

At the Edge of Life: The Autobiography of Nadrian C. Seeman

My father was born in Brooklyn, and despite a college degree, he earned his living as a traveling salesman during the Depression. My mother was born in Pittsburgh, graduated college, and taught elementary school there. She met and married my father in Pittsburgh in 1938; along with my maternal grandmother, my parents moved from Pittsburgh to Chicago in 1942. I was born in Chicago at the end of 1945 as the only child in their middle-class Jewish family. My father sold fur garments in Chicago (from 1953 in his own store), but my mother did not return to teaching until my grandmother died in 1963. In 1951, we moved to the Chicago suburb of Highland Park, where we remained until I went to college in 1962. I was a quiet child who preferred reading over sports, a characteristic that has persisted. Sputnik was launched in October, 1957; a year later, I became a 'Sputnik Kid' who was brought daily to the high school in the early morning, where I took a special algebra class, before spending the rest of the day at my middle school. As a nocturnal person, I didn't do all that well, but I was set on a path of advanced math and science courses from then until the end of high school. A year earlier, my father had begun a campaign to convince me that I wanted to be a physician. The math and science that I liked were not incompatible with my father's goal, so he gave me no flack about them. At about the time I got to high school, I lost whatever faith I might have had, and I've been an atheist ever since.

The most important scientific influence I had in my early life was my high school freshman biology teacher, John E. Broming. The school year was divided into six 6-week segments, and he devoted the first of these to teaching the class the rudiments of chemistry and physics as they applied to the structure of matter; this emphasis instilled in me the sense that life is a physico-chemical phenomenon, and that's where my head has been ever since, on the cusp of the physical and biological sciences, at the edge of life. In addition, when we did get to biology, I found it was pretty neat, with lots of nifty structures and shapes and an apparently logical nature that appealed to me. The sophomore chemistry teacher was not nearly so engaging, but the junior-year physics teacher, Ronald Townsend, was much better. I got a high school diploma at the end of my third year and went off to the University of Chicago as a pre-med. At the time, I didn't yet know that my job as a professor of science existed: I thought a university professor just did the same thing as a high school teacher, only teaching more advanced material. I had no idea that I could spend most of my day having fun by doing research and also get paid to do it. That was the most important thing I learned at Chicago.

It was damn near the only thing I learned. As Mark Twain put it, I didn't let college interfere with my education. I was a poor student, getting grades that were mediocre on a good day, and there weren't many of those. The only things I remember from my undergraduate science courses are the Watson-Crick pairing rules, that A pairs with T and G pairs with C. My grandmother died during my first year in college, and I recognized both the inevitability and finality of death. The notion of spending my life keeping other people alive for a few extra years lost any appeal it might have had for me. When I learned that a university career offered the pleasures of doing research, I announced to my parents that I wanted to become a biochemist, which I thought was the area closest to my interests. My father greeted my decision to become a scientist instead of a physician much as I imagine he would have welcomed a decision to become a mobster.

Biochemistry at Chicago in the middle 1960s turned out to be a great disappointment. The field as taught at that time treated little of the information content of molecular biology, which I sensed was really neat. Rather, it had been developed by organic chemists, and was basically the study of the metabolic transformations of small

molecules, not the study of the macromolecules that made biology special. When the realization of what biochemistry actually was all about sank in, I switched to physical chemistry, where I didn't do well, either. In the end, I was rejected by all the chemistry graduate schools to which I applied. I went to the Chemistry Department's advisor to present my predicament: I asked, "What can I do, nobody wants me?" His reply was, "That's not true. Uncle Sam -- he wants you!" This outrageous remark was uttered in the middle of the Vietnam War, to which I was staunchly opposed, both because of my left-wing politics, and also because I didn't want to return from Southeast Asia as a putrefying corpse in a body bag. Needless to say, this incident dampened my enthusiasm for my undergraduate institution.

Nevertheless, I managed to fast-talk my way into Chicago's graduate Biochemistry Department, where I didn't do much better in the basic biochemistry courses the second time around. During my spring vacation that year one of my roommates and I took a drive-around to San Francisco; the 46 hour continuous drive to Reno (as far as the car was going -- we rode a bus the rest of the way) with minimal sleep gave me hallucinations without drugs, and cleared a lot of cobwebs from my brain. I spent the week walking around Golden Gate Park, and decided that perhaps there were interesting things to be done in science, even though Watson & Crick and Monod & Jacob seemed to have solved all the big problems of which I was aware. I did a lot better the following quarter, but my performance was still inadequate. The key difference this time was the graduate student advisor in biochemistry, John H. Law. He saw that I was probably talented, but was not really interested in what was offered there. At the end of the year, he told me I should leave, and managed to get me into the new crystallography/biochemistry training program at the University of Pittsburgh. This was the single greatest favor anybody did for me before I left Chicago.

