Balancing on the road less traveled

Published, Papers in Press, March 28, 2019, DOI 10.1074/jbc.AW119.008136

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Sitting down to the task of writing, I found my pen drifting inexorably to a personal recollection of the metaphorical transcontinental road that I had traveled to become a scientist, instead of reviewing a facet of our scientific contributions. Factors that prepared me for my improbable journey in an era when international calls were operator-assisted and unaffordable and the internet was the stuff of science fiction were my family’s love and the sheltered environment of my all-girls school and college experiences, which nurtured my self-confidence. The path of scientific inquiry is heady, and it is hard. The paucity of diversity, of women and minorities, particularly as the road steepens, helps perpetuate stereotypes and inadvertently encourages disparities. It is my hope that by sharing snippets of my journey, enriched as it has been by a diversity of mentors, mentees, colleagues, and friends, and the opportunity to express my curiosity and creativity, that a young person contemplating the scientific road will find encouragement.

Picking the path

Born an army brat, my early life was one of perpetual motion, a blur of changing geographies, schools, languages, and faces. By the time I graduated from high school at the age of 14, I had changed 10 schools, skipped three grades, and crisscrossed India a few times. My father served in the Indian Army; my mother was the General’s wife! As the second of three daughters educated in all-girls convents by Irish nuns, I was brought up to be independent. I coasted through school without any particular disciplinary proclivity, and it was not until my final 2 years that I became hooked on Physics. As the time for applying to college approached, I overheard a conversation between my father and an older cousin about the impracticality of the Indian Institutes of Technology (or IITs) for my academic pursuits. The IITs were hallowed places for STEM study. In those days, women represented about a couple of percent of the incoming class. Heeding their concern, I headed for an all-girls college instead, Miranda House in Delhi University. I selected the honors program in Botany because that was the strongest science department in the college. It was not until my M.Sc. degree (also in Botany from Delhi University) that I stepped into a coed class for the first time!

I coasted again through college, studying at the leisurely pace afforded by a curriculum in which annual exams constituted the only form of evaluation. This unstructured learning environment bereft of assignments and busy work was ideal for affording me time to dabble in theater, politics (I was President of the students’ union in Miranda House), yoga, and dance. A few outstanding teachers prominently stood above the fray and served as important guides. I remember them for their perspicacity, their love of science, and their balanced interest in the arts. One, Dr. Nirmala Maheshwari, regularly invited me to her home where I browsed through her personal subscriptions of the major journals, a rare treat in an environment where the dusty libraries were woefully dated. I was also afforded on these occasions audience with Prof. Satish Maheshwari, her husband and fellow botanist with a formidable reputation. I felt spoiled by their attention and greatly benefited from their personal interest in and early guidance of my career. Another highlight of those years was two summers spent at the Tata Institute of Fundamental Research, Mumbai, where I got my first taste of research, working on α-glucosidase in fruit fly legs in Prof. Obaid Siddiqui’s laboratory. It was a heady experience and sealed my interest in research. It also introduced me to a fundamental tenet of experimental science, i.e. the importance of controls. I had been reluctant to repeatedly sacrifice precious tarsi, my enzyme source, which I isolated by sieving frozen flies, only to obtain the expected result from redoing controls. When I found to my dismay that my data without controls were tossed from consideration, I quickly learned my lesson. The tables have since turned, and I repeatedly hammer away at the importance of controls in my group!

Although I had trained classically, steeped in Linnaean taxonomy, embryology, and such, my interests had been veering toward biochemistry, a discipline that did not formally exist in India at the time. I remember presenting Sanger’s sequencing method in one of my classes and being blown away by its elegance and its power. Biology was changing, and I was being pulled to shores where interdisciplinary research was taking form. I applied to a few universities in the United States but was admitted with full financial support to only one. It’s a long story, but delayed graduate record examination scores combined with a chance meeting with Prof. Joyce Diwan visiting from Rensselaer Polytechnic Institute, who handed me an application form, conspired to seal my fate.

