career in CV surgery. My switch to urology was based on many reasons, but the most pertinent one was that I saw urology as being more conducive to an enduring career in academic surgery and laboratory research. Thanks in large part to the encouragement of Dave Paulson, soon to be the Chief of Urology at Duke, I transferred to the University of Minnesota under the direction of a new chair, Elwin Fraley. Dr. Paulson had previously worked with Dr. Fraley for 3 years at NIH. At the University of Minnesota, I was privileged to work in the laboratory of Dr. Tom Hakala and took over that lab when he moved to become chair of the University of Pittsburg. Soon after, I began an association with a tumor biologist, Robert Vessella, PhD, that now has lasted over 32 years. Increasingly, under his direction, the laboratory endured and flourished. We were fortunate to be continuously federally funded throughout this time. As I will explain subsequently, almost all of the "advances" that I was involved in were directly or indirectly due to this association.

I learned so much from Dr. Fraley; his mentorship was extensive and long; I will be forever grateful for what I gained from this association. Dr. Hakala was also very influential, as were many of the other trainees during this period (e.g., Bill DeWolf, Ricardo Gonzalez, Arthur Smith, Dick Williams, and Ralph Clayman) who then went on to much more stellar careers in academic urology. There was a spirit there that can only be incompletely described: a conviction that academic life was a laudable goal; that hard work, vigorous clinical training, and concentrated research exposure would almost always produce meaningful success; a disrespect for the status quo; and a celebration of curiosity. After 15 years in Minnesota, Dr. Vessella, the laboratory, and I moved to Seattle where I served as Chair of Urology for almost 20 years. During that time we trained a significant number of people who have (or had) notable academic careers. Currently I direct the Institute for Prostate Cancer Research, an affiliation of the University of Washington and the Fred Hutchinson Cancer Research Center.

At the risk of self-aggrandizement, tedium, or false memory, I need to briefly list some of the primarily clinical activities that I was privileged to be associated with, which might be labeled as "advances". I have chosen not to detail these activities or explain exactly how I became involved in them. Rather, I will briefly list them to legitimize some things that I think I've learned about academic urology and to validate some of my observations about its future, especially urologic oncology.

1) A variety of initial observations about the usages of ASF and hCG in testis tumor. That led to several early observations about nerve sparing radical retroperitoneal lymphadenectomy.
2) Early experiences with radiation therapy as adjuvant and salvage after radical prostatectomy.
3) Early observations about the value of PSA for screening and monitoring after initial therapies.
4) Observations about the prevalence of persistent disease in the pelvic area (e.g., prostatic fossae) in patients who had elevated PSA after radical prostatectomy.

5) Initial observations that the mode of onset of bladder cancer that required cystectomy was usually advanced at entry, thus stimulating renewed thinking about bladder cancer screening. This refocus possibly galvanized the development of molecular urinary markers.
6) The initial development of endourology, which took place at the University of Minnesota, though I must hasten to add that much of the advances were due to others, especially Arthur Smith and Ralph Clayman.

Throughout the years, Dr. Vessella and I (as time would permit) continued to work on many areas in the laboratory, especially in the field of tumor immunology and later, tumor biology. While most of these activities did not reach the level of familiar clinical applications, some are getting close, and accordingly they add to the "story" I wish to tell. These include:

7) Observations about molecular markers of circulating prostate cancer cells initially with PSA RT-PCR and later actual circulating and disseminated tumor cells. These observations have added important evidence to the phenomenon of "dormant cancer" and to the hypothesis that the dissemination of tumor cells to distant sites (e.g., bone marrow) is an early event.
8) Persistent (> 20 year) efforts in developing animal models for prostate cancer, including the use of rapid autopsies to obtain relevant tissue, resulting in the development of the LuCaP-xenograft collection, which is proving very valuable in testing biological hypotheses and new therapeutic agents. These resources, together with a rigorous effort in patient-material collection, helped attract many talented investigators to our prostate cancer research environment.

So what have I learned during the course of these activities?

For many years I called these activities "accidents of good fortune." But now as I reflect back on my story, and more importantly the stories of many others who deserve the accolade of surgeon scientist, I realize that these were no accidents, but rather, they were the result of a mind prepared by research experience and the interchange between bedside and bench side. For example, our work on the clinical value of serum markers for testicular cancer (e.g., AFP and HCG) and for prostate cancer (e.g., PSA) could not have occurred without a laboratory and serum and tissue banks that were the "spin offs" from our work (then cutting edge but now largely outdated) in tumor immunology. These tumor-marker studies led to other more technical observations: in testicular cancer, they led to nerve sparing retroperitoneal lymph node dissection for nonseminomatous germ cell tumors, and in prostate cancer, they led to experiences with adjuvant and salvage radiation therapy and to doing needle biopsy of the anastomotic area after radical prostatectomy. Our work on blood-group antigen expression in bladder cancer ultimately did not prove that these were clinically useful as markers. But this work directly led to then unique observations about the onset of muscle invasive disease, and debatably, also led to greater efforts to look for other molecular markers for that disease.

