LEGENDS IN UROLOGY

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"It's not that I'm so smart, it's just that I stay with problems longer." ~Albert Einstein

I was hesitant to write this piece when I received the invitation. I googled the definition of "legend" and found some interesting answers. One answer is "an extremely famous or notorious person, esp. in a particular field". I'm certain that I do not qualify for that. The other definition is " someone who very many people know about and admire". In the field of sexual medicine and erectile dysfunction, many people are familiar with my work, however I don't know if I am admired. With that in mind, I thought a little summary of my career might be helpful to those who are just entering urology and are still wondering what to do in the future.

I grew up in a small, poor farming village in central Taiwan, which I believe greatly influenced my philosophy on life and my work ethic. Both my parents had only elementary school educations. My mother was adopted by a poor family shortly after birth. My father, at the age of 17, "volunteered" to substitute for his older brother who was drafted by the Japanese Army. He was listed as "war dead" in Rabaul, New Guinea, and after returning from World War II, he had no job and no money. Since my mother's parents were also quite poor, my mother was persuaded to marry a jobless man, and as such no dowry was required. After I was born, my parents borrowed money to buy a small Chinese medicinal herb shop in a small village. They hired a retired traditional Chinese doctor to teach them herbal medicine. The village had just 95 families so the business barely survived. After a few years, they managed to save money to buy a few acres of farmland to grow various crops.

Our tiny home had three sections: the herbal medicine shop was in the front, the middle contained a single wooden bed for two adults and four children, and the back contained a kitchen without running water, a shower or a toilet. Going to the public toilet 100 meters away at night, and trying to avoid stepping on feces at the toilet (which was essentially a wooden stand over a concrete pit) was a major nightmare as a child. Being the oldest of four kids, my job was to sell postal stamps in the shop and work on the farm during school vacations. My parents worked hard so that I could get an education, and they constantly stressed the importance of study to me. However, when friends and neighbors were unavailable to help work on the farm, I would work under hot, humid conditions with bare feet and bare hands. When I tended the shop, I would count up our day's income and I would worry about how our family would survive.

My elementary school was in another village about 2 miles away and drew students from seven villages. All the kids walked with bare feet to school on a dirt road. Pebbles were lain in the center of the road to provide better traction for the occasional truck or bus. Only five children in my class of 90 scored high enough on their exams to enter junior high school, and I was the only one in my class to go to college. I became the first person ever from my village to graduate from college.

Just like most medical schools outside the United States and Canada, medical school in Taiwan combines undergraduate and medical education in 7 years. Based on the Taiwan College Entrance Examination Report, I knew I had the lowest score among my peers in my medical school class. With this in mind, I was quite nervous about attending medical school, but I felt that there was no alternative because I would otherwise have to serve in the military. I quickly learned that there was one scholarship a year for the top student of the class. I knew many of my classmates were

smarter than me, but I had no choice. I studied long hours, gave up most of my recreational activities (except two movies in 7 years) and was fortunate to win the scholarship every year for 6 years. I also learned an important lesson: perseverance and hard-work can compensate for my humble upbringing and unremarkable intelligence.

After graduating medical school, I did 2 years of general surgery residency at a Taiwanese hospital. During that period, I experienced the joys and sorrows of the field of urology. On the first day of my urology rotation, I learned how to pass a cystoscope into the urethra and bladder. I also noted that inserting a catheter into the bladder immediately relieves the agony of a man in urinary retention. Unfortunately, during the rotation, I also witnessed tragic complications from TURP due to poor instrumentation (a resectoscope with a tiny incandescent light bulb) and the use of distilled water for irrigation. The postoperative period was an excruciatingly painful experience for patients and residents alike. I began to consider going abroad to receive better medical/surgical training.