Pittsburgh was a totally different experience. I was immediately engaged in crystallography research, which was a lot of fun. Between Bryan Craven's crystallography course, Bob Rosenstein's tutelage and Helen Berman's friendly advice, I learned how to do crystallography, and more importantly how to think about 3D structure and symmetry. The laboratory was run by G.A. Jeffrey, whose gentle directing hand kept us fairly happy and adequately funded. Bob Stewart's Friday afternoon seminars at the Craig Street Inn taught me that one could learn, discuss and think productively about scientific matters over a beer. I have probably never done anything that I enjoy as much as solving high resolution small molecule crystal structures, both in Pittsburgh and later, but deep down the purely analytic nature of crystallography left something in me unsatisfied. Nevertheless, I was having fun and I was doing well, so I figured that I could deal with whatever problems there were at a later time.

The world was never far from us in those days; I solved my first crystal structure in 1968, presented it at the August American Crystallographic Association meeting in Buffalo, and returned to find a notice from my draft board that I had been re-classified 1A (prime candidate for drafting) and was called for my physical examination. Knowing a little about physiology, I ate a quarter pound of butter (absorbed into garlic bread) and a quart of soft ice cream, and was able to urinate sugar for them, enabling me to fail the physical. During my second year in Pittsburgh, I finally came to terms with my father. I drove to Chicago for my parents' anniversary, arriving at 3 am, totally exhausted. My father came out of his bedroom and told me my hair was too long. I replied in the harshest possible terms that I was an adult, that I was successful and self-supporting, and that if he did not change his attitude towards me (that I was a bum because I had no interest in medicine) he would never see me again. He capitulated, and we had a tolerable relationship for the remaining 20 months of his life: I handed him my thesis and he dropped dead the following day.

I got my degree in August, 1970, my self-confidence restored (arguably over-restored), and went off to Columbia University as a postdoc to work on the protein folding problem, which seemed to be important and interesting. I went to the laboratory of a prominent pompous person who turned out to be of light-weight intellectual heft. To describe our relationship euphemistically, we got along like oil and water. Within 4 months, I realized I had made a serious mistake, and started trying to leave for Alex Rich's laboratory at MIT. To do so entailed getting fellowships, so I suffered in the Columbia laboratory for over a year until they kicked in; at least I was in New York, which I loved. In the meantime, I was instrumental in the solution of the first dinucleoside phosphate structure, and garnered a little notoriety that way.

I really enjoyed Alex's lab for the first two years. During that period I was central in solving three more dinucleoside structures, including one that showed A-U Watson-Crick base pairing at high resolution for the first time. This resulted in more recognition, and times were briefly good. Alex always devoted a lot of energy to making the lab a fun and exciting place to pursue science; I really enjoyed the intellectual environment he created, mixing crystallographers with molecular biologists. This atmosphere stimulated me to write my most highly cited early paper, on protein-nucleic acid recognition. The structure containing the A-U base pairs was a lucky punch. I hadn't designed the crystal, it just happened. The final dinucleoside structure I solved contained an intercalating drug, but it was an unlucky punch, I didn't find what I was seeking, and it was the hardest of all to solve. It left a somewhat bitter taste in my mouth to have so little control over the structure of the crystal, a problem I would ultimately address. It's worth pointing out that I had crystallized none of these structures myself, I had just used my structure-solution skills to determine them.

By 1974, the crystallographic game was changing. Small molecules were becoming less and less important, and the key skill transformed from being good at solving structures to being good at crystallizing important macromolecules, usually proteins. I was totally unskilled at generating crystals, and I also had become unenthusiastic about proteins: Nucleic acids are very general, but every protein seems to be unique. I am just not suited to devoting years of my life (which it took in those days) to isolating, producing, and teasing out the structure of one of thousands of different proteins. This was a bit of a quandary. In addition, the mid-1970s were a bad time to be seeking an independent position as a biological crystallographer: We were considered expensive, and those of us competing for jobs were often vying with non-crystallographers whom the hiring departments preferred. I spent two years seeking an independent position, and was turned down by all the desirable and most of the undesirable departments where I interviewed. I used to kick the wall in my bedroom from frustration: I had spent almost a decade at my work, was widely recognized, and still I could not get a job. The hole in the wall wound up with a diameter over half a meter.

