LEGENDS IN UROLOGY

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I had the good fortune to begin higher education early, at age 15, when I entered the College at University of Chicago – not so rare then as now. It was not the chance to do even more science and math that mattered. It was, rather, the general education, especially the now much maligned 'classics' that gave me a footing in world knowledge, a lifetime compass for self-education, and unerring criteria for excellence handed down, as it were. At 18 I was offered a place in the School of Medicine, which I entered at twenty. The 2 years in between were given over to math and music, mostly, and a brief but important time doing science – to determine the origin of one carbon atom of riboflavin.

I had no real sense of purpose apart from medicine. Professors nudged toward academics, to me more foreign than the moon. My family hoped I would join my uncle in his successful Internal Medicine practice, not unreasonable at the time. Radically unknown was my future in kidney disease, and the pathogenesis and treatment of nephrolithiasis, radically because it was beyond imagining.

A medical school classmate was performing renograms as part of her research and asked me if I had any sense of the equations that might describe the entry and egress of isotope through the kidneys. I did, and during house staff training published four papers on that topic. Training was at Michael Reese Hospital, where I thought I might cultivate a more earnest clinical sensibility than usual in university hospitals.

Reese was first in the region to purchase a hemodialysis machine and two friends and I were paid extra money to run it. Dialysis was only for otherwise well people with acute kidney failure. Primitive access and no one to do it but the three of us set absolute limits. Dialysis was heroic then, life saving, utterly important. But it did not attract me as a career because kidneys were absent, and I had not educated myself in medicine to run machines. I did, however, publish a paper on the kinetics of salicylate removal in children.

One might think renograms and dialysis led to nephrology and eventually kidney stones, but no. All physicians were then drafted into military service because of Vietnam. I was an Air Force reservist. My orders were to report to the School of Aerospace Medicine in San Antonio, Texas, to study effects of highly toxic hydrazine-based rocket fuels on the kidney. My five papers marked me as a kidney expert, or at least the best the Air Force had, then, for this work. I ran a lab for 2 years, and demonstrated, to my surprise that kidneys secrete hydrazines even though in all of evolution they never could have encountered them.

In all, by the end of my 2 years as a USAF captain I had 12 papers published about kidneys but had not secured any training spot in that or any other specialty of medicine. In fact, I rather favored the liver as my future organ, it being so big and all organs seeming more or less equally important and interesting. In the Spring of my second year, without a job, I wrote to liver programs at Harvard and Oxford. Both took me because I had published so much. But, as I thought about the matter, by then I knew a lot about kidneys and decided to stay with them.

I wrote to three famous programs – Dr. Robert Berliner at NIH, Dr. Robert Pitts at Cornell, and Dr. Donald Seldin at UT Dallas. All had a place for me, but Seldin sent an airplane ticket, and I flew there – a very short trip from San Antonio!

He and Floyd Rector were towering intellectuals and scientists in renal medicine. Seldin, Chair of Medicine, had built a cluster of Quonset houses into a world-renowned medical center and reigned Magister Ludi among deans and chairs in the US. From them I learned modern renal physiology as an education, meaning how to study it and therefore grow roots in that soil. All emphasis was on sodium and potassium. The divalents – calcium, magnesium – beneath discussion, mere passengers as the free energy of sodium transport spread out to energize miscellaneous secondary routes.

When I returned to Chicago, Reese was part of the University of Chicago and I stationed myself there and began life as an assistant professor. I was an academic, educated in kidney physiology, and with 4 years of kidney research behind me. But my plan was vague – what was to be the focus, the general plan for a whole career?

The latter was already in place, at least in theory. While in Dallas, I understood how equal were science and medicine in their demands, their sheer scale - each a profession in itself. My only hope was to fuse them, somehow, achieve what Yeats had called 'unity of being'. My search for unity yielded a life equation: Patient care = research. The equal sign is literal – discovery through the study of the patients I see; enlarge and perfect my patient care using what I have discovered.

