CHEMICAL HERITAGE FOUNDATION

NADRIAN C. SEEMAN

Transcript of an interview
Conducted by

W. Patrick McCray

at

New York University
New York City, New York

on

5 and 6 December 2011

(With Subsequent Corrections and Additions)

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This oral history series is an important resource for the history of nanotechnology, documenting the lives and career of key scientists and engineers that shaped and contributed to the contemporary practice of science and technology.

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Program Manager, Oral History
The Chemical Heritage Foundation
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Philadelphia, PA 19106
dcaruso@chemheritage.org
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(Date) 01.10.12

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(Date) 1/11/12

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NADRIAN C. SEEMAN

1945	Born in Chicago, Illinois on December 16, 1945

Education

1966	B.S., Biochemistry, University of Chicago
1970	Ph.D., Crystallography/Biochemistry with G.A. Jeffrey, University of Pittsburgh

Professional Experience

Columbia University, New York City, New York

1970-1972	Research Associate with Cyrus Levinthal

Massachusetts Institute of Technology, Cambridge, Massachusetts

1972-1977	Postdoctoral Fellow with Alexander Rich

State University of New York, Albany, Albany, New York

1977-1983	Assistant Professor, Biology Department
1983-1988	Associate Professor (tenured), Biology Department

New York University, New York City, New York

1988-present	Professor, Department of Chemistry
2001-present	Margaret and Herman Sokol Professor of Chemistry

Honors

1963-1966	Illinois State Scholar
1967-1970	NIH Predoctoral Trainee
1970	NATO Advanced Study Fellow
1972-1973	Damon Runyon Fellow
1973-1976	NIH Postdoctoral Fellow
1974	Sidhu Award, for the demonstration of RNA double helices in single crystals
1978-1981	Basil O'Connor Fellow
1982-1987	NIH Research Career Development Award
1993	Popular Science Magazine Science and Technology Award, for the construction of a DNA cube
1995	Feynman Prize in Nanotechnology, The Foresight Institute, for founding DNA nanotechnology
1997	Discover Magazine Emerging Technology Award, for DNA tinkertoys

1998	Honorary Distinguished Prof., Univ. Peruana Cayetano Heredia
1998	Elected AAAS Fellow
1999	Margaret and Herman Sokol Faculty Award in the Sciences, for excellence in research in the Faculty of Arts and Science at New York University
1999-2003	Charter Member, BBCA NIH Study Section
2003	Outstanding Mentor, Siemens Westinghouse Competition
2004	Tulip Award, DNA-Based Computation Community
2005	Nanotech Briefs Nano50 Innovator Award for DNA nanotechnology
2005	World Technology Network Award, for biotechnology
2005	Elected Fellow of the Royal Society of Chemistry
2005	NIH MERIT Award
2006	Festschrift Volume, Nanotechnology: Science and Computation, (J.Chen, N. Jonoska, G, Rozenberg, eds.), Berlin: Springer-Verlag,
2008	Nichols Medal, New York American Chemical Society, for structural DNA nanotechnology
2009	Frontiers of Science Award, Society of Cosmetic Chemists
2010	Alexander Rich Medal, MIT
2010	Kavli Prize in Nanoscience, Norwegian Academy of Sciences
2010	Elected Foreign Member, Norwegian Acad. Science & Letters
2011	ISNSCE Award, ISNSCE
2012	Guggenheim Fellowship
2012	Chinese Academy of Sciences Albert Einstein Professorship Award
2012	Distinguished Alumnus Award, University of Pittsburgh
2013	Thomson Reuters Citation Laureate
2014	Elected Fellow of the American Crystallographic Association
2014	Jagadish Chandra Bose Triennial Gold Medal, Bose Institute

ABSTRACT

Nadrian C. Seeman grew up an only child in Highland Park, Illinois, a suburb of Chicago. His father owned a fur store, and his mother had been a teacher. He was inspired by his high school biology teacher to focus on the interface between the physical and biological sciences. Seeman entered the pre-med program at the University of Chicago, but soon switched his major to biochemistry. He next obtained his PhD in crystallography from the University of Pittsburgh; then took a postdoc at Columbia University, working with Cyrus Levinthal, and a second postdoc in Alexander Rich's lab at Massachusetts Institute of Technology. Rich discovered hybridization, which is the basis of all of Seeman's DNA nanotechnology work although he never really appreciated it at the time. Seeman began his professional career in the biology department at State University of New York at Albany. He went to Leiden, Holland, to learn to make DNA. When Neville Kallenbach left the University of Pennsylvania to become chairman of the chemistry department at New York University, he recruited Seeman to join the NYU faculty.

Seeman was influenced by the Escher print *Depth* to develop both three-dimensional (cube-like and similar) lattices of DNA, a process requiring branched DNA and sticky ends. This work Seeman calls "structural DNA nanotechnology," which he defines as "using the chemical information in DNA to control the three-dimensional structure of objects, lattices, and nanomechanical devices." As a result he is often referred to as the father of DNA nanotechnology. (He says he is sometimes called the father of single-stranded synthetic DNA topology because he recognized that DNA is the ideal synthetic topological component.) He founded the International Society for Nanoscale Science, Computation, and Engineering (ISNSCE), whose members are mostly computer scientists, physicists and chemists. His biophysical work analyzing branched DNA and its ramifications was funded by National Institutes of Health. He headed a Nanotechnology Interdisciplinary Research Team (NIRT) working on DNA-based nanomechanical devices; it was funded by the National Science Foundation. He has had funding from the U.S. Navy, the U.S. Army, the Department of Energy and briefly had support from the Defense Advanced Research Projects Agency (DARPA). He feels that other applications of his work include nanoelectronics and a way to look at what happens in living systems on the molecular scale by using DNA crystals to scaffold biomacromolecules to establish their structures and interactions with other species.

Seeman shared the 2010 Kavli Prize in Nanoscience from the Norwegian Academy of Sciences with Donald Eigler for their "development of unprecedented methods to control matter on the nanoscale." Seeman, in a picture with Eigler and President Obama, is wearing his best—indeed his only—suit, which he bought in Hong Kong on his way to Oslo; he tells a humorous story of the Kavli notification phone call. Seeman founded the field, but there are now more than a hundred groups worldwide in DNA nanotechnology; Seeman names about two dozen of them. Seeman's current work deals with extending the crystallographic aspects of his DNA constructs, as well as automatic molecular weaving. Seeman concludes his interview with a discussion of his extensive travel.

INTERVIEWER

W. Patrick McCray is a professor in the Department of History at the University of California, Santa Barbara. In 2011-12, he was also the Eleanor Searle Visiting Professor in the History of Science at the California Institute of Technology. McCray entered the historians' profession via his original career as a scientist. He has degrees in materials science and engineering from the University of Pittsburgh (BS and MS, 1989 and 1991) and the University of Arizona (PhD, 1996). He also held an NSF STS postdoctoral fellowship (1998-99) and served as an Associate Historian at the American Institute of Physics (2000-2003). He has written widely on the history of science and technology after 1945. His book *Giant Telescopes: Astronomical Ambition and the Promise of Technology* (Harvard University Press, 2004) explored how scientists build and use today's most modern telescopes. A subsequent project examined the activities of citizen-scientists during the Cold War (*Keep Watching the Skies: The Story of Operation Moonwatch and the Dawn of the Space Age* (Princeton University Press, 2008)). After he arrived at UCSB in 2003, McCray became interested in the history of nanotechnology. He is a founding member and co-PI for the NSF-funded Center for Nanotechnology in Society at UCSB. He currently leads one of the CNS's research initiatives; this explores the history of nanotechnology and its place in the broader context of the technological enthusiasm and industrial policy in the late 20th century. In 2013, Princeton University Press published his 4th book; titled *The Visioneers: How an Elite Group of Scientists Pursued Space Colonies, Nanotechnologies, and a Limitless Future*, it explores the work of people who used their expertise as scientists, engineers, and popularizers to promote visions of a more expansive technological future. McCray has received numerous awards and fellowships including grants from the National Science Foundation, a Collaborative Research Fellowship from the American Council of Learned Societies (2010), and election as a Fellow to the American Association for the Advancement of Science (2011).

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INTERVIEWER: **W. Patrick McCray**

LOCATION: **New York University**
New York City, New York

DATE: **5 December 2011**

MCCRAY: Okay. Well, it looks like it's working, so we'll just trust it.

SEEMAN: Okay.

MCCRAY: I'm going to set that there, and the microphones are pretty good on it, so it should be able to pick up . . .

SEEMAN: Okay.

MCCRAY: . . . our conversation.

SEEMAN: Cool.

MCCRAY: So like I said over the many emails that we exchanged, this is a biographical interview, so it's going to be, you know, starting with, you know, childhood, teenage years, and hopefully, you know, time permitting, coming up to the present. So, you know, not to sound like a bad therapist, but, you know, why don't we start with your early years? I know you grew up in Chicago, [Illinois], but I don't know much about your family background, so you can start there.

SEEMAN: [. . .] I didn't send you my Kavli [Prize] autobiography?

MCCRAY: [. . .] You sent me your speech and a short CV [curriculum vitae].

SEEMAN: My speech where?

MCCRAY: The Kavli speech.

SEEMAN: So that was *the* science?

MCCRAY: Yes [. . .].

SEEMAN: [. . .] I was born on the North Side of Chicago. About the age of five, we moved to a northern suburb called Highland Park, and then I [. . .] went to the University of Chicago, when I was slightly young. And [. . .] then at the end of my time [at] Chicago, I left Chicago not to return, basically.

MCCRAY: What did your parents do?

SEEMAN: So my father [Herman Seeman] was a furrier. He didn't make them; he sold them. And by coincidence, his father had also been [a furrier], but he was here [in New York City], and, in fact, he was a witness to the Triangle Shirtwaist [Factory] fire.

MCCRAY: Oh, wow.

SEEMAN: Because this was the garment district in 1911—I guess 100 years ago—when the fire took place. I never met my father's family. He had some rift with them; and his father was dead by the time that I was born.

So he sold fur. My mother [Emma Klaman Seeman] was a teacher. She was from Pittsburgh, [Pennsylvania]. During the Depression, my father was a traveling salesman, selling chenille bedspreads wholesale; his territory was sort of upstate New York. I don't think he ever got to New England, but also Pennsylvania, [West Virginia, and] Ohio, I think as far as Detroit. And then he met my mother in Pittsburgh. And they married there in the late thirties. Then in 1942, his territory was transferred to Chicago, and six months later, the boss's daughter got married and the new son-in-law needed a territory. So he was out of work, and he hired on someplace as Christmas help, and he was very good at what he did, so he stayed on there and became the manager of this fur store. This was [. . .] during the war, [so] there was nothing you could buy.

MCCRAY: Right.

SEEMAN: No industrial goods of any sort. But there was a lot of money around, because of the war, so people bought fur. So he did quite well for some other guy. [In] 1953, [. . .] he struck out on his own [. . .]; by then there were cars, there were washing machines, televisions, whatever, so the fur business, you know, kept us going. But wasn't the kind of megabuck-a-year business by any stretch of the imagination that the business he built up for this other guy had been because the demand was elsewhere then.

MCCRAY: What did your mom teach?

SEEMAN: She was an elementary school teacher. She stopped teaching when we got to Chicago—when they got to Chicago. I was born in '45, three and a half years later. She didn't teach while she was there . . . my grandmother [Anne Klaman] lived with them as well. And then when I was young she didn't teach. And when I was old enough for her to go back to teaching, her mother got cancer, and she had to spend the next five and a half years taking care of her.

And then at the very end of that period, that was when I graduated high school [Highland Park High School], and so I was out of the house. I was no longer a problem. [. . .] A little less than six months after I got to college, my grandmother died. Then my mother went back to teaching, now within the City of Chicago. And she taught until '73 when she was forcibly retired because of her age. She continued teaching [. . . in a] one-on-one school, **<T: 05 min>** part-time, until she was about seventy-nine.

MCCRAY: Did you have siblings?

SEEMAN: No.

MCCRAY: No? Only child?

SEEMAN: Only child.

MCCRAY: [. . .] What did you like in school? What subjects were you good at?

SEEMAN: Well, [. . .] I guess I mostly liked science and math. I was a Sputnik kid, which was . . . I don't know if you know what that means exactly.

MCCRAY: Oh, yeah. I mean, if you were born in '45, Sputnik was . . . you were 12 when it went it up.

SEEMAN: I was twelve, so the following fall, a bunch of the better students were taken up to the high school for some exams. And the better of that group, according to those exams, were then taken every morning up to the high school for an algebra class. And then [. . . after the class] we went back to the eighth grade in the middle school. And then the following year we were put in advanced science, and something like an advanced English class, and I think those were the only three. And so it was advanced math, advanced science, advanced English, and then, you know, whatever else you wanted to take for the fourth class.