Eventually, I landed a position in the Biology Department at SUNY/Albany. The only thing worse than looking for a job was finding this one, because Albany was in many respects a scientific death sentence. Unlike MIT, many of my colleagues seemed far more interested in their families than in their science. In my generation, many of the students in Biology/Biochemistry Departments had the same appreciation of the importance of chemistry and physics that I did, but that tradition had died out by the time I got to Albany. The graduate student complement in Albany consisted largely of mathophobic failed pre-meds, and during my first seven years I recruited no graduate students, and as a beginner at an undistinguished institution, I attracted only ineffective postdocs. Without a full-time labor force, I was unable to grow crystals of anything

interesting to me or to anybody else, and thus was unable get my crystallographic show off the ground.

The good thing that happened there was that in the fall of 1978 Bruce Robinson (a postdoc with Leonard Lerman at the time) came into my office and asked if I could build a model of a Holliday Junction, a DNA branched junction structure that is an intermediate in genetic recombination. When we looked at the model, we discovered some asymmetries that we thought might have some impact on the kinetics of branch migration. Since I had nothing else working for me, I was able to write some code that simulated the process, and I started thinking about branched DNA. One of the problems with what Bruce and I were doing was that any hypotheses we might generate were untestable. This was because the symmetry of naturally-occurring branched molecules led to branch migration, whereby the branch point migrates all over the place, producing a polydisperse solution that ultimately resolves to duplex DNA. Thus, our project started off as a scholastic enterprise, rather than a scientific one. In the spring of 1979, I flew to the American Crystallographic Association meeting in Honolulu with Greg Petsko. During the flight, Greg mentioned that it might be possible to crystallize structures resembling intermediates in the hemoglobin oxygenation pathway by mixing iron-containing hemoglobin with cobalt-containing hemoglobin. This comment planted a seed in my head that one could use tricks to isolate analogs of intermediates like the Holliday junction. In a conversation shortly thereafter with Kathy McDonough, an undergraduate in my lab, that seed grew rapidly into the notion that by using synthetic DNA one could eliminate the symmetry inherent in naturally-occurring branched molecules, resulting in immobile branched junctions. This would enable us to test hypotheses, and also perhaps allow structural characterization.

I was elated with this idea, and started building more models; I showed one to Malcolm Casadaban, who visited my office on a trip to Albany. He asked if it were possible to make junctions with more arms than the four in a Holliday junction. I had no idea, but soon worked out that an evident structural constraint would permit eight arms in an immobile junction, although that is no longer the limit. In September, 1980, I went to the campus pub to think about 6-arm junctions. While drinking a beer, I realized that 6-arm junctions were structurally similar to the fish in Escher's woodcut 'Depth'. The fish in that woodcut are organized periodically in 3D, just like the molecules in a molecular crystal. However, thinking of the fish as nucleic acids, I imagined their contacts being programmed by sticky ended cohesion; these are single-stranded intermolecular interactions that occur between the overhangs that arise when one strand of a DNA duplex is a little longer than the other. Sticky ends were familiar, because they had been used by genetic engineers since the early 1970s. Thus, I had the idea of self-assembling crystals, rather than using trial and error.

I've had a number of insights in my life, but this was my major epiphany. I realized that branched DNA molecules could be self-assembled into N-connected objects, lattices and other networks using the specificity of sticky ends. The idea felt great -- it still entailed working with nucleic acids, it still involved symmetry and crystallography, but now, I imagined that I would have a target for my creative urges. I re-oriented my research direction towards implementing this idea, even though it was extremely dangerous to do this in the 4th year of my 5-year assistant professorship. Nevertheless, this notion has grown into the field of DNA nanotechnology.

It took a lot of time. I started collaborating with Neville Kallenbach, then at Penn, who taught me how to work with DNA in solution. He also bought the DNA that made the first immobile junctions. It was clear to me that I had to learn to make DNA myself. I handed in my very weak (but ultimately successful) tenure package in May, 1982 and

headed to Leiden for the summer, where Jack van Boom had offered to teach me how to make DNA. I wasn't very good at it, but I was able to handle the chemistry when I convinced the NIH to include a DNA synthesizer in my grant renewal. That put us in charge of our own materials, and ended my 15-year period as a measurer who had to beg for everything he measured.

