Tiny unseeables

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The graduate student arrived for our meeting. She jumped right in.

"I want to forgo research and just teach medical students. Like you do."

I never saw that coming. Forgo research? Just teach? She'd misunderstood everything.

I've always considered myself a researcher at heart. For 25 years, I studied the physiology of kidney nephrons—one million crammed into each kidney.

Those tiny unseeables had been my life's work.

In graduate school in the early 1970s, I got hooked on the kidneys' role in calcium homeostasis. The field offered big unanswered questions. For starters, where in the nephron is calcium transported? (Nephrons have 12 distinct parts, each with a different function). Do hormones modulate calcium, and do the hormones talk to each other? Does calcium regulate itself (an intriguing idea)? The topic of calcium and diuretics was its own gold mine. To study these questions, there was no shortcut. I had to go straight to the nephrons.

Cornell Medical College was the mecca of nephron micropuncture, so it was the place to study the calcium questions. For five postdoctoral years at Cornell, I learned the art of collecting and analyzing nanoliters of nephron fluid. (That's one-billionth of a drop.)

Micropuncture was only possible because of "Herr S." in Germany. He made high-power microscopes to visualize nephrons on the surface of rat kidneys, "kidney cups" to stabilize the lima bean-sized kidneys, pullers and grinders to turn molten glass into sharp micropipettes (with tips the diameter of a human hair), micromanipulators to steer the pipettes, and ultra-micro chemical measuring devices. Once a year, he visited Cornell to calibrate his equipment. He twiddled tiny knobs and screws, while muttering under his breath in German. Then he was out the door, not to be seen again until the following year.

In a typical micropuncture experiment, the researcher hunches over the setup for hours, peering at rat nephrons, trying to find a "good one." The goal is to aim a sharp micropipette at the good one and collect its fluid without mangling it. The pipette is steadied with infinitesimal turns on micromanipulator knobs, as the rat's breathing and heartbeat threaten to dislodge it. An elite researcher can manage several pipettes and manipulators at once.

And there's one more thing. Initial studies suggested that calcium is regulated in the "distal" nephron (the last of the 12 nephron parts). Distal nephrons rarely come to the kidney surface to be micropunctured, perhaps one or two out of the whole million. So getting one distal would be a good day. Botch that, and the experiment is a bust.

The lab is pin-drop quiet except for an occasional sigh or curse.

When the search for distals is finally exhausted, the researcher straightens up, red-eyed and headachy. If the collection of nephron fluid has been successful, it goes straight to the chemical analysis phase. Nephron samples don't keep.

When a nephron makes it to the finish line, numbers are crunched and entered in neat notebook columns—volume, flow rate, water reabsorption, calcium concentration, calcium reabsorption, length of nephron (measured with a latex cast), reabsorption factored by length. Breath is held as the data emerge. Will they be consistent with the previous days' and move tentative conclusions forward, or will they be outliers and suggest new possibilities?

All told, these were ten-hour days, spent in complete focus, mostly alone.

Micropuncture's mantra is: do whatever it takes. Little did I know then that this mantra was also preparing me to be a teacher.

After my extended postdoctoral training, I brought nephron micropuncture to a faculty position at the VCU School of Medicine.

The calcium questions were a gold mine. However, research doesn't pay for itself. I would need an NIH "RO1" (research project grant for independent investigators) to pay for specialized equipment from Herr S., experimental animals, supplies, travel money for meetings, and a technician's salary.

The stakes were clear—no grant, no research, no job.

My first NIH grant was funded 12 months after starting the faculty job. I wasted no time digging into the calcium experiments. I would need to show significant progress in a renewal application within three years. That's the typical cycle for competitive research.

At scientific meetings, a small club of fellow nephron warriors from around the world encouraged each other and commiserated. We all agreed that the grueling experiments took a toll. To survive in research, we had to train graduate students to do some of the hands-on work.

And this was my predicament. Most prospects would rotate through my lab, take one look at the micromanipulators and flee for greener pastures. A braver cohort, undeterred, would agree to give it a whirl, but quit after a week of trying to pull even one viable micropipette. (It was impossible to explain the flick of the wrist that was needed; it was a feeling that had to be developed and they didn't stay long enough to get the feeling.) Still others would last longer and make it all the way to anesthetizing a rat, exposing a kidney, and finagling it into the kidney cup without ripping it out of the animal. One student made it that far and proudly called me over to see his work: it was a clean surgical field without a drop of blood, but I had to break the news that his rat was dead. We parted ways.

Who could blame the students? They wanted a PhD before the dissertation clock ran out.

I was semi-panicked much of the time, dreading a future where I was chained to the nephron setup. If I couldn't train others to do some of the hands-on work, how would I have time to keep up with the literature, apply for grants, write research papers, give talks at meetings, and teach?