So I stayed a year ahead of myself then. And my father's business was actually on the South Side of Chicago, [and] we were in a northern suburb. [. . .] At my current age, I [. . .] find it amazing [. . .] that he was so tired from the commute that he did—he did an hour and a quarter each way each day—and so in his middle fifties [. . .]—he was forty years older than I—he [started saying], "Well, you're getting all these extra credits and whatnot. Why don't you just graduate high school a year earlier [so I can move close to work]?" So I did. Probably a mistake, but anyway, I did that.

MCCRAY: So you would have graduated in, like, '61, '62?

SEEMAN: [. . .] Sixty-two.

MCCRAY: Sixty-two. Okay.

SEEMAN: Yeah. And I went to University of Chicago, and [. . .] I went there as a pre-med, because I didn't know anything else existed. [. . .] I didn't have a very [. . .] shall we say "warm" relationship with the University of Chicago. They treated me like garbage, and [. . .] I wasn't a star or anything there, at the time. And the main thing that I got from the University of Chicago was [learning] that this job exists. I didn't know that.

MCCRAY: This job meaning a chemistry professor?

SEEMAN: Being a university professor and that it's different from being a high school teacher.

When I went to college, I honestly believed that a college teacher just taught more advanced [material; I thought it] was just like a high school teacher but teaching more advanced material to somewhat older students. I had no idea that [. . .] one could basically play all day doing research and get paid for it. When I found that out, I immediately abandoned the notion of being a pre-med, because there was something better [suited to me] that attracted me, and that was how I sort of spent the rest of my life.

MCCRAY: Okay. Did the space race interest you at all? Did you, you know . . .

SEEMAN: Not a lot.

MCCRAY: . . . they spent a lot of money being put into that at the time.

SEEMAN: Yeah. [. . .] I mean, there was money being put into science at that time. We're talking about the early sixties. This was what was referred to by the late sixties as the Golden Age. [. . .] But by the time I got to graduate school, the Golden Age was already over [. . .]. I mean, I remember when, [in] graduate school [. . .]—at [University of] Pitt[sburgh]—my first year, somebody came up to visit one of the postdocs in the lab, and he said—[it] was during the Biophysical [Society Meeting] that happened to be taking place in Pittsburgh . . . . So he came up to visit one of the postdocs, and I just was listening to their conversation, and he said, "You know, I just applied for a job at the University of New Mexico, and I . . . ," which, when I had been applying to [college] in high school, was like, "Where is [. . .] that?" And he said, "And they said, 'Well, we're really happy to examine your application.'" This is what they wrote back to him. "But we have to tell you that there are 200 other applicants for this position." So I knew by then it was over. From then on it was going to be dog-eat-dog. It wasn't going to be sort of a walkover. Anyway, so the Golden Age was over.

But, no, I wasn't particularly interested in that. [. . .] My key scientific influence, when I was in high school, was my **<T: 10 min>** high school biology teacher, [John E. Broming], and he was the first [science teacher]. I had a bio teacher, chemistry teacher, physics teacher, whom I liked in the order, one, three, two. The chemistry was the least interesting, [arguably because the teacher was least engaged with the students]. The physicist was second most interesting. And the biologist was just fantastic. He was older than the others. He was obviously one of these guys who was screwed by the Depression, right? [. . .] When I took bio from him in '59/'60, he was fifty, early fifties, something like that. I mean, when you're that age, you can't actually tell—you know, when you're thirteen, fourteen.

MCCRAY: Right. Yeah.

SEEMAN: And, you know, had the Depression not come along, he'd have probably gone on to do something more technically demanding than being a high school teacher. But he just did a great job of it. [. . .] The school year was administratively broken up into two semesters, each of which was three six-week periods long. And he divided the school year up, you know, as he saw fit. And it was a series of what he called units, where you had to put together something that was maybe eighty or one hundred or maybe more [pages long], depending on the unit [. . .], where you answered a bunch of questions in as great detail as you could, and, you know, some of those answers entailed pictures of things you'd see in the microscope in the bio class and some [things he had outlined for us]. But the first unit was about five weeks long, and it was all chemistry and physics, because none of us knew anything about chemistry and physics—you know, we'd come out of grade school. And the point that he was trying to make to us, which came through loud and clear, was that biology is a physical chemical phenomenon. And that's where my head has been ever since. All right? Sort of right on that cusp.

MCCRAY: Okay.

SEEMAN: [. . .] At various times I've tilted a little bit toward the biological side, and then [at other] times I've tilted a little bit toward the physical side. Right now, I'm probably closer to the physical than the biological side. But my first position was, in fact, in a biology department.

MCCRAY: So the early sixties, there's all this exciting stuff happening in molecular biology, you know, following [Francis] Crick [and James D. Watson's announcement of the structure of DNA].

SEEMAN: Yeah. Of which I was totally ignorant.

MCCRAY: Okay.

SEEMAN: Okay? [. . .] I mean, this high school teacher, [. . .] his name was John Broming [. . .]. Every day he'd put up some picture we were supposed to copy down and then [. . .] put into these units that we were making. And one of the last ones in the year was a picture of a cell, and [. . .] the word DNA was on it, and somehow the word RNA was on it. I don't think he understood in 1960—I don't think it was well-understood in 1960 exactly how DNA related to RNA related to proteins. [. . .] It may have been known at the more advanced institutions.

MCCRAY: Yeah, but I mean, you know, [Marshall W.] Nirenberg and those people were still working out the . . .

SEEMAN: Yeah. The genetic code. When I took biochemistry the first time in the fall of ’64, the genetic code, it was sort of known that it was three, but it was just kind of sort of known. They didn’t present that in the class as a hard and fast fact.

MCCRAY: Okay.

SEEMAN: It was like, “We think it’s three. There’s some data suggesting that, but we don’t really know yet.” About two years later I heard a lecture from [Har] Gobind Khorana and—by then it was clearly three—he talked about his experiments and so forth [and the amino acids to which various codons corresponded].

MCCRAY: Yeah. So you picked biochem as your major for . . .

SEEMAN: I picked biochemistry . . .

MCCRAY: . . . undergrad?

SEEMAN: . . . as my undergraduate major because it was, again, on what I thought was [the] cusp.

MCCRAY: Okay.

SEEMAN: And at Chicago, that was a terrible decision. Biochemistry at Chicago had nothing to do with what seemed to be the neat part of biology, namely the stuff that seemed to involve some kind of arguably teleological logic. [Biology] seemed to [me] to be interesting in terms of neat structures, anything like that. As far as they were concerned [at UC, they taught] biochemistry as developed by the organic chemists; and their concern was the metabolic transformations of small molecules. You know, how does glycine get made? What happens to it when it gets made? That kind of stuff [. . .]. I mean, it was my third year before I actually took a course in my so-called major, and I really wanted to barf. I mean, it was revolting. Okay? And I might add, I didn’t **<T: 15 min>** do [very well]. I mean, when I told my father in particular that I was going to be a biochemist and not a proctologist, he treated that [news] like this was a decision to become a mobster instead of a distinguished person. [. . .] So there were inner conflicts [. . .] during that whole period, and also, after a sense, I didn’t really let college interfere with my education. So I was a shitty student, okay?

MCCRAY: Okay.

SEEMAN: There's no [. . .] secret about that.

And so I didn't get along well with Chicago; Chicago didn't get along well with me. None of it worked out very well. I switched from what I thought was [boring] to something that I thought might be more interesting, which was physical chemistry. It turned out not to be terribly interesting. I went back and forth between the two of them [. . .] a couple of times.

Comes March, comes the spring-ish period of 1966, and I'm supposedly graduating in the spring, and I [had applied] to graduate schools in chemistry. My grades suck. My GREs [Graduate Record Examinations, including the Chemistry GRE)] are great but my grades suck. And I don't get in anywhere. [. . .] Technically I'm a biochemistry major, but I was [. . .] applying to graduate schools in chemistry because it seemed [. . .] closer to what I was interested in. [. . .] I certainly wasn't interested in this bullshit about what happens to glycine or any other amino acid. [I was rejected by all the graduate schools I applied to].

And I went to the advisor [N.C. Yang] there, and I said to him [. . .], "So what am I going to do? Nobody wants me." And he says, "That's not true. Uncle Sam, he wants you." Now this is [at] the height of the Vietnam War.

MCCRAY: Sure.

SEEMAN: So I just walked out of his office. I didn't really say anything.

MCCRAY: So you weren't too enthused about enlisting?

SEEMAN: [No] I wasn't. [. . . My politics were on the other side]. The University alumni magazine just did a very nice spread on me, okay? But, you know, for years they would ask me for money, and I would tell them, "You want money from me? I mean, get it from this ['advisor'] because [. . .] as far as he was concerned, I could come back from Vietnam as a putrefying corpse in a body bag. He wouldn't have given a [damn]."

MCCRAY: Okay.

SEEMAN: Right? I mean, that was his advice. And so I mean, once I sent them a check for two cents, which they refused to [cash, and I said that] this more than repays the care and interest of all the faculty there.

Now that wasn't entirely true at the very end, right? So when I was rejected, I didn't quite know what to do. One of my friends [Robert "Bob" B. Gennis] said, "Well, why don't you see if you can get at least into the biochemistry department at Chicago," which was a pretty crappy department in those days. I mean, they had one or two guys who may have been okay, [but] they were [largely undistinguished] from what I can tell. But there was a new graduate student advisor there, somebody who hadn't been around on my first round, [. . .] a guy by the name of John Law, and he got me into [. . .] a nascent crystallography biochemistry program at Pitt. And that kind of [. . .] launched me, [as well as saving me]. So he was the only person that actually ever did me any favors in what turned out to be five years that I was at Chicago, because I did that year again. I didn't do much better that second year.

MCCRAY: Now you had family connections through your mom still in Pittsburgh, or had that sort of gone by the wayside?

SEEMAN: Yeah. [. . .] My Pittsburgh relations had nothing to do with that. [. . .] That was just coincidence.

MCCRAY: Okay. So two questions, actually, which . . . or two points. So first of all, I went to Pitts as an undergrad.

SEEMAN: Oh, yeah?

MCCRAY: And second of all, my . . .

SEEMAN: What years were you there?

MCCRAY: I was there . . . I know this, '85 to '89.

SEEMAN: Okay. So many years later.

MCCRAY: Yeah. But my major was materials science, so I have to say, when you talk about crystallography, just for the sake of the interview, I'm thinking face center cubic, crystal . . . you know, metallic crystal structures. So I . . . I'm that . . .

SEEMAN: [. . .] I was doing biological crystals.

MCCRAY: Yeah. So I'm going to have to work to get my head around the idea of organic crystallography, because when I think of it, I tend to think of it in terms of, you know, perovskites and whatever. So anyway . . .

SEEMAN: [. . .] I'll show you a picture, later, of a molecular crystal which actually influenced me a lot, even though it's a piece of art. Anyway, [. . .] so this was biological crystallography. [. . .] I went there in '67, and [. . .] that was about the time that the third protein structure had been done. We're not counting DNA, about which, you know, I knew what it was by then, [. . .] and what its structure more or less was by **<T: 20 min>** then. But by that time, myoglobin and hemoglobin [(hemoglobin is basically four myoglobins put together, so I don't count them as two different structures) had] had their crystal structures done. Lysozyme had been done. So the first two were at [University of] Cambridge, the next one was at [University of] Oxford, and the first American structure, or that I know of, was ribonuclease that was done [at Roswell Park Cancer Institute] in Buffalo, but I'm not quite sure when carboxypeptidase was done at Harvard [University].

But [. . .] it was the year when protein crystallography was starting to take off, [. . .] so that was the justification, I believe, for Pittsburgh putting together this biochemistry crystallography training grant.

So they had a training grant there. They needed warm bodies. I was the kind of person who, even though I was a shitty student, I seemed to have a sort of mathematical inclination, and you needed some kind of talent in that direction to make it in that business.

MCCRAY: Okay.

SEEMAN: So I went off to Pitt then in the fall of '67. And was out of there by '70. I mean, I was all done in three years.

MCCRAY: Three years?

SEEMAN: Yeah. I didn't do all that much. I did a crystal structure of an amino acid, non-standard amino acid. [. . .] I was interested in phasing, [. . .] although I never made any impact in the field. But I knew enough about it that I was a good phaser when you came to actually solving crystal structures.

MCCRAY: What is phasing?

