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A reminiscence:

Serendipity steers surgeon to discovery

by

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“The pioneers, the first who struggle out of the established systems and who form new and useful conceptions, appear only half right, incomplete; and their names stay remote. But they are perhaps more to be cherished than those who come after, who clear off the debris and offer a neater, more full-blown view”

—Jacques Barzun, *From Dawn to Decadence*

The Golden Age of Surgery

In 1955, at age 28, I was a second-year surgical resident at Cincinnati General Hospital aspiring to be an academic surgeon, receiving room and board for services and a check for \$5.26 every two weeks. The money, they said, was for coffee and cigarettes. The room and board, they said, was to keep us near and attentive to our patients at all times with as little distraction as possible. We worked all day and two nights out of three in the hospital. It was our life.

It was what some might call the “Golden Age of Surgery,” learning at the feet of great surgical giants, such as Zollinger, DeBakey, Ravdin, Heuer, Cutler, Welsh, Churchill, and Altemeier. It was a time for the big operation for the small cancer and bigger operations for the big cancer. It was a time for radical neck dissections, radical mastectomies, hemi-pelvectomies, four-quadrant arm and leg amputations, huge aneurysms, and removal of 80 percent of your stomach if you had intractable duodenal ulcer symptoms like I did. The professor repeatedly told us how lucky we select few were to be learning this great craft, but if we wanted to be university surgeons like him, we had better make some original contribution to medicine during our residencies.

Most of us were veterans of two recent wars, World War II and Korea. Many of us still plied the hallways in our khaki pants or Marine brown shirts under our white coats, worn as much as a badge of pride as a wardrobe convenience. There was a macho quality about the hierarchy that we naturally honored and a mock insouciance for the anguish and travail we quietly endured together. The service had prepared us well for this environment. Complaint was taboo, discipline was re-

spected, and stress was internalized without complaint.

In those days, internalized stress was considered the major cause of routine peptic ulcers, and, in my case, there was no need to invoke any other reason for the symptomatic ulcer deformity I had developed in my duodenum. Keeping with the program, I suffered in quiet distress and discomfort, gobbling milk and antacids through 10-hour operations, often dead on my feet with fatigue and pain, always hoping I could survive without bleeding again until summer rolled around and I could have a restful vacation.

The professor, in his infinite wisdom from the Heights of Parnassus, had decreed that each resident should take a month off every summer. With a little imaginative trading off and interpolating weekends and holidays, you could parlay this into five or six weeks away, mercifully time enough to heal your wounds.

Introspecting over my affliction and my high ivy university life, I came to feel I might be aspiring to levels in medicine I was not emotionally suited to pursue. As a result, and much to the distress of my family and girlfriends of the moment, I decided to spend my vacation that year working as a general practitioner in some bucolic paradise where there were restful, languorous days. I would read the poems of W.B. Yeats, ruminate on ultimate values, and help people by making them simply feel better about themselves and their lives.

Rural revelations

I wrote to 20 state medical societies that seemed geographically appropriate to my aspirations and, to make a long story short, had to choose between West Virginia and Maine. I ended up taking a locum

tenens in Kesar Falls, ME, a small mill town 60 rocky miles west of Portland in the foothills of the White Mountains near the New Hampshire border. I was to fill in for Paul Marston, MD, the local physician who hadn't had a vacation in 40 years.

The other decree from the professor was that his residents find a permanent and progressive sense of serendipity as they progressed through the formative years of surgical training. With all the opportunity for patient care, he emphasized that the fresh associations that burst forth from youthful minds could create new and original ideas. It was a bonanza just waiting to be harvested by fertile young minds. It was present every day before you, "a movable feast," he said, one you should take with you on your holiday when you would have time to reflect on original ideas. Thus was serendipity, the gift of finding valuable or agreeable things not actively sought: Einstein watching moving trains and hitting on the idea of relativity, Darwin in the Galapagos thinking up the theory of evolution while observing the flights of finches, Fleming accidentally noting the effects of penicillin mold on a dish of bacteria. In the vineyard of research it is always hoped one will experience a moment of epiphany that will ultimately lead to a contribution for the betterment of mankind. Serendipity was the only thing I took with me from the university for my vacation in Kesar Falls.