The antidote to my semi-panic was teaching physiology to medical students. I said "yes" to more teaching than was necessary—"Sure I'll take those extra lectures." Easy topics, hard topics, topics no one else wanted to teach. I loved greeting the students with, "it's surfactant day," or, "where do we stand on hemoglobin day?" Their expressions would run the gamut from, "ooh, can't wait," to "whatever, I'm so tired." Still, sharing physiology with medical students lifted my spirits with its possibilities. Teaching added a human dimension to my life of chasing nephrons in the lab—research felt more meaningful when it was part of something larger.

I was tooling along, balancing research and teaching, when I received an unexpected offer to become one of the deans for medical education.

"You mean full-time?"

I deliberated long and hard. Leaving basic science research and not renewing my NIH grant would be irreversible decisions. Yet the medical education job was an opportunity that might not come again.

I tried to picture my professional life without the singular focus of finding distals. I brooded over breaking an unwritten pact to contribute to science "til death do

us part." I worried that my colleagues would think less of me. None of these ruminations could help me decide. Either way, something cherished would be given up. Either way, I would be taking a leap of faith.

After more than 25 years in the trenches of research, I said goodbye to my lab and gave away the specialized equipment. Except for the custom-made kidney cups—I just couldn't. I tucked them away in a desk drawer with my vintage slide rule from high school, fond reminders of bygone days.

To avoid regret, I stopped following nephron calcium research. I lost touch with my fellow warriors. Since I was no longer in the trenches with them, what would we talk about? They knew I'd chosen to walk away.

Meanwhile, I was busy with teaching, running the medical physiology course, and dean duties of overseeing the preclinical medical curriculum. There was no time to think about my earlier life in research.

Until about ten years later, when a groundbreaking kidney discovery hit the news. Suddenly, the research that I'd ignored for a decade summoned me. I had to catch up on nephron calcium. Several labs had made significant progress on hormones and diuretics since I'd left off. As I read, I was stunned to see my earlier research cited as "the first." I needed a double take to recognize myself. But yes, it was me.

Nostalgia for the research days rushed in—the kidney cups, the flick of the wrist, the manipulators stationed around a tiny rat kidney, the pressure to find the rare distal, the burning calcium questions. Some of the fondest memories were of talking science with colleagues after long days in the lab. We were unabashed science nerds, holding forth on ion gradients, driving forces, and single channel methodologies. To settle friendly disputes, we did what science nerds do—we pulled journals off shelves and agreed to agree on whatever the data showed. There was never a final conclusion, only the promise of "to be continued."

Those reminiscences sparked an "aha" that I had totally missed before. Nephron research may have been in my past, but I had been replicating the research ethic in my physiology teaching the whole time. The research ethic, deeply learned over 25 years, is also my teaching ethic.

I returned to the medical school classroom with this realization. It was all there. The drive to push knowledge forward, the diligence to hunch over rat kidneys and search for distals in a sea of not-distals, the delight in the unexpected and the not-knowing, the seeking out of colleagues who raise the bar. Just as the researcher does, I ask the students to join me in, "how does it work, what have we missed, and why, why, why?" As a teacher, I must welcome whatever comes my way, whatever questions are asked, whatever wild speculations are made. "I don't know, let's go after it together." And books are pulled off shelves.

Of course, some students think that this "how, why, what else?" kind of teaching is a waste of time. They slouch in their seats, roll their eyes, and mouth, "Let's wrap it up." This teaching approach won't speak to every student—it doesn't need to. I protect it for even one student who lights up at the exceptions, who obsesses over the coolest thing they learned that day, who questions, "How do we know that?" I protect it too for even one student on the fence, because I know that fires can be lit by classroom moments.

Nothing in this picture says, "forgo research and just teach." Everything in this picture says, "more depth, more seriousness, more rigor."

Early in my time as a post doc, I'd peer through the glass doors of the medical library at Cornell and see the same regulars every day. They sat at long communal tables, poring over journals. I wanted to be like them, a medical library regular. During breaks in lab action, I went in to read the latest issues of the *American Journal of Physiology* or *Journal of Clinical Investigation.* I was trying on the cloak of scholars.

When one of my students was about to start a fellowship at Cornell, I told her about the glass doors and the library habit. "I'll do that, too," she said, lighting up. Now, years later, she's a professor at a medical school, caring for patients and teaching students.

So the mantle passes.

As a teacher, I am entirely born of research—of decades of midnight oil burned, of minute turns of micromanipulator knobs so that the "good one" didn't slip away, of library habits unbroken, and of the embrace of scholars who raised the bar.

Unseeable and elusive as distal nephrons.

You might have missed it, unless you knew what to look for.