SEEMAN: Okay. So when you collect a diffraction pattern, what you've got there is the—just stop me if I say something you don't understand—you've got the Fourier transform of the power spectrum of the structure. All right? So no phases. So it's . . . each of these guys, call it F, so F is a complex number: $Fe^{i\alpha}$ . . . you know, of that F, it's the estimate of the $I\alpha_H$. [F is the Intensity that is collected, except for a couple of known factors. It is real, and the value of F is complex, so you lose the phase]. H is a three direct dimensional vector, and there's one corresponding to every one of these little spots in the diffraction. What you collect [. . . corresponds] to the amplitude F^2 . . . you know, $e^{i\alpha}(e\text{-}^{i\alpha})$ . . .

MCCRAY: This is bringing back all these, like, buried memories of x-ray diffraction classes.

SEEMAN: Right.

So you lose the phases.

MCCRAY: Okay. I remember hearing a lot about phase spaces in undergrad.

SEEMAN: That's different.

MCCRAY: Ah, okay.

SEEMAN: Okay. Phase space has to do with directions and XYZ and momenta for every particle in an ensemble of whatever. That's different.

MCCRAY: Okay.

SEEMAN: [. . .] Each of these observations has an amplitude and a phase associated with it. So the amplitude is some length, and the phase is some angle between 0 and 360. And you lose that

information. Completely. But you can derive that in various ways from the data, [. . .] from the fact that it's the power spectrum, you can kind of work backwards from the power spectrum to the structure, because it turns out that the power spectrum is kind of the convolution of the structure with itself. Or with its enantiomorph, really. But we don't have to go into that in too much detail.

MCCRAY: So this is . . .

SEEMAN: But I was good at it [. . .].

MCCRAY: So a couple of questions along the lines. I'm guessing you're someone who's very good about visualizing objects in space. That's something . . .

SEEMAN: Yeah. I'm pretty good at three-space. Yeah.

MCCRAY: Okay. And the other question I had is—and this is a real naïve question, but I need to ask it—what's the main difference between inorganic crystallography and organic crystallography?

SEEMAN: Well, from the point of view of the x-rays and the analysis, not much. It's just a matter of what [. . .] you're making your crystals out of. And otherwise there's no real difference at all. I mean, it's just crystalline matter, all right? So crystalline matter is matter, Let me just show you [. . .] the picture that sort of inspired my field, [. . .] it's like the most important picture in my life. And it's an Escher, okay.

MCCRAY: This is the [M.C.] Escher "Depth" picture [from 1955]?

SEEMAN: Yeah. You know it?

MCCRAY: Yeah.

SEEMAN: Okay. So let's just talk about that one for a second. And then you'll see what I mean here. **<T: 25 min>**

MCCRAY: So just for the record, this is the Escher print "Depth," and I can't recall the year [. . .].

SEEMAN: My year or his year?

MCCRAY: No, his year. When . . .

SEEMAN: I have no idea what his year was.

MCCRAY: [. . .] But this is sort of the 3-D fish is how I think of it.

SEEMAN: Yeah. It's a 3-D fish.

MCCRAY: Okay.

SEEMAN: And we'll talk later how [. . .] it had impact on my thinking. But you can see that it is periodicity front to back, periodicity top to bottom, periodicity left and right. So that's what a molecular crystal looks like.

And it always pissed me off that in freshmen chemistry and introduction to [. . .] physical sciences, they show sodium chloride, because that's, in its own way, a much more complex notion than this, because here, all you have to think about are these fish in three dimensions. [. . .] Recently, I've had to spend a lot of time in San Francisco, [California]. You drive in from the airport, there's some military cemetery there, that's a two-dimensional crystal: just headstone, headstone, headstone, headstone in this row, and then another row, and another row. So it's 2-D rather than 3-D.

MCCRAY: Okay.

SEEMAN: You just imagine stacking these dudes up and you get a 3-D crystal. It doesn't matter what the material is, whether it's inorganic stuff, whether it's fish, whether it's proteins and ribosomes or DNA motifs or what have you. It's strictly a matter that it repeats in a simple periodic fashion. And this doesn't talk about the quasicrystals that somebody who won the Nobel Prize [for] this year [Dan Shechtman, Nobel Prize in Chemistry, 2011]. That's a more complex notion.

MCCRAY: Okay. So what . . . you know, when you're training to become a crystallographer, around 1970, how does one learn how to do it? I mean, what's the process?

SEEMAN: Well, you solve crystal structures. I took a couple of courses. There were four courses in the series. [. . .] And it was great, because they were offered at night, and I'm a night person. I mean, I'm nocturnal and a night person: nocturnal in the sense I prefer to work after dark; and a night person in the sense that the better half of my day is the second half of my day rather than the first half of my day.

So [. . .] the courses were offered like 7:30 or 6:30 at night, so I actually didn't [do] so badly in them. And so there [. . .] were two courses in, like, you know, [. . .] what's this all about? And then a course in sort of advanced diffraction theory, from which I can repeat a couple of things, but don't really remember much. And then a course in biological crystallography, which was totally meaningless.

And so you take courses, but science is learned by doing. So I was given a relatively simple crystal structure to solve, and it took me about three weeks to do it, and I did it. [. . .] I guess I learned [three] things at Chicago [. . .]. But the first thing was that A[denine] pairs with T[hymine] and G[uanine] pairs with C[ytosine]. I mean, the second thing was an experimental thing that I didn't really realize that I had learned until I saw one of my students doing it wrong, and which was just simply mixing something. And thirdly [. . .] I learned how to write code, Fortran code. It's still the only language I speak besides English [to] any [extent]. I mean, I can read a little French, but [very little].

MCCRAY: And this would be stuff that would then go to a mainframe?

SEEMAN: In those days, yeah. It went to the mainframe. I don't know what it was like at Pitt in the eighties, but when I was there . . .

MCCRAY: Yeah, we . . . we just started to get VAX machines.

SEEMAN: Yeah. [. . .] There was an IBM 1130 in the lab. Do you know where Thaw Hall is or was?

MCCRAY: Oh, yeah. Yeah.

SEEMAN: Okay. So that's where I was. I was on . . .

MCCRAY: Yeah. I had classes in Thaw Hall.

SEEMAN: Okay. I was on the third floor of Thaw Hall, and at least in my era, Thaw Hall was the building without the door, right? You either went in through engineering or you went in through Space. [laughter]

MCCRAY: Okay.

SEEMAN: You know? And you know who Harry K. Thaw was?

MCCRAY: That I don't know.

SEEMAN: Oh, that's interesting, because he was . . . actually, I don't know which Thaw that building was named after. Probably the father. But [the son was the] robber baron's son. Are you familiar with the movie *The Girl in the Red Velvet Swing*?

MCCRAY: Yeah, yeah. Yeah.

SEEMAN: Okay. So that was Harry Thaw, the guy who shot Stanford White, the architect.

MCCRAY: Oh, okay.

SEEMAN: Because he was jealous of his earlier **<T: 30 min>** affair with Evelyn Nesbit. [. . .] I may have even seen it when I was in Pittsburgh. I'm not sure. I mean, just by chance. But, you know, local figure, if not hero.

MCCRAY: Yeah. I had no idea that's who the building was named after.

SEEMAN: Yeah. Yeah, yeah. I think it was his father who probably gave the bucks for that.

Anyway, so I was in Thaw Hall, and [. . .] my official boss there was a reasonably distinguished guy by the name of G. [George] A. Jeffrey. But when I first got there, I was

working for some assistant professor who [. . .] didn't get tenure and was sort of stupid. But he had struck up a relationship with Klaus Hofmann, who didn't die all that long ago, who was an old-time protein chemist, the kind of guy who could make a peptide. [. . .] Like a 20-mer, 30-mer peptide. And he was exploring ribonuclease [. . .]; there's an active site there that involves two histidines, one of which is on this thing called the S-peptide, and the other which is on the bulk of the rest of the protein. It's got 100 some-odd amino acids on it. And [the peptide has about 20]. And at position 12 there's a histidine, and he replaced this histidine [. . .]; he replaced the imidazole with a pyrazole, so this was called pyrazole alanine. And that was my first crystal structure. So it had no heavy atoms on it, and I became a little bit of a snob about not doing crystal structures with heavy atoms on them.

And [. . .] I solved this in about three weeks, and then [. . .] afterwards I wrote a lot of code, because we got this 1130 in the lab. It had replaced an old IBM 1620 that I didn't really know how to program very well. I mean, I could program it, but it [. . .] was an older computer. It was, in fact, I think it was organized in some sort of decimal fashion. I don't remember exactly what the difference was. But the 1130 was like, you know, the next generation. And occasionally I would write something [. . .], but not very much for the 7090 that was in the Cathedral [of Learning]. So, you had to go up to the seventh floor to submit your jobs then. And I managed to get myself appointed as the student representative to the computer users' committee there. And I was able to get them to actually let us submit our jobs after midnight when it closed. [. . .] These professors didn't understand how we all worked. And they said, "Well, what are you going to do if you get your job in at midnight?" I mean, I said, "Well, you know, we could go home instead of having to wait till [. . .] the morning to [submit them and then wait a day for] the answer." They said, "Oh, okay." So we actually were able just to stack up the jobs and then pick them up when we came in the next day.

MCCRAY: Yeah. The next day. Yeah.

SEEMAN: Because [. . . there were] some jobs, if the job would take less than 15 minutes, you could run it any time of day, but if it was over 15 minutes, it could only run after midnight. So you had to [be able to] submit the jobs after midnight [not to lose a day].

MCCRAY: The ability to do coding, was that common for people doing crystallography, or were you . . .

SEEMAN: In that era, yeah.

MCCRAY: It was? Okay.

SEEMAN: Yeah. [. . .] Coding in that era was sort of like, 20 years earlier electronics had been, and 20 years earlier than that in chemistry glass-blowing had been. And you saw certain amounts of that all the way along the line.

MCCRAY: Sure.

SEEMAN: I never learned anything about electronics, but I [. . .] was a pretty good coder. I don't know if I was a good coder, but I was certainly competent and enjoyed it.

MCCRAY: What was the x-ray diffraction equipment like [that] you were using? I mean . . .

SEEMAN: Okay. So [. . . in that era] there were, of course, cameras around, where we could take preliminary photographs to characterize our crystal. But I used a four circle diffractometer that was [. . .] a Picker diffractometer. I forget the model name of that one. I think it was just the Picker diffractometer, four circle. And it was run off of IBM cards. So it was connected to a card reader. Did you ever use a card reader?

MCCRAY: I've seen them.

SEEMAN: Okay. Or . . . I mean a card . . .

MCCRAY: Never used them.

SEEMAN: . . . a card . . . a key punch.

MCCRAY: Sure. Yeah.

SEEMAN: So the key punch had a read station and a **<T: 35 min>** write station. And in the other half of the lab where we had the computer, the computer could punch. We never printed anything out on the computer because time on the computer was so valuable. We had a lister that was just wired up. I mean, it could do some calculations, but we never used it for that. We had real computers by then. But we could list things on it, and we could also just punch directly [. . .]. There was a real coder for what everybody else did, all right? And for what I did, too, for the most part. But, he was a professor, and he [. . .] made sure everything was right. But, you know, I was a student. Most of what I did was more or less right. Not very efficient. And what

we would do is we would punch out the instructions to the diffractometer and stack them up in the card deck, where [. . .] on an ordinary key punch you just have blank cards. And then [. . .] some signal would come from the diffractometer, "I've just completed doing whatever I'm supposed to be doing. Give me my next instructions." So two cards would come down, and the first one would be read, and then it would be reproduced [. . .] about the first 40 or 50 columns [. . .] gave the various angles that this thing [should rotate to]; it was an Eulerian cradle, okay?

MCCRAY: I'm sorry. A what?

SEEMAN: Well, it's an Eulerian cradle. So [. . .] it was a big circle like this, and then there was a small circle hanging off of it that changed its orientation. And then there was a third circle down here that changed the angle of the detector. And then on the other end was the x-ray source.

MCCRAY: What was the source?

SEEMAN: [. . .] That was a matter of some controversy. But by and large we used copper.

MCCRAY: Okay.

SEEMAN: I mean, I had this assistant professor who was retarded, and he wanted to use like molybdenum, which, when you're doing biological crystallography, what you want is intensity and you don't worry about diffraction effects—absorption and extinction, crap like that—not on the first pass, anyway. What you care about is intensity. Copper's radiation [has a wavelength of 1.5418 angstroms, and scattered intensity is] proportional to wavelength cubed. Molybdenum is approximately half of that, [. . .] anyway, 0.7107. Yeah. [. . .] So that's half as much. You get about a tenth of the intensity. But at any rate, we used a closed x-ray tube. It's just a local source. I mean, I don't even have x-ray equipment here. When I need to do x-ray crystallography, I go to Brookhaven [National Laboratory] and use the synchrotron.