I had no problems connecting with Dr. Marston at the Portland Airport. I couldn't miss him. He was a big bull of a man with a barrel chest, a protuberant abdomen, and a broad infectious smile. He was an extreme extrovert, the kind that finishes your sentences for you.

That afternoon, before going home, he took me on rounds to orient me to his patients. We drove the first of what turned out to be 10,000 miles of driving for me in six weeks of making house calls on the halt and lame, the dead and dying, the infirm and mentally ill, the goldbricks and compulsive eaters, and all manner of sights, sounds, and smells of human pathology, both soluble and insoluble, appreciative and hostile. Mostly Dr. Marston told me, "When in doubt, give them a shot of B-12. Tell them it's the latest and greatest." I knew B-12 had been found curative in pernicious anemia, especially in old people whose stomachs no longer secreted acid, but it seemed a little dis-

honest to give it out routinely as a placebo. By the time I had reached 3,000 miles in my driving, however, I was giving B-12 shots to everybody, and they loved me for it.

As I think back on my time in Kesar Falls, cases pile in upon my memory attached to real faces and real people as if it were yesterday. I remember the in-home delivery of a baby of a multiparous woman who knew more about unraveling a strangulating umbilical cord from her newborn baby's neck than I did. I remember an angry, old, intoxicated employee who sat on the end of a logging chute in protest against his employer who warned him once to move, then sent a log crashing down that broke his back and eventually killed him. I remember caring for a woman the whole time I was there who had been operated on for a simple breast biopsy at the Massachusetts General Hospital by one of the country's finest breast specialists, who had caused her wound to form a huge blood clot and a smoldering, disfiguring infection. I remember the excitement one night of correcting congestive heart failure with the old-fashioned technique of rotating arm and leg tourniquets because I was out of medication, of reversing childhood asthma attacks with intravenous aminophyllin, and of removing splinters from toes and cinders from eyes at all hours of night and day.

I write of these memories not to distract, but to show how, with all my real doctoring going on, serendipity was, nevertheless, gradually making its mysterious inroads into my healing ulcer. It had come about just as the professor had said it would: from seeing and talking with a patient, W.D., who had come into my office two weeks after my arrival complaining of a persistent ulcer-like stomachache and a lump in her neck. Feeling the lump, it seemed high to me, high and on the right, a 2 cm mass separated from the thyroid, possibly an enlarged parathyroid gland. Getting to know her, talking with her over a period of two or more weeks, the truth finally came out. She had been to Boston and seen the great endocrinologist Fuller Albright, MD, who had done some tests, told her that her serum calcium was elevated, made the diagnosis of parathyroid adenoma, and recommended curative surgery, which she had refused.

In the early 1950s, Albright had beautifully delineated the function of the neck's parathyroid glands, showing how they regulated calcium me-

tabolism in our body by maintaining a factored chemical metabolism with phosphorous in our bloodstream. The normal absorption of calcium was through our intestine and only from our bones whenever the body was not getting enough for proper balance with circulating phosphorous. When there was a functioning tumor, however, such as W.D. had described with her parathyroid adenoma, there was a massive outpouring of hormone that caused calcium to be removed from bone and to circulate at toxic levels in the body.

The mnemonic drilled into us for such parathyroid adenomas was that they caused “stones, bones, and abdominal groans.” The stones were kidney stones resulting from the precipitation of calcium salts secreted in superabundance in the urinary system, usually small but sometimes growing to staghorn size, and always painful. The bone symptoms came from calcium demineralization in the skeleton, from weakness in support, causing pain on motion and often stress and spontaneous fractures. If hypercalcemia caused the stone symptoms and hypercalcemia caused the bone symptoms, it seemed to follow as the night the day that hypercalcemia also caused the abdominal groans. But, we are all products of our time, and that was not the way the medical wind was blowing then. When I left Kesar Falls, I had persuaded W.D. to have her operation and myself that parathyroid hormone itself was causing ulcers.

Beliefs about ulcers

“Kein geschwur ohne sauer.” Translated from the German, it means “no ulcer without acid.” It was our mantra. The work of Lester Dragsted at the University of Chicago had sensitized all of us to the powerful effects of gastric hydrochloric acid. If you took a beaker of gastric juice and put it on the mantle, he claimed, you could add any protoplasm in the world to it and see its ability to digest all living tissue. That’s what it is doing with the stomach when ulcers form. It’s astounding we can control it at all, that it doesn’t digest away our insides.