Arriving in the United States

My incessant travels as a child had not prepared me for my next station; getting to the United States felt akin to interplanetary travel, and once here, a deep sense of isolation set in. I...
missed the cultural vibrancy of the city that I had left behind as I joined a small private school with a nerdy reputation. These challenges were offset somewhat by the excitement of discovering bioorganic chemistry. After the very first lecture in an enzymology course, I knew that I had found in the instructor Jim Coward my Ph.D. mentor and switched to the newly formed Biochemistry graduate program. As the first Botany student accepted into Jim’s primarily synthetic organic chemistry laboratory, I floundered for the first 2 years, striving to optimize the synthesis of $^{17}$O- and $^{18}$O-labeled compounds, which I subsequently used to demonstrate the intermediacy of acylphosphate species in reactions catalyzed by dihydrofolate synthetase and folylpolyglutamate synthetase (1). Over time I also grew to enjoy living in New England; on many weekends I escaped to hike and to climb rock faces in the Adirondacks or the Shawangunks. And occasionally when my finances allowed it, I escaped to the cultural riches of the Big Apple.

As I wrapped up my graduate research in 4 years, I began looking for postdoctoral positions in Switzerland, motivated by personal entanglements at that time. I did, however, consider a single United States laboratory in response to a letter from Rowena Matthews that Jim handed to me. I had met Rowena a few months earlier at my first scientific meeting in Airlie House in Virginia, which Jim had flown me to in a private four-seater. I vividly remembered the excitement of an after lunch walk with Rowena and Steve Benkovic down a grassy path, discussing one-carbon metabolism. During my interview at the University of Michigan, I presented my thesis research at the Monday evening “Chatters” club graced by the presence of Vince Massey, Charles Williams, Dave Ballou, Martha Ludwig, and of course, Rowena. The stimulating interactions during that visit combined with Rowena’s personal touch and the vibrancy of life in Ann Arbor made my next career decision an easy one.

My postdoctoral training period was one of significant scientific growth. I arrived in Rowena’s tightly knit enzymology group and was tasked with cloning and manually sequencing B$_{12}$-dependent methionine synthase (2). Rowena was on sabbatical leave during my first year. Because my only real research experience was in synthetic organic chemistry, I regularly hiked from the Biophysics Department on North Campus to the laboratories of Prasanta Datta and Fred Neidhart in the medical school for guidance. My first contribution to Rowena’s group, however, was deeply embarrassing. I managed in the first week to erase the hard drive of the only shared lab computer at that time! To my relief, the computer jocks at Michigan were not too concerned and retrieved the data relatively quickly. The interesting cast of characters in John Langmore’s, Sam Krimm’s, and Dan Axelrod’s labs in the Biophysics Department at that time enhanced my postdoctoral experience. I also spent long hours working initially with a very small group of inexperienced lab members, I felt slow to get my research off the ground. One of my early postdocs, Shinichi Taoka, was, however, superbly trained. He was much older than me and initially had a lot of trouble adjusting to the idea of a young female boss. We locked horns regularly as he continually opposed my scientific input. I often felt exhausted from battling issues at multiple levels that were brought on unwittingly by my gender. I was unprepared to deal with these challenges as I had trained with two very fine mentors and had no prior firsthand experience with women-in-science issues.

Looking back on my Nebraska years makes me smile now as warm memories abound of my interactions with my colleagues and with the community. At some point along the way, I decided that I had to pick my battles to avoid frequent migraines and to be productive. At some point too, the doubts about my commitment to science seemed to dispel among my colleagues who looked increasingly to me to lead. In retrospect, we could have eased the path had I been less inclined to outrage and my colleagues more inclined to give me the benefit of the doubt. I stepped in as interim chair in 2001 and, in 2002, started the intercampus and multidisciplinary National Institutes of Health (NIH)-funded Redox Biology Center. What followed was a period of rapid expansion and connection at many levels as the Center invested in building research infrastructure through core facilities, made excellent hires across departments, mentored junior faculty to independent funding success, started the Gordon Research Conference on Thiol-based