MCCRAY: Wow. That's a big change.

SEEMAN: It's a huge change.

MCCRAY: Interesting.

SEEMAN: I mean, some people do have local sources. For me, [. . .] crystallography, until recently, wasn't that much of my program yet, or again [. . .], and it wasn't worth the investment.

MCCRAY: Okay. So what was your PhD research specifically?

SEEMAN: So I did the crystal structure of this amino acid; I did the crystal structure [. . .], I sort of worked out how to solve the crystal structure of a sugar, because there was a program on those in the lab; and I wrote this piece of code; and I failed to solve the structure of a short peptide. That was my research. But I learned a lot. And then when I went off for my postdoc, I was in a position to solve some problems that otherwise probably wouldn't have been solved without me, without sounding too pompous about that. There [. . .], I went off to Columbia [University] for my first postdoc.

MCCRAY: You were Columbia, then MIT [Massachusetts Institute of Technology], right?

SEEMAN: Yeah.

MCCRAY: So how many years at each?

SEEMAN: Twenty-one months at Columbia. Sixty-two at MIT.

MCCRAY: Okay.

SEEMAN: So at Columbia, I mean, I went there because I was interested in the protein folding problem, and almost as soon as I got there, I realized that I was working for a bunch of bozos who didn't know shit from Shinola about protein folding or about chemistry or about anything. They had come from physics, kind of, and there was this generation of people who came from physics to **<T: 40 min>** biology and really created the molecular biology revolution, starting with Crick and . . .

MCCRAY: People like [Erwin R.J.A.] Schrödinger.

SEEMAN: Well, Schrödinger wrote his book [. . .],[1] and everybody read his book. I mean, when I was a postdoc I read his book, too. And I was, you know, incredibly impressed with the notion, which I think actually originated with [Max L.H.] Delbrück, that genetic material would be an aperiodic crystal. Man, I said, "Jesus, if anything describes DNA, that's it." But Schrödinger didn't actually do any work.

MCCRAY: Right.

SEEMAN: I mean, you know, people like Crick; I think Monod but I'm not sure; well, certainly Delbrück; and others; and this idiot that I worked for [Cyrus Levinthal] at Columbia. [And the guy at Columbia and his cohort] didn't understand anything about chemistry. They didn't understand about lone pairs. They didn't understand about the directional nature of hydrogen bonding. None of the things that are ultimately going to have proved or are going to prove incredibly important in solving the protein folding problem, if it's ever solved. I mean, while I was at Columbia I realized—somebody actually pointed out to me, I wasn't smart enough to pick it up myself—that if in the structure of insulin, which had been solved in '69 by Dorothy [Crowfoot] Hodgkin's group finally, the six sub-units in fact only had trigonal symmetry, i.e., so they were made of [three dimers in which the monomers were] different [from each other], he said, "Well, doesn't that mean that the structure isn't 100 percent determined by the sequence?" I said, "Holy shit, yeah, I'm wasting my time here." I mean, I knew that anyway, because they were yoyos there. They just wanted to use me as a handy-dandy postdoc programmer. They didn't really [. . .] care about science.

MCCRAY: So they had a very much more physics approach to looking at the . . .

SEEMAN: No, they had a bullshit approach to it.

MCCRAY: Okay.

SEEMAN: It wasn't physics. Physics I could appreciate. This was total bullshit. [. . .] The asshole who ran that laboratory really, you know, wanted to rule the world from 8K. I mean, he didn't really understand what was going on.

MCCRAY: From 8K?

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[1] See, for example, Erwin Schrödinger, *What is Life? The Physical Aspect of the Living Cell & Mind and Matter* (Cambridge: Cambridge University Press, 1967).

SEEMAN: That was the size of a small computer in those days. And, you know, he was just a total jerk.

MCCRAY: Okay. So you left there and you went to MIT.

SEEMAN: I went . . . I left there . . .

MCCRAY: Was that a happier experience?

SEEMAN: Much happier experience. At least the first couple of years, and then the game changed. [. . .] So, you know, first couple of years that I was there, I mean, what I was doing [was] more of the same. I mean, at Columbia I solved this dinucleotide structure, which had been sort of hanging out for about four years, because nobody else could solve it. And then I went to MIT and I solved two more, and then a third one, [. . .] and the first of those that I solved was the first demonstration of—and, again, I mean, I was working with other people, but I [. . .] don't think anybody would argue that I was a central character—that the most important of those actually demonstrated for the first time Watson-Crick AU based pairing, or AT-base pairing. It happened to be a U. But there had been like 20 unsuccessful [co-crystals of A and T or A and U], and they never came up with Watson-Crick base-pairing. So I was working on a bigger fragment, which took such skills as I had in those days to solve, and once it was solved, then that was the answer.

And so [. . .] we confirmed the Watson-Crick hypothesis, basically, in terms of the details of the hydrogen bonding. Everybody knew it was A and T. Everybody believed that it would be this form of base pairing, because the two base pairs were isomorphous, but the only thing that was ever seen in a single crystal was the so-called Hoogsteen [base pair or the reverse Hoogsteen base pair or the reverse Watson-Crick] base pair.

MCCRAY: What's this?

SEEMAN: [. . .] The Watson-Crick base pair has a six-membered ring over here for the T and a six-membered ring and a five-membered ring for the A.

MCCRAY: Okay.

SEEMAN: And they pair over on the six-membered side of it. But in Hoogsteen base pairing, this guy donates over to the [. . . five-membered ring]. I can show you a picture if you want to see it.

MCCRAY: It's a bit like a covalent bond with the sharing? Not at all?

SEEMAN: No. Let me just get you a picture of this. [. . .] <**T: 45 min**> So your ordinary Watson-Crick based pair looks like this. When donation is to the six-membered ring, and then it accepts over here, and . . . and on the oxygen. In the Hoogsteen base pair, [. . .] the donation is to this nitrogen, and then the other hydrogen on that same amino group accepts. Or, sorry, donates to the T. And this was what we'll see in most of those structures. [Fig.1] And you can actually get this triple helix, but that's a [. . .] separate issue.

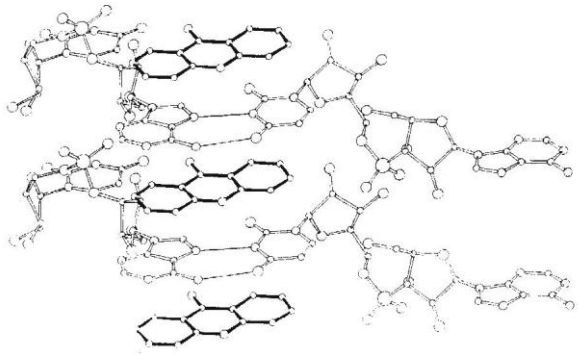

Figure 1. Example of Hoogsteen base pairing

MCCRAY: So in order to do that kind of research, how do you go . . . you know, how are you going about doing it? I mean . . .

SEEMAN: Single crystal crystallography. And [. . .] again, I was the guy who solved the structure. I didn't grow the crystals. I didn't do squat [experimentally].

MCCRAY: I guess that's sort of what I'm saying. So where would you get the crystals from?

SEEMAN: Well, we had . . .

MCCRAY: Or how . . .

SEEMAN: Somebody had to buy, basically, because none of us were chemists, somebody had to buy it. Again, it was a crystal that had been hanging out for years and years and years. The data had been hanging out. It wasn't very good data, because at MIT my boss [Alexander Rich] was, at the time, [. . .] in a very competitive race for the crystal structure of transfer RNA, in which I was not involved . . . until the very end. [I was just] a kind of a spear carrier on that project. And they gave these crystals to a graduate student [John M. Rosenberg] who was very smart but [at that point] never seemed to be able to do anything experimentally. And they wouldn't let him on the diffractometer, so what he did was to collect the data on film, and it was crappy data.

And one day the boss is out of town, and the other guy, the guy who [Bud Suddath] ran the diffractometer in the lab said, "Listen, [. . .] we should do this guy a favor." And he collected the data on the diffractometer. And then I got interested in it, and then eventually [. . .] the structure got solved. And then [. . .] because it was kind of a major thing: I and this graduate student wound up with our pictures on the AP wire and so forth for all this. If you do something at NYU [New York University], nobody gives a fiddler's fuck, but if you do something at MIT, I mean it's a big deal.

I remember my boss was also involved at one point in coming up with anti-sickling agents, and he came up with about the fourth or the fifth of these things of the same ilk, and it wasn't [. . .] a big deal. But boy, I mean, did that one get emblazoned [. . .] at least in the local media, and perhaps on some . . .

MCCRAY: Yeah. Could you say something about the . . . I mean, you were at Pitt, and Columbia, at MIT, at interesting periods of time for those institutions. I mean, I know . . .

SEEMAN: Yeah. Not Columbia. It wasn't interesting at Columbia.

MCCRAY: Okay. I mean, can you just kind of give me a sense of what the . . .

SEEMAN: Well, at Pitt, it was a first class crystallography lab. It was the only crystallography department in the western hemisphere at the time. It doesn't even exist anymore, because they decided that something that didn't have an undergraduate program shouldn't exist. So they attritted the program down to one guy [Bryan M. Craven] and they told him, "Well, you can either teach a class of 400 screaming proto-proctologists, or you can retire." So he retired. He had a farm, it turned out, in . . . do you know Indiana, Pennsylvania?

MCCRAY: Yeah.

SEEMAN: Okay. So he had a farm out near there. So he moved whatever was left of the lab out to Indiana, Pennsylvania, and he worked out there for a few more years.

MCCRAY: Wow.

SEEMAN: And I visited out there maybe three, four years ago, gave a talk. And now he's [. . .] almost 80, and [. . .] his health is not the very best, so he, just in the last month, has moved to Florida [. . .].

So there's no more crystallography department there. [There are] still [. . .] crystallographers [. . .], ironically, the student who worked with me [John Rosenberg] on this ApU structure that I was telling you about, he wound up getting a job at Pitt. So he's on **<T: 50 min>** the faculty there. He did something that seemed very important at the time [. . .].

Anyway, so at Pitt at the time it was a great place to learn to do crystallography, [. . .] to learn to do the technical aspects of crystallography. I mean, there are some notable people who came out of there, not just me. I mean, there's Sung-Hou Kim, who actually was the leader of that tRNA project at MIT. He wasn't the boss. He was like, you know, the straw boss. And he [is] a member of the National Academy [of Sciences]. He's at [University of California], Berkeley [. . .].

There was Helen [M.] Berman, who, to all intents and purposes, founded the Protein Databank.

MCCRAY: Oh, yeah. I know that name. Yeah [. . .].

SEEMAN: And [. . .] she's still a good friend. She's at Rutgers, [The State University of New Jersey]. And [. . .] a little bit junior to me, we shared the office, was George [T.] DeTitta, who ran the Hauptman-Woodward [Medical Research] Institute in Buffalo, [New York], for many years. And he was a student of this guy who [. . .] just moved to Florida, Bryan Craven. So the boss there was a guy name of George Allen Jeffrey, and he was a very good crystallographer. [. . .] I mean, he did a couple of things that were well-known. He was a very solid crystallographer. And he established this laboratory that was really [. . .], out of nowhere. Basically they gave him a department at Pitt ultimately. It became a department while I was there, actually. [. . .] Many institutions have this, have a mechanism for a pre-department. You know, at Pitt they call it a Laboratory. At Chicago they used to call it a Committee. And then at some point the committee on blah blah might become the Department of Blah Blah. And at Pitt it was the Laboratory of, [and] it would become [a Department of], so the Crystallography Laboratory became the Crystallography Department.

MCCRAY: Okay. So what were the sorts of publications or conferences and professional societies, say, in the early seventies that you were going to? I mean, what was it like to be a . . . ?

SEEMAN: Okay. So [. . .] I was a very hardcore crystallographer, so I went to the American Crystallographic Association, and, I mean, what I'm telling you about is sort of like the first half of my non-independent career.

So three years at Pitt, [. . .] maybe it's a little more than the first half. About two years at Columbia, where the emphasis was basically molecular graphics, not crystallography. And a really childish approach to using computers in other things. And then the first two years at MIT.

Around '74, the game started changing, my game started changing. [. . .] While I was at MIT it was very exciting in many respects, because the tRNA structure came out crystallographically. I did these two or three crystal structures. I'll tell you about the third one of those in a moment, because that influenced me almost more than the other two because it was a failure. And then there was a lot of molecular biology going down there that was really exciting.