Kidney stones came by chance. I had started and rejected hypertension: brilliant, undoubtably important, but a bit sterile for human research, then. Computers were coming into use and to me seemed medicine's future with their access to world knowledge and power to execute treatment algorithms. I won my first NIH grant to apply computers in medicine, but it was too early, and I failed.

A friend mentioned stones. Very many patients, long lived, and the disease seemed complex and rather underserved in relation to stone prevention. It was 1969. I read what others had discovered, and realized I needed to measure many constituents in 24-hour urine samples. Being experienced, I opened a lab for this purpose, let my friends know I was starting a special clinic in stone prevention, and began to study and care for their patients – to prevent new stones.

Not much happened. Patient data accumulated. My computer grant was aimed at treatment algorithms using the 24-hour urine data, but the software was too primitive to support the complexity I needed. However, I did have access to a computer because of a grant from Lyndon Johnson's Great Society program, bought originally to create a state-wide hypertension registry. That registry failed, but I had the machine and stored in it every lab datum from every patient, from the beginning. Likewise, I stored the dates of all stone events, procedures, and medications.

That was what set things forward. I gathered up my stone counts in patients to whom I gave thiazide, a well-known drug to lower urine calcium. Likewise, from those I treated with allopurinol to treat their calcium oxalate stones. This latter was an observation. Their urine uric acid was high. I thought uric acid might crystallize as a urate salt and nucleate calcium oxalate. Their stone recurrence was much reduced, and I published that in the Lancet.

By about 1973 I had quite a few patients treated with thiazide, allopurinol, both or neither and gave a presentation at a national meeting. I was the last speaker in a near empty room near noon, but as I began people sifted in, crowds formed – the title spoke of prevention, and everyone wanted to know what I did. The hallways, even, were filled. I showed my graphs, so many stones before, so few with meds, so many without, and there was a sense that things had changed. Trials were needed, prevention was realistic, and physicians needed to do it if the trials worked out. A major journal solicited the work. I began my first book and was invited to do the chapters on stones in major textbooks. Thus, suddenly, from nothing, I had what I needed.

In 1976 the NIH offered five kidney stone center grants, and I was invited to compete. Our group won, and we have remained funded, more or less continuously, ever since, up to this day. Charles Pak, in Dallas, and Birdwell Finlayson, in Gainesville, also had centers and we became colleagues. The five centers created the ROCK society

as a forum to share results. The second meeting was in Chicago, and the dinner was at my home. I never expected the ROCK to become so prominent, but time has proven me wrong.

For all of us, an obvious problem was high urine calcium that Rubin Flocks first noted in 1936. Joan Parks and I proved it was familial, a fact confirmed in innumerable subsequent studies. David Bushinsky who joined us from Tufts and went on to a wonderful career as renal chief at Rochester, bred animals for hypercalciuria and worked out some of the basic mechanisms, particularly increased vitamin D receptor abundance and consequent increased tissue vitamin D activation. Murray Favus joined me from Beth Israel in Boston and showed that the high urine calcium in humans with idiopathic hypercalciuria could not possibly be due just to increased GI absorption; balance studies dating from the prior century of work all had shown such patients easily went into negative calcium balance unless dietary calcium was high. Murray went on to found the Primer of Mineral Disorders and was a founding member of the Bone and Mineral Society. David, Murray, Joan and I collaborated for over 30 years.

Eventually, after decades of work, Elaine Worcester, originally my own protégé, proved in humans that the kidney causes hypercalciuria, and therefore bone mineral is at risk. Her work showed why reduced bone mineral and fractures were abnormally common among stone formers. It was crucial knowledge against a low calcium diet, and strong support for low sodium diet as a rational way to lower urine calcium without compromising bone.

Despite reviews, chapters, and my own single and multiple authored books, what we were publishing about prevention and mineral metabolism moved only very slowly into practice. One reason, often told me after I had spoken at meetings, was a lack of excellent 24-hour urine testing. In 1995, Joan Parks, John Asplin – a brilliant protege, and my two children and I opened Litholink to bring outstanding testing to the US. It became a national company by 2001, and LabCorp bought it in 2006. A key part of its usefulness was computer algorithms to help physicians understand the many numbers and offer suggestions about treatment in each individual case for every individual test. So, my beginning desire for computers in medicine satisfied itself, finally, at Litholink.