While most of us entered medicine and specifically urology in order to be involved in patient care, an academic career also requires successful participation in research along with teaching. I have found that academic pathway immensely rich and satisfying. And it is important, for we are, especially now, one generation from ignorance and two from obsolescence. Yet such a career is not for everyone. These individuals usually must demonstrate above-average abilities in completing the gauntlet of training including its technical, intellectual, endurance, and social-interaction benchmarks. This is not to diminish the importance and demands of private practice. Furthermore, the academic career is best suited not necessarily for those whose ambitions are inclined to power, doing the "big cases," or achieving fame, but really for those who are curious and want to be around the world of ideas. I have met many exceptionally capable residents who were genuinely NOT interested in ideas. I am suspicious of those who claim they want to pursue an academic career because they like to teach. Almost everyone thinks (and in interviews, claims) they like teaching. But whether they truly like it and whether that becomes their primary passion is something that develops after many years.

It is also useful to have the personality (and confidence) to be attracted to the notion that embarking on an academic career sometimes offers opportunities for some discoveries, but more often offers a chance to fail. To some this increased chance of failure, over and against what might be envisioned in purely clinical practice, is a cause for fear rather than excitement. Similarly, the academically inclined should not be strongly motivated by the accumulation of wealth or material goods.

It is my belief that one can succeed in becoming both an excellent clinician, especially if the area of expertise is restricted (e.g., urologic oncology), and a successful and enduring researcher; but not all at once. Today, besides excellent clinical training (which will usually involve fellowship training), one must be involved in research activity

almost full time for at least a year or two and then at least 40% of the time for an additional period of up to 5 years. During this process, the aspiring surgeon scientist should establish a solid association with a research partner (such as a PhD.) or a laboratory partner who then assumes more responsibility for the day-to-day operations of the lab, as the surgeon scientist's clinical activity grows. But this passing of the operational baton should never mean the lack of presence or translational influence in decision making. Also, surgeon scientists should always maintain their special access to patient materials as one of their "entrance passes" into the arena of research legitimacy. This latter requirement is especially vital now with the increasing trend to centralize the acquisition and storage of patient materials. What is most important to convey is that with persistence and a mind alerted by research training, scientific insights are usually forthcoming, though often they are initially called serendipitous and usually they are in areas removed from the subject of the research training.

So what does the future hold? There are those who paint a bleak picture. Currently, federal research funding is very hard to obtain and maintain. Appropriate improvements in the governance of patient rights are leading to an inevitable "bodyguard of rules," which is becoming difficult, expensive, and some would say suffocating to the investigator engaged in translational research. For a variety of reasons, many embarking on the career of physician view it as a job rather than a way of life. There is a tendency for the aspiring surgeon scientist to train and function in so-called "dry labs" and exclusively follow the outcomes, epidemiology, or clinical trial pathways, and we need to be reminded of the significant contribution to knowledge that this area has made. But I worry about the stampede of aspiring surgeon scientists into this field, because it appears the easier road to success. It is becoming overcrowded, and it mostly answers the questions of where we were and where we are, rather than where we are going. Also, I think wet lab knowledge by surgeon scientists is essential for an optimal translational research environment. Finally, there is the concern that urologists, especially in some subspecialties (e.g., urologic oncology) will become merely "proceduralists." I have previously commented on the dangers associated with this trend.[2] Ultimately, the manipulative arts will always become progressively trivialized; it's the cognitive arts that increasingly in medicine will reign supreme. If we do not heed this wisdom, urology will become marginalized.

Despite the aforementioned pessimism, a life of clinical care and research (e.g., the academic life) has been and will continue to be richly rewarding, feasible, and productive. The explosion of biological knowledge and technology is almost astronomical. Thus the ability to do heretofore-sophisticated things will become almost a simple lab test; things like northern blots, or PCRs, or searching in human tissue for a gene or protein that was just elucidated in a worm, or doing affordable complete genome sequencing. And it will soon be simple to convert a phenotype into a genotype, be it from populations of cancer families, groups of patients with unique responses to therapy, or other traits that previously were thought to be polymorphisms unrelated to a disease. The bed-bench-bed-marketplace traffic has never been greater. I tell my residents I would gladly relinquish all my articles and accolades to start over again.

Thus the physician scientist will not fade, and research funding will improve, for who will select and bring the cornucopia of wonderful opportunities that modern biology is producing, to the bedside? And neither should the surgeon scientist fade because they have a unique perspective into the patient. For example, with cancer, they see and feel the tumor, caress the organ, and experience all those other intangibles that when imprinted on a mind alerted to the technological opportunities and concepts of the new biology, result in creative and useful insights.

In closing, let me say that I have been extremely fortunate to have had the mentors, opportunities, and luck that resulted in such an exciting and rewarding medical career. Yet in looking back, perhaps predictably, what I have come to value the most about my journey is the opportunity to watch the development and success of the people I helped train. The timeless aphorism is more true than not: "The true meaning of life is to plant a tree, under whose shade you do not expect to sit!"

1. Lange PH. Genitourinary oncology and it's surgeon scientist: triumphant past, but does it have a future? *Urol Oncol* 2007;25(1):2-10.
2. Lange PH. The future of urologic oncology: proceduralists or continued primary physicians and leaders. Editorial. *J Urol* 2008;179:2085-2086.

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