So [. . .] there were two groups. [. . .] This was Alexander Rich's laboratory at MIT. And Alex was just here, actually, on Friday, for something. I mean, he's still active. He's eighty-seven.

And he had two groups. He had his crystallography group over here. I mean, he more than almost anybody maintained the two thrusts of molecular biology that had made molecular biology what it was in the fifties and sixties, namely [. . .] sort of molecular biophysics on the one hand and molecular genetics on the other. There was apparently a *Festschrift* for Delbrück that was reviewed I think in *Scientific American* . . .

MCCRAY: I can check.

SEEMAN: . . . by John [C.] Kendrew, which was sort of the opening shot in a war, where basically it was a book that [. . .] was called like *Phage and the Origins of Molecular Biology*.[2] And it was all molecular genetics, no molecular biophysics. And Kendrew, [. . .] you know who he was?

MCCRAY: Yeah.

[2] John Cairns, Gunther S. Stent, and James D. Watson, eds., *Phage and the Origins of Molecular Biology* (Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 2007).

SEEMAN: Okay. So he just **<T: 55 min>** lambasted the book, saying, "Listen, molecular genetics is important and all that, but so is [. . .] molecular biophysics." So Alex kept both groups going in his laboratory.

MCCRAY: Okay. Okay.

SEEMAN: He had a group of biochemists, people who did things with the molecules, and then he also had crystallographers.

MCCRAY: Okay.

SEEMAN: And [. . .] over the course of five years in his lab, the groups waxed and waned. So he brought in a whole bunch of crystallographers in 1974, but they weren't very talented, in my opinion, and so I used to hang out more with the biochemists or the virologists, whatever, you know, the molecular biologists, who were much more fun, and they had a practice of every day they would do their experiment in the morning, which usually started in that lab around 11:00 or 12:00, and they would get it all ready to go by 4 o'clock, they'd put their gel on at 4 o'clock, it would run for about three hours, and then we'd all go over to the Muddy Charles Pub and wait for the gels to run.

And even I did a little gel running when I [was] in my last years there. And so that's where I learned all my molecular biology, but I remember going over to there one day and, you know, there's Phil [Phillip A.] Sharpe and his group celebrating because they've just discovered splicing. [. . .] Yeah. You know, he later got a Nobel Prize [in Physiology or Medicine, 1993] for that. And there were other talented people there. But that's where the interesting stuff was going on then. It wasn't so much going on at that point in the structural biology.

So I keep saying the game changed in '74 . . .

MCCRAY: Yeah. I want to hear . . .

SEEMAN: So let me talk about '74. All right. [. . .] I spent all of '73 trying to solve a crystal structure that would have another one of these dinucleosides that I worked on, plus an intercalator—that's a flat drug that goes between the bases, unwinds them . . . so normally the bases look like this, and then you unwind them . . .

MCCRAY: Okay.

SEEMAN: . . . and stick the drug in there. And [. . .] those kinds of drugs were used to some extent to work out the fact that there were three bases in the genetic code, because you would get these frame-shift mutants if you hit the cell with that, and you'd find three frame-shifts, and you'd get [. . .] something like a revertant.

So that was how Crick worked it out. I mean, you know, [Gobind] Khorana and the others did it in other ways. [. . .] But I was just trying to get the crystal structure of this. And I kind of knew—this was the hardest of all those that I actually solved—and I [. . .] knew ahead of time [. . .] that I didn't have the right cell dimensions to get what I wanted to see. And in the end, in the same way that the crystal structure that I did get that showed that the Watson-Crick base pairing was a lucky punch, this was an unlucky punch. And that influenced me very much, that I [. . .] didn't want to be the victim [again] of crystallization conditions. What I wanted to do was control what I was going to look at in a crystal, and that's still true. [. . .] So that was one influence. The other influence was that [. . .] phasing macromolecules wasn't the big deal now. Sooner or later you get a derivative and sooner or later—because it's done a different way from the sort of thing that I was doing—and sooner or later you get your derivative and sooner or later you solve the structure, and you don't have to be smart. What you have to be good at, which I never was, was growing crystals, convincing these damned things [. . .]—whatever molecule it is you're interested in—to come down in this periodic array that looks like the fish there.

MCCRAY: Yeah.

SEEMAN: And I sucked at this. I mean, I never really had to do it until I was on my own, ten years after I started. And I wasn't any good. [. . .] And I didn't really have any talent for this at all, and I didn't have a labor force to do it, either, up in Albany.

MCCRAY: So you're learning to do this yourself, then, eventually?

SEEMAN: Well, I didn't learn how to do it. I mean . . .

MCCRAY: Okay.

SEEMAN: . . . let's be blunt. I failed. Okay? But by '74, about three years before I left Alex's lab, it was clear that this was the way the game was going. People that who did do it—you know, some I respected, some I didn't respect—but by and large, [. . .] your crystal growers

were far more important than the people [. . .] who could **<T: 60 min>** like solve problems and stuff like that.

In a sense, getting stuff to crystallize is a problem, but you really have no idea what you're doing wrong. I mean, I've done a lot of experiments in this lab. Although [. . .], until I set up on my own I had never done any experiment other than an x-ray diffraction experiment. And I knew how to do that experiment pretty well. But it was the only one I ever designed. Now since then I've done many, many [. . .] experiments in this laboratory because we've done many, many things besides crystallography. And in all those experiments, you might have [. . .] half a dozen different parameters, all of which have to be optimized before you've created the window, in parameter space, for you to be able to do your experiment and do it right. You need the right temperature, the right concentration of ions, the right concentration of DNA, the right concentration, perhaps, of some protein, the right identities of cations. You know, blah blah, right? You know, dielectric constant . . .

MCCRAY: So producing the material that you want to study is the . . .

SEEMAN: No, I'm talking about designing the experiment now.

MCCRAY: Okay.

SEEMAN: All right?

MCCRAY: Okay.

SEEMAN: In any experiment, you have to have the right conditions. But in any of the other experiments, those are independently optimizable parameters. What should be the right temperature? [. . .] pH isn't usually a problem for most of what we do. But what's the right temperature? What should be the right magnesium concentration? What should be the DNA concentration? What should . . . you know, et cetera, et cetera. Those are independent parameters. You can maximize the quality of your result along the temperature axis, along the cation concentration axis, along the DNA concentration axis, and so forth. And in four, five, six dimensions. When you get all done, you might want to go to that joint maximum and maybe tweak it a little bit. And then you can run your experiment and get a result that you can believe. With crystallography, those are not independent. If you have everything right but one parameter, you don't know. Okay? You just fail. So [. . .] think of it like opening a safe. Right? You've got one hundred numbers on the dial, and you've got say five numbers in your combination. So that's ten to the tenth possible combinations. What a safecracker, from what I can tell, does, is he takes a stethoscope and he listens, and when he's listening, he can hear what happens on the

first round. He hears tumblers slipping into place and so forth. That means he only has to go around once to find out which of those hundred numbers is the right one. Then he goes back, then he goes back. So he, instead of having to test ten billion possible combinations, he has to test at most five hundred possible combinations. And that's . . . basically factoring that product. And that's what you can do in every other experiment except the crystallization experiment.

MCCRAY: Okay.

SEEMAN: Crystallization experiment, you don't have a safe that's talking back to you.

MCCRAY: Okay. So you . . .

SEEMAN: Somewhere out there in those ten million combinations, there's the right answer, probably.

MCCRAY: Right. So you could have all the variables right except one, but you're not going to which of the . . . which of those is not . . .

SEEMAN: You don't know which of them is wrong. And you don't know if you have all of them right except one. You could have all of them wrong.

MCCRAY: Okay.

SEEMAN: I mean, there's just no hint.

MCCRAY: So you could have five of the variables wrong and you're not sure.

SEEMAN: You have five . . . you can't tell the difference between one wrong and five wrong.

MCCRAY: Okay. Well, I mean, that begs the obvious question, which is, so how does anyone ever get it right?

SEEMAN: Lots of trial and error. It's all trial and error.

MCCRAY: Huh.

SEEMAN: In all of it. And that's what we're trying to eliminate. And at least in one case we have, but sort of. But that's the whole point. I mean . . . so that the fact that I couldn't really grow crystals, and the fact that I had that failure in trying to get into the intercalator [crystal], you know, made me kind of a control freak. So [. . .] the crystallographic game changed. That was the key point.

MCCRAY: And this is all happening around '74, and so you . . .

SEEMAN: Around '74, '75, '76. Seventy-seven, I left Alex's lab for the only fucking job I could get, this dump up the river in SUNY [State University of New York] Albany.

MCCRAY: Yeah. I gathered from sort of a few things I've read and the various interviews, you didn't like Albany <**T: 65 min**> very much.

SEEMAN: Albany sucked. That's the kindest thing I've ever said about it.

MCCRAY: Okay. As a city or the institution or just . . .

SEEMAN: Everything there sucked. When I got there, I mean, I just left MIT, which was arguably like living in mental peppermint. And . . .

MCCRAY: So you're living the dream at MIT and you . . .

SEEMAN: And then I wind up up the river. Culturally speaking, you can forget Albany, [New York]. All of my colleagues were far more interested in their families than they were in their science. Without question. Here I am, a single guy, [. . . not] very interested in families. I had a cat when I was there. So that was it. And what I wanted to do is my science. And all these bozos were sucking up students like crazy because they were doing molecular genetics, which was easy. It was one-dimensional work. I ultimately had one good friend there [Rick Cunningham]. He came about five years after [I did] in biology, and other friends in chemistry [Ken Karlin and Jon Zubieta. Rod Murphey in biology also became a friend, but he worked in a totally different area, neurobiology] .

MCCRAY: Okay. And you were in the biology department there?

SEEMAN: I was in the bio department, and, boy, was it a B-I-O-logy department. It wasn't like a biochemistry, biophysics, anything department. It was a nightmare. The graduate students were all mathophobic failed pre-meds. Maybe one or two of them wasn't. But[. . .] the way I got there was that the chair of the department [Leonard Lerman] had been promised a warm body to talk to, and he was a [. . .] DNA physical chemist. And, in fact, he was the guy who discovered the phenomenon of intercalation. And he was promised a warm body to talk to. [. . .] He wanted a structural thinker and he wound up with me. It was the only job I could get. I had a really [. . .] a really strong record, I should say. There was no power because nobody was hiring crystallographers in 1977. I . . .

MCCRAY: So the job market was terrible.

SEEMAN: The job market was awful. I went a year and a half, nine interviews, before I could get this job in this shithole up the river. And [. . .] about every other year a student might come along who might want to work for me, and this guy was in an active phase of his career. He would just grab them off and say, "You're going to be teaching this year, but if you work in my lab I'll make you an RA [research assistant]." I couldn't compete with that. So I was screwed from pillar to post, basically. There was no way I could do crystallography. I mean, I recruited an army of undergraduates, but it was all heat, no light. You just can't organize undergraduates. You can't, because they were all pre-meds, and [. . .], if somebody there had had any interest in going to graduate school, I [could say], "All right, you know, so maybe you get a B in [a] class. My letter might get you into graduate school." But, no, they were all going to medical school. They needed As. And you couldn't argue with that. They needed As. They [. . .] couldn't be there to do the next step, it was a nightmare. Total nightmare for seven fucking years.

MCCRAY: Okay. But you got . . .

SEEMAN: No students.

MCCRAY: But you got tenure there eventually, but no students working with you?

SEEMAN: I got tenure based strictly on my postdoctoral record. I wouldn't have given me tenure, having never heard of me before seeing me show up there.

I produced almost nothing. I mean, as a postdoc, I was really highly respected as a crystallographer, and [. . . then] I had this idea to start the whole thing, the story about the Escher fish.

MCCRAY: A little bit. I want to ask you some questions about it.

SEEMAN: We'll go over it, then.

[. . .] I turned in my tenure package and I went to Leiden [in the summer of my fifth year] to learn how to make DNA. I didn't know how to make anything. I was terrified, [. . .] I hadn't taken organic chemistry in almost twenty years. I had no idea what the hell I was doing. And, in the end all I learned was sort of the language. I never actually made anything [useful] myself. But I [. . .] was able to get to the point where I could [. . .] ultimately make DNA in my own lab. But [. . .] not by the techniques I learned in Holland.