John remained after the sale as Medical Director of Litholink and transformed it into a central testing lab for the majority of human and even animal stone researches that needed urine testing. He has enabled multiple highly important new researches and is recognized worldwide for his contributions. Through Mike Grasso, an early adopter of Litholink, I met David Goldfarb, a professor in nephrology at NYU, and helped him begin new research in stone prevention. David went on to become a leader in US stone guideline development, and highly innovative approaches to stone treatment.

Because of Litholink I often spoke at urology meetings, for urologists are main physicians for stone patients and the most knowledgeable, too. I would ask them, on and off, what they saw in kidneys about where stone grew, and how. Marshall Stoller had published grainy but convincing intra-operative pictures of stones growing on Randall's plaque, reopening a field first begun in 1938. I decided we had to get samples of plaque and figure out how stones grew on it, and what physiology produced the plaque. Jim Lingeman, in Indianapolis, told me he could get such biopsies, and his colleague Andy Evan could handle the tiny bits of calcified tissue. We rewrote our NIH Program Project grant to include this new science, and Jim and Andy produced a whole field of new knowledge concerning the plaque and plugging in stone forming papillae. Stoller added much independent and brilliant basic science work over the years. At Mayo Clinic, John Lieske – a protégé I was honored to train, and Amy Krambach – who had been a fellow with Jim Lingeman, published crucially important human biopsy series that confirmed and extended what we had found.

I was not satisfied. Research still trickles into practice through cumbersome and slow channels. In 2015 I opened a website aimed at patients, physicians, and scientists, and devoted to kidney stone pathogenesis and treatment. About 65,000 people come monthly, and to date about four million people have made some use of it. The main articles are up to professional science standards, referenced by peer reviewed papers and rather unsparing. Others ride above them, less moored to research papers and more amenable to a public, or to physicians with limited time to spare. A top layer reviews matters as in a magazine or newspaper article and intends a very broad reach.

The objective of the site: the prevention of stones. The hypothesis: Informed patients will seek prevention; informed physicians will ably provide it. Scientists who come to the site might find new ideas and bring us new knowledge. Unlike in science, I have no specific aims. There is no way to test my hypothesis. But I have glimmerings. About 1/1000 readers ask questions, and from the many thousands of these questions I can sense some facts are becoming better known. I also sense a desire from patients to get whatever is available to prevent recurrence.

I personally answer all the questions I can. Those I cannot answer concern details of foods needed to create the modern low sodium, high calcium, high potassium, low refined sugar 'kidney stone diet'. To help, Jill Harris, who ran the patient service group at Litholink when we owned it, has taken to the web offering help to patients worldwide at a very low cost. She answers to the food details and has written some articles for the site too.

As for me, now, I work full time at 84. My new research concerns sources of systemic acid load, and my funded research efforts aim to help Elaine Worcester, who took over our research group some years ago. I teach the scientific method to younger colleagues in nephrology who want such teaching. Likewise, I see kidney stone patients as I always have, since 1969, when I first opened my lab at Reese. That hospital is gone, and much has changed, but the original life equation never did change nor lose its power over me. And the accumulated data of 60 years remain as legacy if anyone chooses to mine it.

I have read all of the histories in this series, and it seems to me we 'Legends' are much alike howsoever different we may seem. Each career has its peculiar twists, chances, accidents, and charm. But through them all one senses an implied skein of ordering assumptions and goals. It is as if their founding roots all put up a first slender trunk around which much may have grown but, looked at from a distance, stands forth like the hidden but undeniable beams and girders of some elaborate and unique architectural creation. I am honored to add my history to theirs, for whatever insights or entertainments it may provide.

It is a fine thing to look on a life completed. How adequate it seems, how thoughtfully shaped by reason and desire. And yet, in truth, it ran like a running river, all curves and shallows, random, here and there, like to the shifting earth, and the small rains of summer.

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