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# LEGENDS IN UROLOGY

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As other contributors to this section have mentioned, the designation “legend,” although tremendously flattering, is an uncomfortable one. However, as my personal history differs somewhat from that of my colleagues, my story may be of interest to the reader. Likewise, the arc of our department’s growth is unusual in the field of urology and, I believe, may be instructive to younger academicians.

I was born in Egypt and graduated from the University of Alexandria Medical School, where I was trained by Professors A. el Sadr and M. el Ghorab (the former a student of Dr. Ruben Flocks). It was there that my master’s thesis stimulated my interest in the ureterovesical junction. For the topic, “Evaluation of Surgical Repair of Lower Ureteral Stricture (Bilharzia),” I collected 175 cases. Even though surgical treatment was various (meatoplasty, direct reimplantation, nipple reimplantation [later described by Paquin], bladder flap), overall outcome remained unsatisfactory because of the persistence of vesicoureteral reflux.

In 1962, while a Lecturer at the University of Alexandria, I was offered a sabbatical year at the University of London under the guidance of Dr. Roger Pugh, the Chief of Pathology at the Institute of Urology, and Sir David Innes Williams, the renowned pediatric urologist at the Great Ormond Street Children’s Hospital. Before they allowed me to begin my project on the anatomy and function of the ureterovesical junction, they required that I spend 2 months in literature review at the Royal Library of Medicine—advice that, unknown to me at the time, would be vital to the success of my subsequent research career. Such was my enthusiasm that I finished this in 2 weeks.

Anatomy was usually studied by either gross dissection or histologic serial section. Because both have their limitations, I chose an in-between step, dissection under the microscope. Also, instead of following muscle fibers, I elected to follow muscle bundles; not only is this easier, it permits more accurate delineation of anatomic and histologic detail. This work resulted in the 1963 publication, “The Anatomy and Function of The Ureterovesical Junction,” in the British Journal of Urology.

Attracted by the fame of Dr. John Hutch at the University of California, San Francisco, I decided to complete my sabbatical there. With the support of Dr. Donald Smith, we did physiologic studies that confirmed the anatomical work of London, and then applied the same approach to the bladder neck and sphincteric mechanism. At UCSF I enjoyed the cooperative collegiality of Drs. Frank Hinman, Jr., Richards Lyon, and William Smart. Thus, as my family and I prepared to return home, we drove cross-country to visit the leaders in the field who, to me, were the giants of the time: Drs. Ruben Flocks in Iowa, David Utz at the Mayo Clinic, John Lattimer and Victor Marshall in New York, and Wyland Leadbetter in Boston. It was an energizing and enlightening experience.

During my time overseas, major political and social changes had occurred in Egypt. Under the Nasser regime, with confiscation of property and severe travel restrictions, the country seemed to be moving rapidly toward the Soviet bloc. In 1 year, I thrice was denied permission to attend European and American urology meetings after having had papers accepted, and it was made clear to me that I would never be permitted to leave the country again. That finalized my decision to search for a means of escape. In 1966, we left Egypt under the pretense of a journey to the Holy Land at Easter (a once-in-a-lifetime right of Christians). On a family passport, valid for 15 days, we fled with our two daughters (ages 7 years and 10 months), two suitcases and \$200 (the maximum permitted), revealing to no one (except one brother) that we were leaving forever.

After 2 weeks in Jerusalem, we traveled to Beirut, where I joined the American University as a Visiting Scholar until my immigration visa was granted with the help of Senator Frank Church, the Chair of the Senate Foreign Relations Committee, arranged through the intercession of Drs. Robert Ayers and Richards Lyon. In 1972 I attained American citizenship, and in 1974 my Board of Urology license.

### **Research Interests**

At UCSF I resumed the anatomic studies of my sabbatical: we defined the causes of primary reflux owing to poor muscularization of the terminal submucosal ureter and trigone; elucidated the embryogenesis of ureteral duplication, ureteroceles, and non-occlusive ureteral dilatation (megaureter); and described the causes and mechanism of the dilated ureter (vesicoureteral reflux, prune belly syndrome, ureterocele, ureteral duplication, ectopic ureter, functional megaureter).

In an interesting cooperative investigation with NASA after one of the early astronauts came down with an attack of pyelonephritis, we studied the effect of gravity on ureteral peristalsis and showed clearly that antigravity leads to ureteral stasis and dilatation.