Anyway, so this was the summer before the tenure decision, and I come back in August for a week, because I did get a grant and I [wanted to have the starting materials for synthesis] waiting for me, when I came back for real in September, because the grant started August 1. I [wanted to have] <**T: 70 min**> this stuff waiting for me in September so I could dive right in and start making DNA and so forth. And also I wanted to make sure my tenure decision was not being derailed. And first thing I do is I called up a friend of mine [Neville Kallenbach] who was at Penn [the University of Pennsylvania], [. . .] I said, "Yeah, I'm learning to make this DNA. It seems like it's working. I mean, I'm kind of amazed." And he says, "Wow, really? That's great. You know, you may be doing that down here." "Huh?" He said, "Yeah, we may have to hire you, [. . .] as my postdoc or something because you may not get tenure up there." And this is because he had been talking to somebody else over in chemistry who had gone to a picnic with the biology chair [. . .] one of my good friends [Ken Karlin] in chemistry was coming up for tenure, [. . .] he'd said to the biology chair, "We have a really easy tenure case coming up," it was my friend. And [my chair] said, "But we have a really tough one coming up, Ned."

MCCRAY: So word was maybe getting around at that time that, you know, that things weren't looking good then?

SEEMAN: But that was before my letters came in. And my letters were all based on, you know, this guy [. . .] is a walks on water scientist, but all based on what I'd done as a postdoc, because I had produced almost nothing. Now the following winter I wound up with a *Nature*

paper based on the new program,[3] but that was before the decision was made. The decision was already made by then to give me tenure.

MCCRAY: Yeah. Tell me about the funding at this point for your work. I mean, because I've looked through, you know . . .

SEEMAN: Funding is one of the things that I haven't had an awful lot of trouble with. I got a crystallography grant when I first got to Albany and I also got a starter grant from the March of Dimes.

MCCRAY: Okay. The crystallography grant would come from NSF [National Science Foundation] or . . .

SEEMAN: NIH [National Institutes of Health].

MCCRAY: NIH. Okay.

SEEMAN: And that crystallography grant, of course, wound up being deep-sixed. But I then wrote a grant based on the idea of making stable branched DNA, and we're going to do crystallography on it, we're going to [do] six gazillion other things with it that I didn't know how to do. I wrote it [. . .] although I was PI. And that grant came through, and then I had an RCDA, [a] Research Career Development Award, which was going to cover my salary for the next five years after they gave me tenure. So it [. . .] meant, you know, this guy is kind of elite.

MCCRAY: RCDA is also coming from NIH?

SEEMAN: Also NIH.

MCCRAY: Okay.

[3] N.R. Kallenbach, R.I. Ma, and N.C. Seeman, "An Immobile Nucleic Acid Junction Constructed from Oligonucleotides," *Nature* 305 (1983): 829-31.

SEEMAN: [. . .] I mean, the original crystallography grant, I submitted it both to NIH and NSF. I got it from both, but NSF was two years and NIH was three years, and, you know, no brainer.

Anyway, so I had money then, and then the NIH grant that I'm still going on got funded. [. . .] It was a little tricky, because it came out in the first council of the [Ronald W.] Reagan administration, of the first Reagan administration. And they [. . .] gave me a score of 168 at a time when[. . .] they were funding down to about 200, 210, and it turned out they went down to 164 that time, and I was fucked. But [. . .] you're always held in for three councils—at least in those days you were. I don't know what it is now. And on the next council they went down to 168. So I survived. So that meant I had three more years of work.

MCCRAY: Uh-huh. When did you hear on your tenure case, then? Was that . . . ?

SEEMAN: I heard that in, probably, December the year before.

MCCRAY: I mean, the quote that . . . it always makes me laugh, but, you know, I've seen it a number of cases, where you say, you know, "No crystals, no crystallography, no crystallographer."

SEEMAN: No crystallographer.

MCCRAY: You know, it seems to summarize your feelings about that particular, you know, spot you were in.

SEEMAN: Yeah. For sure. Absolutely .

And [. . .] that's why I was not proposing crystallography. We did a ton of solution physical chemistry on branched DNA. I don't know the ultimate value of some of that work, [. . .] it'll ultimately be decided sometime after I'm dead. But in the meantime, [. . .] this whole program for which I'm known was basically bootlegged off of the NIH as well until about 1989. So for about seven years it was completely bootleg, and then I [. . .] started getting support from the [United States] Navy.

MCCRAY: I want to ask you about that when we get to that point in time. But I'm curious for the NIH, I mean, what were they seeing in terms of potential benefits or applications? I mean, what was the . . . ?

SEEMAN: Oh, I mean, the NIH is **<T: 75 min>** not a benefits applications thing. NIH really wants to solve fundamental biological problems.

[. . .] My idea as to how to make stable branched DNA molecules out of oligonucleotides [. . .]—which I had in 1979—[was the basis of the grant], and I started writing immediately, and it took about a year and a half, till December of ’81, for that money to come through [. . .].

Anyway, I didn’t get the RCDA until just before I came back [from Leiden]. But they were seeing this as a way to attack the issues of branched DNA. Branched DNA is an intermediate, the so-called Holliday junction. It is an intermediate in genetic recombination and to some extent in repair.

So [. . .] our focus is still on that for the NIH. It’s evolved a bit in the last decade, and we can talk about that later. But at any rate, that was what the NIH was expecting to get out of it, was, you know, physical characterization of aspects of branched DNA, which, you know, this is DNA branched at the secondary structure level. So we make base pairs that look like that.

MCCRAY: Look at little . . . right.

SEEMAN: Yeah. Look like that.

MCCRAY: So at . . . at this point, I mean, you were still practicing or learning how to make your own DNA, or are you sort of . . . where was that?

SEEMAN: Okay. So [. . .] at this point we’re talking about ’82, ’83, ’84. I was failing to make my own DNA. On the first renewal of the grant, I talked the NIH into giving me a DNA synthesizer.

MCCRAY: This was ’84?

SEEMAN: Five.

MCCRAY: Eighty-five. Okay.

SEEMAN: [. . .] I wrote a grant in ’84 and got it in ’85. And that changed my life. I mean, I should point out that I actually was the guy who used that synthesizer from ’85 till ’98, so for thirteen years I made all the DNA in the lab myself.

MCCRAY: What kind of . . . I mean, what kind of machine was that?

SEEMAN: I can show you its successor downstairs. I barely know how to work it, even though the other one, [I knew its innards . . .]. It's a solvent programmer, and so there are a bunch of bottles of liquids on there. There are four bottles for the four bases. There are four bottles on [. . . it] for different bases. You know, 5-methyl-C or a biotinylated group, or what have you, you know. In the original, there was slightly different chemistry in the original ones. There was a special bottle on there to remove methyls, but we stopped using that bottle years later, because it stunk. [. . .] There was an impetus to get rid of that type of chemistry and replace it with something that didn't smell bad, because you were always leaking around the edge. And [. . .] the area around the machine smelled like a wet fart.

And then there's another thing there for catalyst [. . .]. I'm just going in order. I mean, for the last thing, which is just a little ammonium hydroxide, which would take the stuff off of the solid support. So you were growing it on a solid support. So you have a little rock there. With the first base on there—technically, what everybody else would call the last base, but we make it backwards synthetically—already hanging on there, and then you de-protect that, there's another reagent to de-protect that, and then it's ready to go. And then you add the next base, and then you do a couple of things to it, you oxidize it, and you also so-called cap it. So if this is a failure, because there's always a little bit of failure. Let's say you're making a 50-mer, then, if you fail on the 25th step, you'll have a 25-mer there amongst your products rather than a 49-mer that's missing the 25^{th} base, right? So it's much easier to purify that way.

So you have some capping reagents, the two different bottles, and you have your major solvent as well as the de-protection material.

MCCRAY: Okay. **<T: 80 min>** NIH paid for the machine, or . . . ?

SEEMAN: NIH paid for the machine. It was about $42,000 or something.

MCCRAY: Okay. Was . . . I don't . . . was that expensive at the time or was that . . . ?

SEEMAN: Yeah, but [. . .] it wasn't like an x-ray setup. But it was the most expensive piece of equipment in my lab at that time, without question.

MCCRAY: Okay. Okay.

SEEMAN: Again, it was a fair amount of money, but, I mean, it [. . .] was absolutely worth it, both from their point of view and from mine. We did all sorts of things we'd never have done without it.

MCCRAY: How long would it take to grow a sample, then?

SEEMAN: Okay. So this machine actually could do three at a time, and, you know, it depended what you wanted. Most people who make synthetic DNA today want primers, the little 20-mers, you don't really care how good it is. You're missing a couple of bases on one end or the other, sometimes [. . .] who gives a shit, you don't purify, you just use.

We're chemists. We want everything to be perfect. We want to maximize our yields. We want everything to be dry and everything else. So [. . .] you want to make sure that if you're de-protecting, because the thing is not going to grow [without] the [deprotection], to get the thing to grow to the next step, you have to de-protect something so that it's not growing like during the previous step, right?

MCCRAY: Right.

SEEMAN: So as there is [. . .] a longer and longer strand growing on the little rocks in there, and I say little, I mean like grains of sand, right, then there's a little more back pressure on the machine, and the de-protection happens a little more slowly.

So I would typically do the de-protection step maybe a little bit longer as the strand got longer, that type of thing. So [. . .] I would take maybe fourteen minutes per nucleotide. So if I was making 100-mer, I would go basically four an hour, and it would go overnight. And I didn't care. I have a day job, and making [. . .] the DNA strands was the one thing I did to keep my hand in the lab. I mean, at [. . .] a certain point around '98, '99, [. . .] I started having [. . .] my nose stuck above the horizon, and I started traveling more. The lab got a little bigger. I couldn't supply it with all the DNA it needed, and so forth and so on. So I taught other people to do it.

MCCRAY: Yeah.

SEEMAN: Not well.

MCCRAY: When did you start attracting students? Because I remember you said . . . you know, said when you . . .

SEEMAN: Here.

MCCRAY: When you got here?

SEEMAN: Here. Yeah. I mean, it was seven years there, then I had a master's student [Kathleen McDonough] for one year. Then the next year I had a second master student [Junghuei Chen]. He stayed two years. He was from Taiwan. He's the guy who ultimately became my first PhD student. And sometime [at] the [. . .] beginning maybe of his second year, [. . .] you know, [. . .] I say to him, "How'd you like to stay for a PhD?" And he said, "Well, when I was in Taiwan, all American universities same. Now I'm here. All American universities not same." [laughter] He was a smart guy.

So at the time I was starting my negotiations here, so I said, "Go to NYU [New York University." My colleague [. . .], with whom I'd been working very closely for years, had come here as chair of chemistry. That's how I got here.

MCCRAY: Who is this?

SEEMAN: Neville [R.] Kallenbach.

MCCRAY: Okay.

SEEMAN: And I said, "Go there for a year. Work with Neville. And then . . . you know, if I actually get to NYU, you can come back to me, and if you don't, well, at least you're working with my colleague."

And then [. . .] that same year, that was my tenth year up the river, [. . .] somebody who had been a master's student with Lerman, and who had been so pissed off by Lerman that he said, "Fuck this. I'm going to business school." [came around]. So he was a local. He was Schenectadian, but he had gone to college at McGill [University], and he wound up [. . .] going to McGill [business school]. The French he learned was *huit au coin*, you know, eight ball in the corner pocket. [laughter] And little else. And so he, like me, didn't let college interfere with his education. He came to Albany, and at one point he was working for Lerman, but I was on his committee, <**T: 85 min**> so [. . .] we knew each other. [. . .] And he was in a group meeting with Leonard, and Leonard said to him, "Well, why did you do . . . ?" He said something, and Leonard said, "Well, why did you do it that way?" And he said, "Well, I thought . . . ." And Leonard told him, "I don't pay you to think. I pay you to do what I tell you to do." Well, so

Mueller decided that, you know, maybe this was not for him. And he did [. . .] hang out for his master's degree, and then he went up to McGill, went to business school, [and] came back . . . he was very close with his father, so he came back to the Schenectady, [New York], or [the] Albany area or whatever, and he went to work for Payne-Webber [and Company], one of those guys. And he was a cold-caller for two and a half years. And about once a year we'd meet for a beer. And the third time we meet for a beer, he says, "You know, Ned, I'm . . . " basically it's the line out of *Wall Street*.[4] "I'm selling stuff I don't own to people I don't know. I'm a salesman."

MCCRAY: Yeah. Yeah.

SEEMAN: You know? "I want more out of life than this. Can I come back and work for you?" I said, "You betcha!" Because he was a smart guy. And so he came, [and so he] was my only Albanian PhD student.

MCCRAY: What was his first name?

SEEMAN: John [E.] Mueller.

MCCRAY: John Mueller. Okay.

SEEMAN: And . . . but the other guy [Junghuei Chen] was actually my first [Ph.D.] student, the master's who came here. He got his degree maybe six months earlier.

