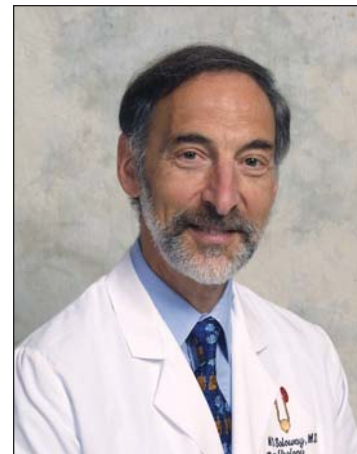

LEGENDS IN UROLOGY

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Naturally, I was flattered and a little captivated by the notion that anyone would be interested in reading about my academic career--nothing of which I felt was extraordinary enough to deserve the moniker of "legend". The word "legend" can be somewhat off-putting. For me, Miles Davis, the great jazz artist, summed it up perfectly saying, "A legend is an old man with a cane known for what he used to do. I'm still doing it!" Although a "seasoned" urologist, I'd like to think that I still have the potential to work on "doing it", too.

If I had been a more political soul, I might have developed a strategy about the best ways to achieve success. But I was a simple boy from the Midwest and it was by serendipity that I was presented with extraordinary opportunities that would soon redefine my notion of what it was to be a physician. Looking back over the forty plus years since I entered medical school, it was chance, extraordinary mentors and collaborators, and my own commitment to work hard to explore the possibilities in myself and others that have guided my choices.

In the summer of 1965, required by medical school at Case Western Reserve to begin two years of a summer research project, I elected to work in the basic science laboratory of a neurosurgeon, Dr. Robert White. Definitely the neophyte in the laboratory, I was quickly engulfed in the frenetic pace and lost in the cerebral blood flow of stroked dogs and "transplanted" monkey brains. Dr. White was charismatic and, although a bit eccentric, he infused me with an excitement about the possibilities of changing the face of medical practice through research. Indeed after my work was published. I was smitten with the world of translational research and with the camaraderie of working as a member of a research team that focused on cutting-edge patient care by applying laboratory findings to the clinical setting. It was the first of many experiences where chance and extraordinary mentorship influenced my journey.

Fast-forward to 1969 and the Viet Nam era. My choices were limited as I finished my general surgical years: either a MASH unit or the prospect, if I were lucky enough, of being a yellow beret in the trenches of the Surgical Branch of the National Cancer Institute. Thanks to the hand of fate, and the wisdom and support of Jean de Kernion, I found myself in Bethesda for two incredible years as a clinical fellow.

By the second year of general surgery (1971-72) I had decided that I was going to be a urologist and consequently was assigned to work with a urologist on staff, George Myers, and "Voila", my interest in bladder cancer began.

For today's residents, what I am about to share may appear representative of the Prehistoric Age of Urology. Forty-five years ago we knew quite a bit less about many aspects of bladder cancer. For example, clinicians had suggested that following transurethral tumor resection, the resultant denuded surface might prove to be more receptive to tumor implantation than normal urothelium. I knew that in order to examine this hypothesis as well as screen new chemotherapeutic agents given intravesically or systemically, it was critical to develop a suitable animal model for bladder cancer.

There were a handful of models in the early 70's that had suggested an incidence of spontaneous bladder tumors. Since my time frame was limited, I searched for a carcinogen induced bladder cancer murine model that might

simulate human tumors most commonly induced by cigarette smoking. I chose the FANFT [N-[4-(5-nitro-2-furyl)-2-thiazolyl]] model. What made this model more superior than the handful of models being advanced at that time? There were four major characteristics of the model that were most attractive: 1) that almost all the tumors that matured were transitional cell and resembled the human bladder tumor grossly and histologically; 2) the primary tumors could be transplanted to syngeneic mice; 3) the transplanted tumors had reproducible growth rates that changed little over transplant generations.; and 4) the transplants were likely to retain their histological appearance after many generations (Urology 4:63-68,1974).

Once I established that the model was viable in the laboratory and had created tumors that could be transplanted, I sought to determine whether transitional carcinoma cells could adhere and progressively grow on either normal or altered bladder urothelium. To examine this, I placed viable tumor cells within a murine bladder that had its epithelium altered by cauterization using a tiny electrode placed transurethrally in female mice, similar to tumor fulguration in humans. I found that the traumatized surface was receptive to implantation and progressive growth of the tumor cells suggesting that some local recurrences in humans were likely resulting from “seeding” of viable tumor cells following endoscopic tumor resection. An identical single cell suspension of transplantable TCC placed in a normal bladder rarely lead to tumor implantation. Using this implantation technique of transplanting transitional tumor cells directly on the denuded bladder urothelium, we were then able to evaluate the effectiveness of various antineoplastic agents placed in the bladder (Cancer Res (part 2) 2918-2929, 1977; Cancer 46:1158-1163,1980).

Following my fellowship at the NCI, I returned to Case Western Reserve for my urology residency. Even though my clinical responsibilities were demanding, I felt I had to seize the opportunity I had been given at the NCI and continue to study the potential of the animal model we had developed. Along with my chief resident, a fellow NCI graduate, Jean de Kernion, we applied for an NIH grant. Although our initial grant proposal was rejected, we were ultimately supported by funding from the NCI, and over the next 15 years, first in Cleveland and then in Memphis, Tennessee, I was able to prove the merit of the animal tumor model in studying the efficacy of intravesical and systemic chemotherapy for the treatment of bladder cancer.