Fetal Surgery: In the early 1970s, intrigued by the association of posterior urethral valves and megaureter and renal dysplasia, we embarked on a series of daring surgical experiments in the fetal lamb to induce three congenital anomalies: posterior urethral valves (PUV), ureteropelvic junction obstruction (UPJ); and renal vascular ischemia. At mid term through the thin uterine wall, we partially delivered the lamb fetus, preserving the amniotic fluid. We then exposed the proximal urethra, kidney or upper ureter, wrapping a small silastic tube around the area of interest loose enough only to limit further expansion. Urethral obstruction resulted in patent urachus and, occasionally, unilateral vesicoureteral reflux. Obstruction of the upper ureter caused hydronephrosis; renal dysplasia did not occur, but there were definite changes in ureteral muscular orientation. Vascular obstruction resulted in a shrunken dysplastic kidney.

Surgical Technique for Complete Urinary Incontinence: In our anatomic studies we had explored the mechanism of urinary continence, proximal and distal sphincteric mechanisms, and pelvic innervation. Based on the knowledge gained of the muscular configuration of the bladder, we found we could turn an anterior bladder flap into a sphincteric tube to replace a damaged or even absent sphincter. In selected patients this surgical technique remains in use today.

Urodynamics, Female Urology, and Colpocystourethropey: Our attention was then directed to the physiology of the bladder, neurophysiology, and the mechanism of micturition. Working with Drs. Frank Hinman, Jr. and Earl Miller and taking advantage of the emerging technique of video urodynamics, our lab developed the most comprehensive clinical urodynamic studies to evaluate neuropathic disorders, urinary incontinence, urinary tract infections, and a variety of voiding dysfunctions.

Interest in female urology was always a driving force behind that work. To differentiate genuine stress incontinence owing to weak support and excessive mobility from mixed urinary incontinence and intrinsic sphincteric deficiency, we conducted detailed studies identifying specific urodynamic findings in each group. That led us in 1970 to modify the Burch technique of bladder suspension, which we called colpocystourethropey (CCUP). To this day, patients with persistent stress incontinence in whom previous repairs have failed are best helped by this approach, unless there has been iatrogenic damage to their sphincteric mechanism.

Neural Stimulation in Urology: In the early 1970s, we began studying neural control of the urinary bladder and sphincteric function, trying to define the neural pathway along the somatic and autonomic nervous systems. Having published extensively on the subject, I was approached by Drs. Karl Frank and Terry Hambrecht, directors of the neuroprosthesis section of the NIH. At that time, Dr. Blaine Nashold, a neurosurgeon at Duke University, had implanted an electrode in the sacral segment of the spinal cord and induced bladder contraction and emptying. Drs. Frank and Hambrecht visited our lab and, after several hours' discussion on bladder neurophysiology, proposed that we contract with NIH. That was the beginning of this exciting work.

Professor Udo Jonas from Germany worked with me in the laboratory, followed by Drs. Richard Schmidt and Joachim Thüroff as research fellows. Testing the stimulation of the sacral spinal cord and comparing it to the direct stimulation of the pelvic autonomic plexus or the bladder wall, we developed 12 different surface or penetrating electrodes. To limit the spread of current, we even attempted microelectrode implantation for the stimulation of the parasympathetic nucleus.

We traced the neural pathway of the autonomic and somatic neurons from various sites in the bladder and sphincter, injecting horseradish peroxidase and tracing its axon transport to the mother nuclei in the spinal cord. We defined the exact location of the pudendal and parasympathetic nuclei in the sacral segment and determined their spatial extension: the parasympathetic nucleus is more confined and the pudendal nucleus extends beyond it. Thus, unless a microelectrode was implanted in the parasympathetic nucleus itself, there was no way to stimulate it without stimulating the pudendal nucleus at the same time.

We moved to stimulation of the sacral root through extradural access. In dogs spinalized above the sacral segment in which spastic neurogenic bladder developed, we implanted electrodes on either the complete root or the ventral motor component alone, with the dorsal component either intact or interrupted. This was done either unilaterally or bilaterally and with either a single root or more than one root. Every specific arrangement was performed on 4 to 6 dogs. The conclusion was that, to gain control of bladder evacuation in spastic upper motor neuron lesions, it was necessary to do extradural dorsal rhizotomy to reduce spasticity and improve bladder capacity and then stimulate the ventral root by a direct implant. Various electrodes were evaluated and the spiral wrap-around type was found to be the best. Also during these studies, we learned that we could regain control in a weakened sphincter by stimulating the pudendal nerve and that chronic stimulation changed the nature of the striated muscle fibers from fatigable to fatigue-resistant to maintain continence.

In the early urodynamic studies in the spastic neurogenic dog, we observed that, when only minimal filling provoked bladder activity, sacral root stimulation immediately inhibited it. However, once the stimulation stopped, the bladder hyperactivity resumed. This finding surprised us initially, but after consideration we recognized it as a natural reflex. If the bladder tends to overact, we can suppress this by overactivating the sacral root; the perineal muscles tighten and this in turn inhibits detrusor contraction. If this could be accomplished in the full-blown spastic neurogenic bladder, we believed it could be beneficial with less severe causes of bladder overactivity. In patients we easily tapped into the sacral root percutaneously for implantation of tiny electrodes; when the bladder went into overactivity, stimulating the sacral root suppressed it. That beginning development has become what is now a very popular treatment known as Interstim®, commercially available from Medtronic.