And so [. . . John] moved with me to New York, although he remained a student up there, and the two of them got their degrees from me, probably [. . .] both in '91, '91/'92. I can look it up.

MCCRAY: Okay.

SEEMAN: But anyway . . .

[4] *Wall Street*, directed by Oliver Stone, 1987.

MCCRAY: Well, before we talk about NYU, let's talk about the Escher picture, which I'm sort of calling your Escher epiphany.

SEEMAN: Yeah. My Escher epiphany. That's fine.

So what happened is, you know, I'm not sure if these two stories happened on the same day or not. [. . .] My office [. . .] was sort of in the middle of the building, it's a long, narrow building, and the men's room was on the end. And one day I'm down in the men's room sitting on the throne, and somebody comes in and says, "Ned Seeman in here?" And I say, "Yeah." He says, "You're my advisor." And I said, "*Not* when I'm in here." [laughter]

And I don't know if it was for that reason that I went over to the campus pub, just to escape this kind of harassment or whether that was a different day. [laughter] So I know I certainly went over the pub [. . .] after that event, and it also happens that I went over there to think about six-armed junctions.

So while I'm thinking about six-armed junctions, [. . .] suddenly [the Escher] comes into my head.

MCCRAY: No . . . okay. So where have you seen this before? I mean, were you a big Escher fan, or . . . ?

SEEMAN: Every crystallographer is familiar with the Escher oeuvre.

MCCRAY: Okay.

SEEMAN: All right? I mean, maybe not every . . . you know.

MCCRAY: Yeah. I didn't know that.

SEEMAN: Yeah. Okay. Because so many of Escher's things have to do with periodic . . .

MCCRAY: Yeah. They do. Yeah.

SEEMAN: . . . matter, and . . . I mean, so all of us [. . . were familiar with his work. In] my youth, there was a well-known book by Caroline [H.] Mac Gillavry, who I guess must have had

some Scottish ancestors but lived in Holland, insofar as I know, who wrote a book, *The Periodic Aspects of M. C. Escher's Art*, or whatever.[5] And she was a crystallographer.

MCCRAY: Oh, okay.

SEEMAN: And [. . .] Escher's stuff was all over your life, if you were a crystallographer. And, in fact, in 1975, the [. . .] International Crystallography meeting, [. . .] I guess it was the third one I went to, was actually in Amsterdam, so you're kind of inundated with Escher and whatnot.

MCCRAY: Okay. Just because of all the artwork having this periodicity to it?

SEEMAN: Yeah. Well, it has a lot of mathematical stuff in it. It's **<T: 90 min>** periodicity, it's hyperbolic things, it's all sorts of polyhedra. [. . .] Transformations that could emulate phase transformations. The kind you were talking about. All sorts of stuff . . . Escher's art. So, I mean, every crystallographer . . . I used to say Escher is every crystallographer's favorite artist.

MCCRAY: Okay.

SEEMAN: [. . .] Apparently amongst artists he's not thought of as having been that technically wonderful. Beats me.

There are good stories and [there are] stories that are well-written. And the same thing is true with art, I guess. There's stuff that's smart and then there's stuff that's super competently executed. And sometimes there's both.

MCCRAY: Okay. So you were . . . I mean, you were familiar, then, with the . . . ?

SEEMAN: I was very familiar with Escher. [. . .] So the whole thing about DNA branched junctions was that [. . .] naturally-occurring branched junctions don't sit still. They move around. I don't know if you know about that or not?

MCCRAY: A little bit. Yeah.

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[5] Caroline [H.] Mac Gillavry *Symmetry Aspects of M.C. Escher's Periodic Drawings* (Utrecht, Holland: Oosthoek's Uitgeversmaatschappij for International Union of Crystallography, 1965).

SEEMAN: Okay. So I think I . . . that may be on . . . yeah, it's actually on this . . . so I can show you what I mean. Okay. So . . .

MCCRAY: So these are Holliday junctions?

SEEMAN: These are Holliday junctions. And they come from DNA with the same sequence. You see ATGT, ATGT, like that?

MCCRAY: Okay.

SEEMAN: So it's the same sequence. This is just an easier way to think about this.

So this C is paired to this G and this C to this G. But there's nothing to stop it from isomerizing, so that this C pairs with this G, this one with that one, and then you're going up this pathway, or you could go down the other pathway with the Ts and the As.

MCCRAY: Now I have a question. Whenever I would read about Holliday junctions, I was trying to understand, does this mean a junction in space in terms of where these are meeting, or is this a junction of sort of like two different chemical pathways that it can go down?

SEEMAN: Well, it's . . . well, those are two different questions.

MCCRAY: Okay.

SEEMAN: [. . .] It's a crossover . . . it's the molecular version of a crossover event. I mean, did you take biology, you heard of the cross . . .

MCCRAY: Long time ago.

SEEMAN: You remember the . . . ?

MCCRAY: From nuns. [laughter]

SEEMAN: Okay. They probably [. . .] weren't the worst. You know, they probably knew about crossover events, probably talked to you about it. Because [. . .] from crossovers, which were postulated, I don't know, back one hundred years ago or something, that was how they were able to map genes. What was the frequency of this [. . .] gene and this gene, you know, both winding up on the same chromosome, opposite chromosomes, whatever. You did these crosses and you figured that out. And the prevailing hypothesis was that you had various crossovers in between the genes. And this is sort of a molecular version of that. I'm simplifying more than is justified. [. . .] Anyway [. . .] this is, you know, one chromosome. This is the other one. And basically, they have the same sequence. It's only very rarely that [there are] little changes. We can go into details of that, but I don't think you're interested, because it doesn't really impinge on my story. But there's this twofold symmetry here in the middle. And that's what enables this C to pair with this G, this C to pair with this G, because they're there. Right? Okay. So I got involved in all of this because of a postdoc of Lerman's by the name of Bruce [H.] Robinson.

MCCRAY: Mm-hmm. Okay. That's . . . I remember coming across one . . . his name . . .

SEEMAN: Yeah. You'll see that name over and over in my stuff. Bruce [is] an EPR spectroscopist, basically. He does other things, though.

MCCRAY: Electron pair resonance?

SEEMAN: Paramagnetic resonance. Yeah. But, I mean, what was he measuring? That's the important thing. He was measuring how much DNA librates[. . .]; you know, libration is sort of a round form of vibration.

MCCRAY: Okay.

SEEMAN: Right? It's about an axis . . .

MCCRAY: So it sort of like moving around an axis?

SEEMAN: Yeah, yeah. Moving about an axis. So he measured that, and Lerman said to him, "[. . .] Now that you know how much DNA wiggles this way, this impinges on branch migration." That's this thing that I'm showing here—but it's the style of not so much in this context as in that context; you know, so this thing could zipper up and down. And so he said, "I

can't imagine what that looks like." And Lerman says, "Well, why don't you talk to Ned? He'll build you a model." So Bruce comes in to talk to me, and [. . .] I build a model. And what we recognized is that there's in fact a certain asymmetry between **<T: 95 min>** what's above this crossover point and what's below it. A way to show that is on another slide. [. . .] This is one of the few things, worthwhile things that I got out of Albany. You ever been to that campus?

MCCRAY: Never.

SEEMAN: Lucky guy. Shithole to work in, and it was a really badly designed campus. It was [. . .] designed by, [. . .] the fellow who designed Lincoln Center: Edward Durell Stone. And, I mean, the windows were terrible. They were all arrow slits. You couldn't put an air conditioner in one. And you had to have a water cooled air conditioner if you were going to have one. I don't mind that much.

MCCRAY: So this is a stairway with . . .

SEEMAN: This is a stairwell there. [Fig. 2] Now if you think about this in the same context as what I was just showing you, right, think of this plateau as being the branch point. Now if you and I were walking down these stairs, me down here and you down there, we'd be facing each other.

MCCRAY: Right.

SEEMAN: If I held onto the green bannister on this side and you held onto the green bannister on that side and continue walking down, our backs would be to each other. In the DNA world, that's the equivalent of the major grooves facing each other. You know what a major groove is?

Figure 2. This staircase from SUNY/Albany shows the characteristics of a Holliday junction.

MCCRAY: A little bit.

SEEMAN: Either you do or you don't.

MCCRAY: Not very well.

SEEMAN: Okay.

MCCRAY: Please tell me.

SEEMAN: All right. I'll show you in the model. Anyway, this would be the equivalent of the major grooves facing each other above the junction, and the minor grooves facing each other below the junction. So here's a DNA molecule, and, you see, the bases in DNA are attached on the same side. This side over here and that side over there. And the DNA in between here is called the minor groove because [. . .] between [. . .] there and there, that's a relatively small angle. It's about 90 degrees, but actually if you go out, and sort of think about the backbone, it's actually more like 140 degrees, sort of like from the middle of this to the middle of that. And then there's the other angle that goes the other way around, which is much larger, and that's called the major groove.

MCCRAY: Now where . . . okay. Can you show me where that would be?

SEEMAN: Okay. So that would be going around the rest of the way. So starting here and going around this surface.

MCCRAY: Okay. How many degrees is that, then?

SEEMAN: The 360 minus 140, whatever that is.

MCCRAY: Okay, 160 . . .

SEEMAN: Yeah, 220.

MCCRAY: Two twenty. Right.

SEEMAN: And actually, that ratio is not too far from the golden ratio, if you want to get mystical about it. All right. So there's a major groove and a minor groove. They're chemically different. [. . .] So Bruce and I realized that there was this difference. And so, you know, here I am, a failed crystallographer, [I've] got a tenure decision coming up, this is now January '79. I mean, [. . .] and I've only been there like fifteen months. My lab has not even been set up yet. I mean, they haven't given me the space yet. They haven't remodeled it for me so I could run x-rays. It took twenty of the sixty months I had to get tenure, just to get space. That was where I could have x-rays and whatever. Not that I was expecting much to happen with the x-rays, because I didn't have any crystals, you know, because who cares about the x-rays [without crystals]?

So I realized, well, gee, you know, I mean, at least I can write code. We can simulate this process. And there's this asymmetry, so maybe there's something interesting going on here. To make several long stories short, there was nothing going on. Technically speaking, it was symmetric. You know, we left out a very important term. [. . .] Not much came of it, but it [. . .] got me thinking about branched DNA. The other thing is [. . .] that, what we were really doing was a scholastic rather than a scientific enterprise, and I sensed that, because, you know, even if we sucked a bunch of Holliday junctions out of **<T: 100 min>** some bug or whatever, how were we ever going to test any hypothesis we generated? Forget about it. Let's say we said, "Okay, branch migration would happen faster if two arms were long and two arms were short." Possible hypothesis, you know. Right, wrong, who knows. We couldn't test that because we have a heterogeneous population of these guys all over the place. So I was not too pleased with what we were doing, but, you know, whatever.

So then in March I go to Hawaii. I fly to Hawaii with my friend Greg [Gregory A.] Petsko. I mean, I don't know if you know his name. At some point you'll undoubtedly do one of these on him. He's a very well-known guy.

MCCRAY: What year is this? It's 1980?

SEEMAN: Seventy-nine.

MCCRAY: Seventy-nine. Okay.

SEEMAN: [. . .] Greg [was] a very well-known protein crystallographer at the time. He still is, of course. He does more than protein crystallography now. [. . .] He's always been a guy with a lot of ideas, and one of the ideas he mentioned while we were flying to Hawaii from [Boston]—

he had just moved to MIT—was that he was thinking of seeing if he could isolate [a mixture of] iron-containing hemoglobin and cobalt-containing hemoglobin to see if he could get a crystal of what would be the intermediate in the oxygenation pathway, because iron changes its spin state and deforms the porphyrin to which it's [bound] . . . I don't know how much of this you know about.

MCCRAY: I know iron will react with oxygen and cobalt will react with oxygen at different rates.

SEEMAN: Well, [. . .] this isn't the rates. This has to do with different sizes of the iron-oxygen, I guess ion. So it isn't so much reaction, because [. . .] you don't change from iron plus two to iron plus three, and God knows what cobalt does in this case, but you change spin states. And [. . . one has] five independent spins—[. . . the other is] one up, one down, one up, one down, and one up. And the one with the five independent spins is bigger [than the other one], and that deforms the porphyrin, and that doesn't happen with cobalt, apparently.

So [. . .] Greg just, you know, dropped this hint that maybe he would try that experiment someday, and he finally may. I have no interest in hemoglobin. But it set a germ in my mind that maybe you could fool a system into giving you an intermediate that was stable, where you didn't have to trap it in time. You could trap it by being clever. And then about a month later I'm sitting there talking with one of my undergraduates [Kathleen McDonough], who's now a PI on her own, coincidentally in Albany, and I'm saying that, "Gee, isn't there some way we can just get these branched things to not go anywhere?" Because I knew that in one direction [. . .], there's this thing called cruciform extrusion, where if you have super-coiled DNA and you have a palindromic sequence, it will extrude a cruciform in one direction, then it stops, as you lose the symmetry. So it's local symmetry but it's not a global symmetry in the DNA.