Taking Dragsted’s lead, all efforts were directed at acid control, including 80 percent surgical resections of the stomach, which removed nearly all the acid-producing cells, the parietal cells, at the extreme top of the stomach. All efforts short of

surgery were being directed to control the production of acid by finding the source of its stimulus. Rather than block the acid, we looked for the cause of its secretion. There were no *H. pylori* bacteria to implicate and no H2 acid blockers like we have today, virtually eliminating the acid component of routine ulcer disease. We looked to the cause of acid release. We looked to emotions and hormones.

In the 1950s, the medical world was in awe of psychiatry and endocrinology. Psychiatry was the only course we were required to take every term for four years at Columbia University’s College of Physicians and Surgeons. Psychiatry’s handmaiden was endocrinology. Together they described the hypothalamic-pituitary-adrenal axis, which involved the seat of our emotions in the brain neatly influencing the body’s hormonal response to stress. A state of fear or anxiety was relayed to the pituitary master gland, which signaled the adrenals to produce adrenalin, which got your heart racing and your stomach churning as excitatory impulses releasing acid were also delivered from the brain to the stomach via the vagus nerve.

About that same time, the surgical world was electrified by a report from Zollinger and Ellison at Ohio State indicating they had found a state of hyperacidity in a small series of patients in whom ectopic tumors of the bowel were found at a distance from the stomach that actually produced a powerful circulating hormone, gastrin, which had been known for years to act on the parietal cells of the stomach, causing release of acid in large amounts. Gastrin had been discovered in the lining of normal hog stomachs 30 years earlier with little fanfare. But suddenly, with the knowledge that Zollinger’s patients had been afflicted with gastrin toxicity, all developing large recurrent ulcers in the stomach and small bowel, associated with massive diarrhea, the thrust of research on ulcer formation was once again intensely refocused on the endocrinological basis of ulcer disease. Three stages of stomach digestion were delineated (cephalic, gastric, and intestinal), all of which were carefully described as having a hormonal basis that became dysfunctional in ulcer disease.

In this atmosphere, it was a very small step to think that parathormone could profitably join the parade of hormone experiments to delineate a cause of ulcer disease, as it had already been implicated by virtue of so many ulcers being found in

patients with parathyroid tumors. So, research was rapidly conceived to demonstrate the influence of this hormone on gastric secretion. These experiments were mostly of an acute nature because any prolonged administration of the parathyroid hormone gave rise to a severe immune reaction, meaning there was never an experiment successfully sustained long enough to produce a state of hypercalcemia analogous to humans. Not surprisingly, no changes in acid secretion ever were observed.

A ride in the woods

A few years after my summer in Maine, I was “back in the bullpen” and feeling better, as I had attained the security of seniority, despite the stressful pyramidal nature of a training program that began with eight residents and finished with only four chief surgical residents. I once again thought to take a restful summer vacation prior to beginning my chief residency in surgery at Cincinnati General Hospital. I was offered and accepted a job as staff physician at a dude ranch in Wyoming. In the years since Kesar Falls, I had followed with lingering interest the research literature on the formation of peptic ulcers in cases of parathyroid disease. The focus had remained on parathormone and little progress had been made. One thing I had noticed rather casually in some of my clinical patients was that conditions that released calcium by destroying bone, such as tuberculosis, sarcoidosis, and metastatic prostate and breast cancer, were often accompanied by severe, recalcitrant, symptomatic stomach ulcers. But I didn’t really think about it much until Wyoming.

There are not many places in this world more beautiful than the eastern foothills of the Little Big Horn Mountains in June. At the HF Bar Ranch there was a plethora of children, young girls and boys whose youthful parents were more than happy to unload their care on the reliable young surgeon. I would arrange horseback expeditions for them to explore this enchanted area. One day, on a high noon ride, two children sprang ahead to follow a deer that led us through a ravine to a trail that opened suddenly onto a deep pit wedged between four large rocks. There before us, piled high as the eye could see, was a mass grave—the broken and scattered skeletons of hundreds of deer. With the noon sun overhead, we were able to see the

eburnated bones with shining clarity. It was our own secret Stonehenge. The children wanted to gather the bones immediately. I said they had to promise to keep our secret. My idea was to assemble a deer skeleton in my cabin and teach some anatomy. So, every day for a month we returned and puzzled them together to form a fine deer skeleton.