I am personally disappointed that neurostimulation is not more widely used and that a bladder pacemaker has not been realized. The number of patients with spinal cord injury and loss of bladder control is relatively small and the technology is quite complex. Unfortunately, industry profitability drives progress in medicine. This is particularly frustrating because our subsequent work furthered the technology.

With intraoperative testing, as we did in our clinical trials in 1989, one can choose the sacral root that can produce the most detrusor contraction and the least sphincteric activity. To refine this approach, we studied the anatomy of the sacral ventral root in detail. It became clear that all sacral roots arise from the spinal cord as several rootlets and that, even after joining together, these rootlets maintain their identity throughout their entire intrathecal course, carrying the axon of the nearby neurons in the spinal cord. In S2-4, some would be carrying axon from the pudendal nucleus, others from the parasympathetic nucleus. By dissecting the sacral ventral root into its various rootlet components just before its exit from the dura, we could distinguish the one carrying somatic fibers from the one carrying parasympathetic fibers. By severing the former, we could stimulate the entire ventral root extradurally and produce pure detrusor contraction. This was a major step forward.

In more recent work, we also discovered that we could electrically block transmission along the large somatic fibers and then selectively drive the parasympathetic fibers. This simplified the procedure and eliminated the need for any neurotomy. The technology for the dream bladder pacemaker is at hand.

We also attempted somatic innervation of the detrusor. A few bundles from the femoral nerve were isolated and implanted into the bladder wall; after attachment was gained, stimulation induced bladder contractions. This was a new approach towards somatic innervation of an autonomic visceral organ.

We then attempted somatic augmentation of the detrusor muscle. We transported the latissimus dorsi muscle with intact nerve and blood supply to the pelvis and wrapped it around the atonic bladder, re-anastomising its nerve and blood supply locally. After allowing time for nerve regeneration, electrical stimulation led to muscle contraction, facilitating bladder emptying. This work showed not only the feasibility of reinnervation and revascularization of a transplanted large muscle sheet, but also the effectiveness of its contraction in assisting bladder emptying.

Erectile Dysfunction: As our bladder stimulation work was underway, Dr. Tom Lue joined our lab. While stimulating the sacral roots, we occasionally noted an erectile component, which inspired Dr. Lue to isolate and stimulate the cavernosus nerve. The erection pacemaker was born. Monkey Joe, with a chronically implanted electrode over the cavernosus nerve, became a celebrity in our lab with whom every visitor requested a meeting. It got to the point where, whenever we entered the lab with a visitor, Monkey Joe would lie on his back readying himself for the anticipated stimulation. This was the very first chronic animal model to control erectile function, allowing initiation, maintenance, and termination at will. Dr. Lue's pioneering physiologic and pharmacologic studies inspired revolutionary progress in the treatment of erectile dysfunction.

Jacob K. Javits Neurosciences Award: Our work on neurostimulation has been supported since its inception by continuing grants from the NIH, and in 1985 I was honored with the prestigious Jacob K. Javits Neurosciences Award, which I continued to receive for 14 consecutive years.

Dr. Richard Schmidt, who joined our lab in 1975 as a research fellow and later rose to full professor, deserves special recognition for his major contribution to our neurostimulation research, as does our innovative neuroscientist, Dr. Curtis Gleason.

Tissue Engineering: Early in 1983, we successfully cultured vesical smooth muscle in a petri dish. To use this in repair of urinary tract defects, we grew the culture over Dexon mesh woven in our lab by a talented Vietnamese technician. This impregnated mesh was then folded in several layers and grafted into the bladder defect of the donor animal. The graft survived for a short while, but ultimately ended as a fibrous scar.

Revival of our interest in regenerative medicine took place in the 1990s when we turned to the bladder acellular matrix. When this was grafted on top of a bladder base after partial cystectomy, it completely remuscularized within two to three months and attracted autonomic innervation. Functional studies showed this regenerated bladder to have responses and functional properties identical to those of the normal bladder. When the acellular matrix was cross-grafted from several species (humans, dogs, rabbits, and guinea pigs) to rats, the recipients all survived and the graft showed a lack of antigenicity. It performed similarly in large animals (dog to dog) and in pathologic bladder conditions. Encouraged, we extended the transfer of organ-specific acellular matrix to ureteral and urethral defects with equal success. It was also used to replace defects in the tunica albuginea to simulate repair of Peyronie's disease. We also have limited clinical trials for bladder augmentation and urethral stricture repair, and our early results have been encouraging. Currently, there is great interest in this regenerative medicine and various kinds of reconstruct are being suggested for grafting after being seeded with smooth muscle cells or the urothelial cells or both. We believe, however, that none of these synthetic reconstruct will ever be superior to the organ specific acellular matrix, whether seeded or not.