Despite my broken English, I traveled to the United States. A week after I arrived in Brooklyn, New York, I started my surgical internship. My chief resident was from Haiti and had a strong French accent. Most nurses and patients at Brooklyn Jewish Hospital (now Interfaith Medical Center in Brooklyn) were first generation immigrants from different countries with assorted accents. I had a great deal of difficulty listening to, understanding, and speaking English. As such, I had to pay extra attention to everything, and was really scared that I could be fired at any time. Of course, my only option was to be persistent and work hard. I stayed in the hospital from 6 am to 10 pm almost every night (I was busy taking care of patients even during the birth of my first child), but I also learned a lot during my first year and received the "Best Surgical Intern Award".

After I adjusted to the new environment, I began to realize that general surgery just wasn't for me. I applied to the urology program at the hospital and was rejected even with my "Best Surgical Intern" title. The next year, I sent out 30 applications and received no interviews. The year after, during my third year of surgical residency, I mailed out 70 applications. I was granted two interviews and was accepted by the urology program at Ohio State University. However, my wife was a second year pediatric resident, and could not transfer. With a 2-year-old son, we did not wish to separate the family, but felt as though this was our only option. Two months before I was supposed to move out to the Midwest, I learned that someone had dropped out of the SUNY Downstate Urology Residency Program, so I immediately begged my general surgery chief Dr. Bernard Levowitz to call the Chair of Urology at Downstate and thus was able to keep my family intact.

With a total of 5 years of general surgery training (2 in Taiwan and 3 in the US), I was quite comfortable with my surgical skills when I completed the 3 additional years of urology training. However, finding a job in New York City was quite difficult for a foreign medical graduate. Since my wife had a relative in California, I hoped to join a private practice in California. I asked Dr. Keith Waterhouse, the Chair of Urology at Downstate, SUNY for advice, but he completely misunderstood my request. He thought I was interested in academics and wanted his recommendation for a fellowship. He gave me two suggestions: Dr. Joseph Kaufman at UCLA and Dr. Emil Tanagho at UCSF. The only reply I received was a letter from Dr. Tanagho offering a 1 year research fellowship without pay. I applied to the New York Academy of Medicine for the Valentine Scholarship and I am indebted to Dr. Richard Macchia who fought with the committee to grant me a scholarship to study outside of the New York area.

When I arrived in San Francisco in 1981, Drs. Joachim Thüroff (Germany) and Mohmoud Bazeed (Egypt) were the two fellows in the lab. Under the leadership of Dr. Emil Tanagho and Dr. Richard Schmidt, the team worked on designing and testing a neuroprosthesis for the control of the urinary bladder and sphincter. In the first 3 months, I learned different methods of sacral root neurostimulation and observed its effects on the bladder, urethra, rectum and the penis. However, the sight of urination, pelvic muscle contraction, and defecation all at the same time during sacral root stimulation was not very appealing. I also realized that the bladder pacemaker project would take many years to develop. Since my plan was to spend a year in the lab and then join a private practice, I needed a simple project that could be completed in 6-9 months. After an extensive literature review, I found very little research on penile physiology and neuroanatomy. So I began to trace different branches of the pelvic nerve and noticed that I was able to produce pure penile erection without voiding and defecation when electrical stimulation was applied to certain branches. This was a nice and neat experiment that opened the door to the study of detailed penile neuroanatomy and the hemodynamics of penile erection and detumescence. My two co-fellows, Dr. Takao Takamura (Japan) and Dr. Metadeen Umraiya (India) were very helpful with the experiments. The knowledge I learned during my previous general/vascular surgery training was very helpful in designing experiments. When I had a new "discovery", I would

phone Dr. Tanagho and he would stop his work and come to the lab to witness it. I began to like research because I felt my work was appreciated and the new "discoveries" continued to occur almost weekly. At the end of the year, Dr. Tanagho hired me as a clinical instructor, and I quickly forgot about joining a private practice.