The balancing act

Back in the early 1990s, nepotism rules restricted dual career placements. We ended up at the University of Nebraska-Lincoln where a progressive new chair, Marion O’Leary, convinced his colleagues to extend dual offers, although the faculty was of the strong opinion that I had seemed very disinterested during my interview. In reality, I was in the first trimester of a pregnancy and very nauseous. I remember that I had quickly surveyed each office that I entered for the trashcan, in case I needed to spew into one. Marion, who was in touch with Rowena, was aware of my situation. So, in the late summer of 1991, we relocated to Lincoln, NE, and I showed up at work 8 months pregnant! The next 5 years were very difficult as I struggled to feel at home in a community where curiosity about the name of my church often eclipsed interest in my own name and history. I finally found a salve for this irritation and started to respond that I belonged to the church of cobalamin (a.k.a. B$_{12}$), which appeared to be acceptable! I also struggled at work where another faculty member and I were the first women to be hired in the department. She soon decided to leave science altogether and went off to retrain as an architect. I, on the other hand, continued on the tenure track path, feeling like a Cather Pioneer, the lone nonwhite and woman faculty member in the Biochemistry Department. I often felt that my colleagues viewed my hire as a mistake because I could not possibly be serious about science as I nurtured two, not just one pregnancy, and the children who ensued. Many years later, I became the first Willa Cather Professor of Biochemistry!

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Redox Regulation and Signaling, initiated the National Science Foundation (NSF)-funded summer Research Experiences for Undergraduates (REU) program, edited a book on redox biochemistry published by Wiley, and simply elevated the level of science at the University. We knitted the redox community together through frequent social and scientific interactions. The camaraderie among the faculty percolated down to postdocs and students and fanned out to our families, who gathered at monthly potlucks.

**Having fun with science**

Although I was increasingly getting drawn into administration, my research program was also growing. It had all started with writing my first grant proposal when I was on maternity leave while my daughter slept. I vividly remember the thrill of receiving that first NIH award. I actually enjoy the 4-year ritual of thinking broadly and also specifically about scientific directions as grants come up for renewal. When I started my lab, we were focused on characterizing the two mammalian enzymes that use $\text{B}_{12}$: elucidating the mechanism of posttranslational regulation of methionine synthase and describing the reaction coordinate of the radical enzyme methylmalonyl-CoA mutase (3). The 1990s interest in elevated plasma homocysteine as a risk factor for cardiovascular disease had spurred an intense interest in looking for polymorphisms in human methionine synthase that might be correlated with an increased risk. Cloning the cDNA had, however, proved to be an elusive goal until, as is often the case in science, three laboratories converged on it almost simultaneously. With our collaborators, we had also identified the first mutations in methionine synthase associated with homocystinuria. I remember the tension at the FASEB conference as the three groups became aware of each other’s findings. It was there that I experienced the underbelly of competition first hand as the veneer of civility quickly peeled off. Two of the three groups published their work back-to-back (ours made the cover (4)). No risk-associated polymorphisms were found!