### **The UCSF Department of Urology**

In 1976, on the retirement of Dr. Donald Smith, I was nominated as Chairman of the Division of Urology. I delayed acceptance for 6 months until, with the help of Dean (later Chancellor) Julius Krevans, Urology was elevated to departmental status. I emphasize this seemingly minor issue because I realized early on that it was truly necessary for the success of a progressive agenda.

Resident Program and Spectrum of Research: The rigor of our Resident Program was intensified. With the addition of a research year, it became one of the best in the country. The clinical training was broadened to include every subspecialty: oncology, pediatric urology, stone disease, endourology, fertility, urologic trauma, neurourology, erectile function, and andrology. Unlike many Urology programs, where one area of research and treatment is emphasized, I was determined to make UCSF a magnet for the care of multiple disorders and a focus of research acknowledged world-wide. To this end, I intended by no means to be a one-man show. The goal in our Department was that anyone who joined our faculty would, in two to three years, achieve national and international recognition. For all of them, this became a reality.

The first faculty recruit was Dr. Jack McAninch from Letterman Army Hospital. In a few years, Jack became a brilliant star in academic urology, progressively assuming the presidency of almost every urologic society, including the AUA and the SIU.

Our success can be attributed to three factors: 1) insisting upon departmental status; 2) recruiting excellent faculty (one cannot fail with colleagues such as Jack McAninch, Tom Lue, Marshall Stoller, Richard Williams, Barry Kogan, and Peter Carroll, under whose current Chairmanship the department has reached new levels of renown); and 3) actively welcoming international scholars.

International Fellows. From 1967 onward, 120 postdoctoral fellows from 29 countries over five continents sought out our lab. There they knew they would be given not only intellectual encouragement but also crucial practical support: our preeminently talented artist, the late Paul Stempen; our dedicated editor, Aileen Marks; and our invaluable research assistant of more than two decades, Lora Nunes. The success of the early fellows—both in San Francisco and upon their return to their home countries, where many became Chairs—attracted others to follow. Their energy and enthusiasm helped us increase our publications in peer-reviewed journals from 50 to 120 annually.

### **Awards**

International Honors. Several international scientific organizations have bestowed honorary membership on me: the Urologic Society of Australasia (1984); the Royal Society of Medicine, Great Britain (1987); the Canadian Urological Society (1989); the German Urologic Association (1989); the All-Union Association of the USSR (1990, shortly before the USSR's demise); the Czechoslovakia Urological Society (1992); the Urologic Society of Japan (1994); the Romanian Academy of Science (1996).

American Awards. In the United States, the recognition of one's peers has been extremely fulfilling: the Urodynamic Society's Lifetime Achievement Award for contributions to neurourology (1994); the American Urologic Association's Certificate of Achievement for contributions to education and research (1996); the New York Academy of Medicine's Ferdinand C. Valentine Award (1997); The Raymond Gutierrez Award, the AUA's highest honor, for pioneering efforts in neurourology and innovative ideas in basic research (2000); and, in the same year, the Societe Internationale d'Urologie's Yamanouchi Award in recognition and appreciation of outstanding contributions to urology. To top all of this, in 2006, the American Association of Genitourinary Surgeons, honored me with their highest award, The Keyes Medal.

Endowed Chair. In 1999, the University of California has honored me by establishing the Emil Tanagho Endowed Chair in Clinical Urology, the first recipient of which is that Legend-in-the Making, Dr. Tom Lue.

Egyptian Honor. In an ironic twist of fate, the late President of Egypt, Anwar Sadat, awarded me the country's highest civilian honor, The Premier Medal of Merit. When presented this at the ceremony at the Egyptian Consulate in San Francisco by Egyptian Ambassador in Washington, Ashraf Ghorbal, on behalf of President Sadat, I could only ask myself who might ever have envisioned such a change of fortune.

### **Reflections**

To our young colleagues: An academic career can be fulfilling, provided one is motivated, creative, and perseverant. The pursuit is challenging, but its reward is the opportunity to contribute to advance our specialty and medicine overall. To our young researchers: It is mandatory that you exhibit reportorial honesty. It is not an option, nor can it ever be considered, to expand or embellish positive findings beyond their limit. Never ignore your negative findings. Instead, adopt a best practice standard to reconfirm. If approached with integrity, work that is properly executed and reported will endure and you will always be proud of it.

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