One of the reasons that penile physiology research lagged behind was the accepted dogma at the time that human penile erection was different from erections of animals with the os penis. Dogs have a large os penis and the glans is larger than the corpora cavernosa. Canine penile erection occurs mostly in the glans because the deep dorsal vein is closed off at the base by a specialized muscle. The erection in the corpora cavernosa is difficult to appreciate unless a needle is inserted in it to record intracavernous pressure. Based on these early experiments, I thought I had made some novel discoveries, but I was very disappointed to learn from the prevailing dogma that the results were not relevant to humans. In the meantime, three monkeys were given to us from another lab. I took the opportunity to design survival experiments in the monkeys and found that the mechanism of erection was the same with or without an os penis. Our ambition grew and we implanted cuff electrodes around the cavernous nerves of the dogs and monkeys and called them "erection pacemakers". The electrodes were connected to a subcutaneously implanted receiver for chronic stimulation. A transmitter similar to a garage door opener sent RF signals to a small antenna that was placed over the receiver to send electric impulses to the electrodes. We implanted electrodes on the cavernous and pudendal nerves and noticed that two stages of erection could be induced. When the cavernous nerve was stimulated, the intracavernous pressure could rise to about 90% of the systolic blood pressure (full erection). If the pudendal nerve was stimulated at this time, the penis became rigid and the intracavernous pressure rose to several hundred mmHg (rigid erection). However, if the pudendal nerve was stimulated alone, no erection was noted. We also showed that a high-frequency stimulation produced a short-lasting erection and a low-frequency stimulation could produce an erection that lasted for more than 1 hour. Based on these experiments we proved that the mechanisms of erection are the same whether an animal has an os penis or not.

After the acute and chronic animal models were established, we began to study the pharmacology and hemodynamics of erection. We noted that the venous outflow from the glans was increased but the flow from the corpus cavernosum was decreased during erection. To elucidate the anatomical mechanisms of venous flow reduction, several years were needed because the histological differences between the flaccid and erect penis were difficult to analyze. The breakthrough came when we decided to make and study penile casts from fresh human cadavers as well as canine and simian penises. We noted that the two canine corpora cavernosa were completely separate and we could produce both erect and flaccid casts in the same penis. Using scanning electron microscopy we clearly saw numerous subtunical plexuses draining the corpora cavernosa in the flaccid casts, but there was compression of these plexuses in the erect penile casts. We also noted tortuous helicine arterioles in the flaccid state that straighten and enlarge, opening directly into sinusodidal spaces during erections. This helped us establish that venous compression, not constriction, was the anatomical basis of venous flow reduction during erection. We also performed pharmacological studies to further confirm the theory. Intracavernous injection of epinephrine, a vasoconstrictor, did not produce erection. To the contrary, after erection was established by electrical stimulation, intracavernous epinephrine injection caused a rapid detumescence. In further studies, we also noted that smooth muscle relaxants such as papaverine, alpha blockers such as phentolamine, and cGMP dependent phosphodiesterase inhibitors (which years later became known as type 5 phosphodiesterase inhibitors) such as zapranast, enhanced the partial erections produced by suboptimal neurostimulation of the cavernous nerves in dogs and monkeys. We thus concluded that relaxation of the cavernous smooth muscles led to opening of the sinusoidal spaces, arterial flow increase, and venous flow reduction – the three main components of penile erection. We also noted that rigid erections were a result of external compression at the base of the penis by the ischiocavernosus muscle on a blood-filled corpora cavernosa.

Two personally important events occurred at the 1983 AUA meeting in Las Vegas: 1) Our work on penile physiology won the first prize for laboratory research (and Dr. Patrick Walsh gave me great encouragement after I showed a movie of monkey erection at the plenary session), and 2) Dr. Giles Brindley, a British scientist, demonstrated his own erect penis at the Urodynamic Society Meeting. Giles Brindley and Gorm Wagner (Denmark) had a theory that the sympathetic nervous system keeps the penis in the flaccid state and dis-inhibition of the sympathetic system is the trigger of penile erection. Brindley experimented with oral and penile injection of alpha blockers to induce erections. He then shocked the entire audience (including myself and Dr. Tanagho, who were to speak on the physiology of penile erections immediately afterward) by demonstrating his own erection after a self-injection of