One of our first studies was designed to evaluate whether irrigation of the bladder with distilled water would alter the incidence of tumor implantation. There were urologists who thought that tumor cells floating in the bladder at the time of resection would be lysed by a hypotonic irrigating method, thus obviating the need for intravesical chemotherapy. Using our model, we found that the incidence of implantation and subsequent growth of tumor was high in all the groups and there was no difference whether the bladders were irrigated with water or not. The next step was to test the efficacy of thio-tepa, a chemotherapeutic agent occasionally used intravesically. Despite the reports that thio-tepa had shown a reduction in the rate of recurrence compared with no treatment, there had been few randomized clinical trials testing its effectiveness and, therefore, it was not routinely used. In our animal model, we were able to demonstrate that thio-tepa was capable of reducing the incidence of tumor cell implantation as well as the size of the tumors that did implant and grow (Cancer 45:870-875,1980). Some years later, we were able to show in our animal model that Mitomycin C (MMC) was equally effective and did not have the risk of myelosuppression like thio-tepa. It took nearly 15 years before a large prospective randomized trial proved our animal result. Now post-TUR intravesical chemotherapy is a widely accepted guideline. What has made these undertakings so worthwhile is that our laboratory studies not only offered a research model to investigate modalities to prevent further tumor cell implantation but also suggested clinical implications for treatment.

The MBT-2 transplantable mouse model offered another avenue to study the effect of chemotherapeutic agents. The MBT-2 tumor was a poorly differentiated transitional cell carcinoma and had been proven to retain its histological characteristics throughout serial transplantation in syngeneic mice. Consequently, we now had a primary and transplantable tumor model that could help us evaluate systemic chemotherapy for bladder cancer.

Again fate stepped in to give me a little boost. A new drug, cisdiaminedichloroplatinum II (DDP) had been developed by a researcher at Michigan State University, Barnett Rosenberg. Randy Johnson, a PhD pharmacologist at the NCI was looking at its efficacy in the L1210 leukemia model. He offered the drug for evaluation in my model but said very candidly that he was quite sure the drug would never make it to the clinic because of its nephrotoxicity (later obviated by a mannitol-induced diuresis).

Both at the NCI and in Cleveland, I had hundreds of mice ingesting FANFT. Thus, I accepted his offer and began studying DDP in both the transplantable and primary animal models as a single agent and in combination with other agents. It was soon evident that DDP had impressive antitumor activity in urothelial cancer. Now 30 years later cisplatin is still the most effective single agent for urothelial cancer.

During this era, there was a growing number of investigators who supported the use of radiation therapy as a bladder preservation strategy. Therefore, I decided to look at the possible additive effects of radiation and chemotherapy. Because of the initial success with DDP, I selected it as the drug most likely to demonstrate such a response. TCC cells were placed in the hind limbs of one hundred mice that were randomized into a control and eight treatment groups. Chemotherapy was given intraperitoneally while radiotherapy was administered using a specially designed apparatus which allowed the mice to be completely covered except for the tumor-bearing limb. The most effective modality was 3600 rads + DDP which resulted in the most cures as well as a significant reduction in tumor growth compared to either DDP or radiation alone. As a result of our laboratory findings, the National Bladder Cancer Group, an NIH funded site group guided by George Prout and William Shipley, established a protocol to look at this combination: “DDP”, now referred to as cisplatin, plus radiation in a randomized setting (J Urol 132:899-903,1984).

Once again the animal model was predictive and cisplatin is still used to enhance the response rate when radiation therapy is the primary modality to treat locally advanced bladder cancer. Early on Alan Yagoda, a remarkable medical oncologist at Memorial Sloan Kettering Cancer Center, was impressed by the data from our laboratory findings and began treating patients with metastatic urothelial cancer with cisplatin; I was at the University of Tennessee Center for the Health Sciences in Memphis and, because of my respect for his judgment and foresight and my laboratory results, began treating my own advanced bladder cancer patients with cisplatin. The responses were often dramatic (J Urol 120:716-719,1978; J Urol 128:1031-1033, 1982).

How strange it seems now to talk of those early years. To reflect on the notion that those findings in our laboratory might have proved to be the root of what was later established by evidence based medical findings. Again---chance, mentorship and collaboration---were the constants that continued to shape my research and my clinical practice.

As I said, I have always been a simple pragmatic Midwesterner. Lurking in the background and influencing every research query was the question: Could this have a translational impact on every day practice? When I was approached by Olympus over 25 years ago to be the first in the United States to study a first generation flexible cystoscope, I was not intrigued by its mechanics as other “boys” are with their toys. Rather, I was captivated by the idea that I could take patients who were being followed regularly for bladder cancer and examine the bladder in the office with topical anesthesia. In the beginning, many urologists complained about the faulty optics of the flexible cystoscope; others were merely resistant to change. I kept thinking how this innovative tool might make it more palatable for patients to be followed regularly and long term for their bladder cancer (Urology 25:472-474, 1985).

When I suggested that urologists could actively monitor low-grade Ta bladder tumors without having to resect every tumor as they appeared, many were concerned that the tumors may progress in the interim. The lack of urgency in addressing these “benign” lesions is increasingly accepted. Although these actions were certainly not in the “legendary” category and did little to change the natural progression of the bladder cancer patient’s disease, I was able to affect their quality of life ...and, 35 years down the road that is the essence of what I struggle each day to do as a researcher and as a clinician.

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