I tell this tale to illustrate how serendipity was working its slow, subtle wiles on me in ways that would eventually lead to my one good research idea. Traipsing back and forth on horseback with bones hanging from saddles and rattling in the wind like some ghoulish mobiles, I got to thinking about calcium metabolism once again. I went over in my mind the whole scenario of how people with parathyroid adenomas had peptic ulcers, how parathormone itself could not be demonstrated to cause hypersecretion of gastric juice, that gastric juice was the sine qua non of ulcer formation, that parathyroid disease patients had elevated blood calcium levels, that other patients with elevated calcium levels also got ulcers. Suddenly it came to me that hypercalcemia itself caused gastric hypersecretion and ulcers followed in kind.

Such was my rare moment of epiphany, a brief clear vision after seven long years of muddled thinking. It had happened just as the professor said it would. I felt as Constantine must have felt when he saw the sparkling vision of the cross at the bridge. With the children riding nearby singing, I rode home in perfect peace, watching the sun spread its magnificent colors and sink slowly behind the Big Horns. Stealthy serendipity had done its job.

But I only had my idea. Now I had to prove it.

“Strong” to the rescue

The next year, by extreme good fortune, I received a research fellowship at the University of California in San Francisco and a munificent award of \$10,000. My idea was to set up a group of dogs similar to those Dragsted was using and the kind Pavlov had used, with pouches that would allow me to measure acid secretion. I established a colony of 25 dogs, all healthy, each with a little pouch hanging off the side. They were fed a consistent diet at the same time each day, and the pouches were measured for content and volume

each morning. After a baseline stabilization period of three months, the dogs were rendered hypercalcemic by intramuscular shots of vitamin D. Serum calcium levels were measured regularly, and when they became elevated, the vitamin D was discontinued and the blood calcium level allowed to coast back to normal over time. It was a neat project.

My experiment was going great guns for a year-and-a-half, when a researcher's worst nightmare happened. The dogs became stricken with distemper. Sometimes I stayed up all night with them to nurse them back to health, but to no avail. I was sick, heartbroken. I watched them go. There was absolutely nothing I could do. One by one all of them died...all but one precious dog, a boxer we called Strong because of the special pungency of his urine. You and I and the world owe Strong a debt of gratitude, for while he watched his friends die and leave him all alone, he survived, allowing me to complete my experiment.

Mine was a chronic experiment intended to simulate the human hypercalcemic state by extending it over many months at a time. Strong, therefore, provided us with his own control, exhibiting before, during, and after phases of blood calcium alterations. I was able to show that when his blood calcium level rose, his gastric output of acid increased, and when those elevated levels gradually returned to normal, so did his pouch secretion. With Strong's help, I proved my thesis: hypercalcemia causes chronic gastric hypersecretion, which can cause ulcers. In retrospect, it all seems so simple.

When I excitedly took my results to the chair of the department, he immediately removed from the paper all the names of the colleagues who had so diligently helped me, and said it didn't have a chance for publication because, after all, it was just one lousy dog. But, he said I could send it anywhere under my name alone and without his imprimatur. So I did. I sent it to our most prestigious surgical journal, *The Annals of Surgery*. Miraculously, I received a special delivery acceptance by return mail. Now that it had been accepted, the chairman, without apology, saw fit to add his name to the paper. But, by then, I didn't care because also in the acceptance was a promise for immediate publication due to the importance of the finding. It came forth in volume 155, pages 406-411, 1962, of the *Annals*. My reaction was the time-honored one

of authors, who tell you, yes, it's nice to see it out there, but it was so much more fun doing it.

W.D. had her operation and was cured, Marston continued to give B-12 shots for 25 more years, and although more and bigger studies on hypercalcemia were conducted to prove its exacerbating effect on gastric secretion, Strong's effort was the breakthrough, the seminal pilot study that inspired others to go on to greater heights and international recognition. For my part, I quietly entered the private practice of surgery, far away from people who added and subtracted names to papers. Before leaving, I undid Strong's pouch, hooked him up proper, and kept him as my honored pet, encouraging him to father as many pups as he wanted until his natural death many years later. As I think back on it now in the twilight of my career, it seems time the world heard of Strong and me and of the sunlight just right on the deer bones in their secret hiding place one summer high noon long ago in Wyoming, when an idea came clean to me and finally was born. □

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