The biggest favor Neville did for me was to hire me in 1988 at New York University's Chemistry Department, where he had become chair. After 4000 days, I was rescued from the uncomfortable small-town milieu of Albany. As my friend Stuart Fischer put it, "It is one thing to be a big fish in a little pond and another to be a little fish in a big pond: It is something entirely different to be a fish out of water." Moving to New York ultimately resulted in my meeting my partner, Nora Lapin; we have been together for 17 years. On the scientific front, the move solved my labor problem: Rather than being a person on the fringes of a Biology Department, my interests were relatively mainstream in a Chemistry Department, and I rapidly attracted students.

My NYU laboratory started with two emphases, characterization of branched DNA motifs related to genetic recombination and DNA nanotechnology. They have been highly synergistic. My first graduate student, Junghuei Chen, built a DNA cube-like catenane within the first two years there, and John Mueller, my second, built a deliberate knot a year later. These two projects were the key founding experiments of structural DNA nanotechnology and synthetic single-stranded DNA topology, respectively. Tsu-Ju Fu first built small DNA double crossover (DX) molecules (analogs of meiotic intermediates) in 1993, and a year later, in a rotation exercise, Xiaoping Yang showed that these were rigid motifs that could be used in DNA nanotechnology. It's worth noting that virtually all our results were analyzed by gel electrophoresis.

In the spring of 1995, I attended the first meeting on DNA-based computation, where I met Len Adleman, Erik Winfree and Paul Rothemund. In his talk, Erik proposed that he could use our system, 4-arm branched DNA molecules with specific sticky ends, as cellular automata. We hadn't yet published the rigidity of DX molecules, so I suggested that he use them instead of 4-arm junctions, which we had shown were flexible. After I visited Caltech, and the three of us chatted, Erik and I began a collaboration, which resulted in the first 2D DNA arrays, and the adoption by my laboratory of atomic force microscopy as a major characterization technique. In addition, I became a member of the DNA-based computation community, where my main collaborator has been Natasha Jonoska. This community has been the source of many of the people who have moved into DNA nanotechnology.

The rigidity of DX molecules led to a second development. For about a dozen years we had been trying to demonstrate that one could make a nanomechanical device from DNA. The problem was that without a rigid motif, we could not demonstrate a reliable transformation signal by either FRET or AFM. In 1999, Chengde Mao was able to connect two DX molecules by a segment of DNA that could undergo the B-Z transition when the solution was shifted to Z-promoting conditions. Shortly thereafter, Hao Yan was able to develop a robust sequence-dependent device, based on the PX motif, and operated by the Yurke *et al.* isothermal transition using toeholds. The reviewers of the paper wanted another control, and Hao had already moved on to his postdoc: I sent him the strands to perform the control by an express service on September 10, 2001; we were very lucky that the package got out safely that night, because our local express office had the initials WTC. A few years later, Bill Sherman designed and built the first walker, also using the Yurke *et al.* principle. The sequence-dependent device and a trigonal variant on the walker were later used by Hongzhou Gu and Jie Chao to build a programmable nanoscale assembly line. The PX system demonstrates the synergy

between the recombination and nanotechnology parts of the lab: The motif, developed originally for DNA nanotechnology by Zhiyong Shen, was shown recently by Xing Wang to be implicated in the homology recognition of double stranded DNA by double stranded DNA in biological systems.

So what about 3D crystals? As soon as the 2D arrays were produced, we started trying to self-assemble 3D crystals. We had a lot of crystals, but we did not get crystals with adequate resolution. We were using 2D motifs that we converted to 3D motifs by connecting them with a non-half-integral twist. However, Chengde Mao, now in his own lab, developed the tensegrity triangle, a robust motif whose helix axes are oriented in linearly independent directions. When Jianping Zheng made the edges short enough, the crystals diffracted to 4 Å resolution, and our crystallographic team, led by Jens Birktoft, was able to determine the structure through iodinated derivatives. It had been only 29 years since my afternoon in the Albany campus pub.

Others started noticing structural DNA nanotechnology about a decade ago. My travel and other obligations increased by a large factor, and I found that I needed a trained person to help me direct the laboratory. I was very fortunate to be able to bring my former student Ruojie Sha back to my lab to help manage the effort. The interest in structural DNA nanotechnology has continued to increase. Indeed, the most important development in structural DNA nanotechnology is that there are now at least 60 laboratories involved in the effort: We don't have to have all the ideas anymore, and we don't have to make all the mistakes. The field has been launched.