phenoxybenzamine. Because phenoxybenzamine might cause tumors in mice, Dr. Richard Schmidt and I decided instead to use papaverine, after our favorable experience with injecting it into the monkey penis. A week after the AUA meeting, we injected a patient with papaverine and he developed a priapism for more than 8 hours. Since we knew epinephrine produced detumescence in monkeys, we gave the patient an undiluted epinephrine injection as well. The patient developed acute hypertension, headaches, and EKG changes, and required admission to the ICU overnight for observation. Since then, the use of papaverine (with phentolamine and prostaglandin E1) for inducing penile erection as well as alpha agonists for reversing priapism have become standard practice.

The introduction of intracavernous injection brought us a lot of patients and gave me the opportunity to translate the knowledge we gained in the lab to clinical practice. The first pharmacologic cavernosometry and cavernosography, as well as the first duplex ultrasound arterial flow measurements, were all performed on monkeys and were subsequently perfected for human use. The study of numerous fresh cadavers also helped us understand the neuroanatomy of the cavernous nerve, the complicated microstructures at the hilum, the intricate layers of the tunica albuginea and the importance of intracavernous struts. This anatomical knowledge and the clinical experience in thousands of patients were critical in our development of various procedures: hilum exploration and crural ligation for congenital venous leakage, the 16-dot plication procedure and saphenous vein grafting for Peyronie's disease, the T-shunt and tunneling for refractory ischemic priapism, surgical correction for traumatic priapism, subtunical excision of ossified Peyronie's plaques, transglans correction of impending prosthetic erosions, and the plication technique to correct penile deformities at the time of penile prosthesis implantation. In addition, we also popularized colchicine and pentoxifylline for Peyronie's disease, antiandrogens for high flow priapism, and pentoxifylline to reduce fibrosis after priapism.

In 1998, we established the Knuppe Molecular Urology Laboratory with patient donations and the help of our new department chair, Dr. Peter Carroll. At the time, I had no training in molecular biology and I learned continuously from researchers in the lab (Ching-Shwun Lin, PhD, Guiting Lin, MD, PhD and Hongxiu Ning, PhD) as well as more than 80 fellows and research residents over the years. Taking advantage of the seamless collaboration between MDs and PhDs in our lab, our team has expanded its research into urinary incontinence, diabetic complications, adult stem cells and cancer. The awarding of a MERIT grant from the NIDDK as well as a R01 and a SCOR grant (PI: Jeanette Brown) gave me the courage and support to "think outside the box" and begin working on bigger ideas such as the biology of mesenchymal/vascular stem cells and their potential applications in various fields, not just in urology. We have since made important strides and we believe stem cell-related therapy could become standard medical practice in the next decade.

Over the years, I've spent countless days, nights, and weekends sitting in my office or lab reading papers and writing proposals. I read and write slowly because English is not my native language. I needed more time than others to complete my clinical and research work, and even now, I am often the last to leave the office at the end the day. In order to devote so much of my effort to academia, I am much indebted to my wife, Dr. Su-Mui Kuo, for her unconditional support and love. We were extremely lucky that she found a job only 3 months after we moved to San Francisco which allowed us enough financial freedom to continue my academic career. Later, after my father retired, my parents moved into our house and helped raise my two young sons. While I worked long hours and struggled for months and months writing numerous grants, my parents and my wife carried the tremendous responsibility of caring for and educating my sons. The two young men also learned to work hard and be persistent when they were little and did well in their careers: James graduated from UCSF Medical School and Thomas graduated from Harvard Law School. Without my wife and parents, my career and family could never have been cultivated into such a fulfilling and charmed life. I am forever indebted to them, as well as to all the wonderful colleagues I have had throughout the years. Collectively, they are the true legends in my life.

When one has no other choice, one learns to work hard and be persistent. I learned this as a child growing up in a poor farming village. As a first generation immigrant, my choices were limited. I am immensely fortunate to have had the opportunity to work at a world-class medical institution, which was far beyond my loftiest dreams when I first came to America.

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