Our work on methylmalonyl-CoA mutase led us deep into radical chemistry and quantum tunneling and to interactions with many outstanding collaborators who enriched our science (5). They included physicians like David Rosenblatt, spectroscopists like Tom Spiro and Thomas Brunold, and computational chemists like Piotr Paneth and Don Truhlar. I was equally enriched by interactions with scientists like Jack Kirsch and Judith Klinman, who took an interest in my work, although their own scientific pursuits were focused elsewhere. As I was beginning my career, I heeded Helmut Beinert’s advice to pick a problem that was not moving and to move it. I have not worked in crowded fields, although on several occasions, we have found ourselves in crowded spaces. The road less traveled is in fact an apt metaphor for my scientific journey from its unlikely beginnings in a peripatetic family. I had traveled by rail all over India, and one of my childhood fantasies was to upgrade to air travel and be an air hostess. Although this career aspiration was not fulfilled, I have had more than my fill of incessant air travel. Shaped by the hybrid vigor of cultural miscegenation, I am very much at home professionally in the west with its culture of independence and rational functionalism, and I am very much at home personally in the east with its culture of independence and fatalism. These contrasts always surface in personal attributes like patience. Although I can work patiently over years on unraveling a scientific problem, I struggle with impatience in my daily life. Age and the sage continue to reveal the remarkable promiscuity is reigned in to service cellular needs (8). The biochemistry of sulfide oxidation via a dedicated mitochondrial pathway is also poorly studied, and we have been elucidating its organizational logic, its impact on cellular bioenergetics, and how the committing enzyme, which exhibits remarkable substrate laxity, is regulated (9–11).

I started my career with the idealistic notion that I would always be a bench scientist, relishing the excitement of being present when the curtains parted on an experiment. That turned out to be a pipe dream. I have long since resigned myself to enjoying experiments vicariously and have been extraordinarily lucky to have been surrounded and supported by a talented and diverse group of researchers in my laboratory. Seeing my trainees take steps toward their own scientific maturity and independence is one of the most fulfilling aspects of my work. My academic family has been prolific with 39 postdoctoral fellows, 24 graduate students, and 38 undergraduate students so far. With a family this large, I have refrained from advertising to the contributions of a few. Each has been a teacher, some of easy lessons, others more challenging, but all important.

In the spring of 2006, I remember receiving an acceptance letter for a JBC manuscript within 5 min of submitting the revised version. I thanked the Associate Editor handling the manuscript, Bill Smith. I had not previously met Bill and asked whether he was always this efficient. His response was that he was at an airport with time on his hands. It included a P.S. asking whether I would be interested in considering the newly created Vince Massey Professorship in his department. That was my introduction to Bill’s laid-back Midwestern style and, unexpectedly, to the start of a journey back to the University of Michigan in 2007.

**Some reflections**

Both $\text{B}_{12}$ enzymes reside in the same neighborhood and support sulfur metabolism either directly or indirectly. We have been studying sulfur metabolism for many years with a more recent focus on hydrogen sulfide, a malodorous gas of disrepute but now acknowledged as a product of our own metabolism (7). Enzymes responsible for $\text{H}_2\text{~S}$ biogenesis, notably those in the transsulfuration pathway, also wear other hats, regulating the flow of sulfur from homocysteine to cysteine. Our studies are revealing how their remarkable promiscuity is reigned in to service cellular needs (8). The biochemistry of sulfide oxidation via a dedicated mitochondrial pathway is also poorly studied, and we have been elucidating its organizational logic, its impact on cellular bioenergetics, and how the committing enzyme, which exhibits remarkable substrate laxity, is regulated (9–11).

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companionship of my boundlessly patient partner Dennis Chernin are, however, helping me mellow.

As one grows, it is important to also sow, returning to one’s community, a bit of oneself. My involvement as Department Head and Center Director was too much too soon in my career and left me with a deep inappetence for a major administrative role. I have discovered a taste for editorial work and have revealed in working with the ASBMB administrative staff, particularly Barbara Gordon and Nancy Rodnan. Being an Associate Editor for JBC and Chemical Reviews helps me help others publish in a timely manner. It has in turn helped me develop skills for communicating critical feedback and declinations constructively. Amusingly, my editorial pen spills over to my volunteer work at the only women’s prison in Michigan where I serve women with long-term or life sentences and am the editor of their newsletter.

So as I contemplate the path that led me to the Merck Award and as I look ahead, I acknowledge the sheer good fortune of having found science to express my curiosity and creativity; the support of husbands, family, and friends as a I strove for balance; mentees, mentors, and colleagues, who stimulated me; and children who accepted and supported their geeky mother with undeserved admiration.

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