MCCRAY: Mm-hmm. Palindromic sequence means just . . .

SEEMAN: You can read it . . . it's the same sequence going . . .

MCCRAY: Got you. Like a palindrome?

SEEMAN: [. . .] Technically a palindrome is [. . .] a mirror and this is a twofold axis, but yeah, [. . .] one strand reads exactly the same as the other strand.

And suddenly I realized, *if* you could make the DNA synthetically—and in 1979, that was a large if, not a small if—then you could put together something like this, where you'd have four different [base pairs] flanking the junction. And, Jesus, I mean, I was higher than a kite

when I realized that. And then I [. . .] built a model, because now I'm starting to think about [branched] DNA as something [. . .] we could approach experimentally.

So I build . . .

MCCRAY: So let's stop for a second.

SEEMAN: . . . so I build models.

MCCRAY: When you're saying you're building a model, are you building a computer model or a physical model?

SEEMAN: No, no. Physical model. Physical model.

MCCRAY: Okay. Like the ones we were just holding?

SEEMAN: Yeah, yeah, yeah, yeah.

MCCRAY: Okay.

SEEMAN: Yeah. And so I built a physical **<T: 105 min>** model and there's a visitor to the lab [Malcolm Casadaban], and he says, "Ha, that's kind of neat. Can you make more than four?" "I don't know. I'll think about it." So, you know, based on the various rules that I came up with to make four, I realized that you could make up to eight. In fact, you can make more than eight. Now we've actually made twelve a few years ago. But [at that time I realized] you can make at least up to eight.

So then, I go over to the pub to think about the six-armers, and [. . . I'm thinking of them having snowflake 6-fold planar symmetry], and then I think about [the Escher fish], all right? And I think to myself, "Gee, you know, a six-armed junction doesn't have to be planar. It can be three-dimensional. And if it's three-dimensional, I can organize this thing [It turns out that] we haven't done very much with the six-armed junctions, to be honest. We made them. We found [. . .] they didn't really have nice structures or anything that we could characterize in solution. And we haven't done too much in 3D with them. [. . . Nevertheless], the ultimate thing we made is six connected. That's something different.

MCCRAY: Now the . . . when I first read this story, the part that intrigued me the most was it reminded me of the story of the discovery of the benzene ring, where he [Friedrich A. Kekulé] has the dream, where he sees the snake . . .

SEEMAN: Yeah, the snake swallows its tail.

MCCRAY: And it just . . . it reminded me of that.

SEEMAN: Yeah. In a way it was, you know.

MCCRAY: Okay.

SEEMAN: I mean, you know, it was, you know . . .

MCCRAY: You weren't sleeping, obviously, but . . .

SEEMAN: I wasn't sleeping. I was drinking, which was better.

MCCRAY: Okay. [laughter]

SEEMAN: Just a beer. That's all I drink.

MCCRAY: Okay.

SEEMAN: But yeah, so, you know, I said, "Gee, you know, [. . .] if I could organize these guys this way . . . ." In the preceding three years, I had had to go to listen to other people's students talk about how they made their miserable little constructs.

MCCRAY: What do you mean by miserable little constructs?

SEEMAN: Their genetically engineered constructs.

MCCRAY: Okay.

SEEMAN: And every one of them had done the same damned thing, and I was bored to tears. What they'd done is they'd taken their plasmid, they restricted it [with] either one or two enzymes . . . you know what that means?

MCCRAY: Yeah.

SEEMAN: Yeah. And then they'd taken their gene and they'd put it in there, and they had some way of checking that it was there. And they'd stuck them in there with sticky ends. Sticky ends, you know. I was not unfamiliar with sticky ends. So, basically what I needed was some way to get these guys to talk to one another, and it was immediately obvious that sticky ends was the way to do that. [. . . In] one second, right, from thinking about the Escher, thinking about that, and then, oh, sure, I could hold them together with sticky ends. Bingo. All right. That's the rest of my career. More or less. We've done a few other things, but . . .

MCCRAY: So you're imagining each of those six ends as the sticky end that will then . . .

SEEMAN: I'm imagining the sticky end on this fish's left fin, this fish's right fin, top fin, bottom fin, head and tail.

MCCRAY: Okay. And those are then going to be the points of contact or the points of . . .

SEEMAN: That was what was going to hold them together, and we were going to program it and all of that.

MCCRAY: Okay. So in 1982 you wrote a paper on nucleic acid junctions.[6]

SEEMAN: Yeah. Actually, I wrote the paper earlier, but yeah.

[6] N.C. Seeman, "Nucleic acid junctions and lattices," *Journal of Theoretical Biology* 99(2): 237-47.

MCCRAY: Okay. So I'm trying to get a connection between the paper and this picture that I'm looking at.

SEEMAN: Yeah.

MCCRAY: Okay.

SEEMAN: You want me to say something?

MCCRAY: Yeah. [laughter]

SEEMAN: Okay. So this is the three-dimensional picture. And if you want, I can drag up that paper.

MCCRAY: I have a copy of it here somewhere.

SEEMAN: Okay. Well, I mean, I have it . . . I know where it is here.

MCCRAY: But . . . so you wrote the paper . . .

SEEMAN: "Nucleic Acid Junctions and Lattices."

MCCRAY: Yeah. Yeah. So this . . .

SEEMAN: I had an earlier paper.

MCCRAY: This is in the *Journal of Theoretical Biology* . . .

SEEMAN: That's right.

MCCRAY: . . . in ’82. So I’m guessing you probably submitted it ’81 or so, that by the time it comes out . . .

SEEMAN: [. . .] Well, I submitted an earlier version to a meeting, and then I submitted this. I don’t know, [. . .] yeah, received in ’81, and then revised for them in early ’82. And it got published I think in late ’82 because the proofs arrived while I was in Holland.

MCCRAY: Okay. This was in you were in Leiden learning how to make DNA?

SEEMAN: Yeah. Yeah.

MCCRAY: Okay.

SEEMAN: Yeah. And, you know, so . . . yeah, so here’s the same picture I just showed you.

MCCRAY: Right. Right.

SEEMAN: [. . .] So I had the rules in here as to how to make these things, one of which was . . . the third of which [. . .] somebody told me [. . . is] redundant, and he was right. And then there was the idea of making a partially mobile junction, like this. And we’ve done some of those **<T: 110 min>** just so we, you know, we could study the phenomenon of the things moving. We haven’t really done much of that. And then the next part was junctions and networks. So here, these are stereo pictures of the three connected, four connected, five . . . do you know what connected means in that regard? Every . . . every vertex is connected to three, four, five, and six other vertices.

MCCRAY: Okay. So when this paper comes out, what’s the reaction that you get from the people . . . ?

SEEMAN: Reaction? Zero.

MCCRAY: Zero. Okay.

SEEMAN: No reaction. That paper is now I think my fifth [. . .]. I can show you the citation history on that paper.

MCCRAY: It's . . . yeah.

SEEMAN: I mean, it's like that till about 2000.

MCCRAY: And then it just goes up?

SEEMAN: Yeah. I mean, actually I don't really know exactly what it is. Now it gets about forty/fifty cites a year, because it's the paper that I cite if I'm talking about the notion. Obviously I've published many more recent reviews.

MCCRAY: Yeah. But do you see this as, you know, sort of the starting point of this whole line of research that . . . ?

SEEMAN: Yeah. This paper or actually the previous paper that I [. . .] published in this meeting's proceedings, which was much less detailed than this; [. . .] meeting proceedings, [are] no big deal. But I should point out, this paper was rejected by the lowest ranking journal in terms of quality that exists, *BBRC.*

MCCRAY: *BBRC*?

SEEMAN: *Biochem Biophys* [*Biochemical and Biophysical*] *Research Communications*. And the editor to which I sent it was presumably a friend of a friend of mine, and the guy, undoubtedly he was a member of the National Academy or something, but from what I could tell, he was dumber than dog shit, and he didn't understand anything that I was talking about. And, in fact, the next paper submitted in this series [. . .], that was a paper with Neville, and we used to talk about it as "the bouncer."

MCCRAY: The bouncer?

SEEMAN: Because it kept bouncing. [laughter]

MCCRAY: From where to where?

SEEMAN: Well . . .

MCCRAY: Just different places you were submitting it?

SEEMAN: Yeah. We sent it in and it would bounce back at us. We sent it *Biopolymers* and it bounced back. And, you know, *Biopolymers* is not exactly *Nature*. And then we [. . .] had to submit it twice with a lot of revisions to *Biophysical Journal*, where eventually it got published.

MCCRAY: So why is it being rejected? I mean, what are you proposing to do that . . .

SEEMAN: Hey . . .

MCCRAY: . . . they're not get . . . they're not seeing?

SEEMAN: It's, you know, just nobody understood it. [. . .] One of the problems—if you're ahead of your time you have as much trouble as if you're behind your time. If I were to submit a paper now saying that I think that the Watson-Crick double helix, you know, [. . .] has two parallel instead of anti-parallel strands, I'd be behind my time, I'd be stupid, and I'd be bounced. By the same token, if you're ahead of your time, [the same thing happens]. It's not the first time that happened to me. I'd already had that happen with Alex. [. . .] The paper that was until about six months ago my most highly cited paper . . .

MCCRAY: Which one is this? This is your list of . . .

SEEMAN: Well, this is . . .

MCCRAY: This is your short list. Is it on there?

SEEMAN: No, it's not . . .

MCCRAY: Okay.

SEEMAN: It's not on this, because this is a list of my own work. It starts in '82, you know.

MCCRAY: Okay.

SEEMAN: Work that was associated with Alex I would leave off that list. It's a paper in *PNAS* [*Proceedings of the National Academy of Sciences, U.S.A.*], it has about 900 and some odd cites. It's about the recognition of nucleic acids by proteins using hydrogen bonding.[7] And, basically, we just laid out the rules for it, and this was, again, sort of my work. Alex did help on that somewhat, [. . .] in the sense that [. . .] I went to push too hard on [. . .] certain things, and [he says correctly], "Wait a minute, [. . .] you're not really saying what you're really seeing there." That kind of thing. But we went back and forth on it. That one [. . .] was rejected by [the] *Journal of Molecular Biology*. A lot of my stuff was rejected by *Journal of Molecular Biology*. I [don't] even want to send stuff there anymore, they're just such a conservative, backward journal. I've sent them [. . .] so much good stuff over the years, stuff that's ultimately fairly heavily cited, and they just, you know . . .

MCCRAY: So do people not see **<T: 115 min>** the biology? And I ask that . . .

SEEMAN: Yes.

MCCRAY: . . . because there was this recent article in *Nature* . . .

SEEMAN: Yeah.

MCCRAY: . . . early this year . . .

SEEMAN: In *Science*, actually.[8]

MCCRAY: Yeah. And that's . . . sorry, you're right. In *Science*, where . . .

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[7] Nadrian C. Seeman, John M. Rosenberg, and Alexander Rich, "Sequence-specific recognition of double helical nucleic acids by Proteins," *Proceedings of the National Academy of Sciences, U.S.A.* 73(3): 804-8.
[8] Robert Service, "DNA Nanotechnology Grows Up," *Science* 332 (3 June 2011): 1140-3.

SEEMAN: Yeah, in *Science*, about what happened in *Science*. Yeah.

MCCRAY: Yeah. Where you get some review back and the response is . . .

SEEMAN: The guy says, "What's . . .

MCCRAY: . . . "Where's the biology?"

SEEMAN: "Where's the biology?"

MCCRAY: Yeah.

SEEMAN: And I said, "Well, there isn't any. This is chemistry." Or it's whatever. And the editor, she just didn't get it. I mean [. . .] the story was the story. You know, that one guy, and I can only guess who the "Where's the biology" [reviewer] was [. . .], but the other one, I know who he was, and he said, "This paper founds a new field." And the other one said, "Where's the biology?" If it was who I think it was, we may have been somewhat competitors in other areas, and maybe he was just trying to zap me. But [. . .] that's just a guess as to who that was. But the editor backed that one up, you know, and "Well, where is the biology here?" And I said, "Just because it's DNA doesn't mean it has to be biology."

MCCRAY: That's . . . okay. So that's something I wanted to ask you about.

SEEMAN: Sure.

MCCRAY: I had that for later on, but since you brought it up let's just ask about it now. I mean, one of the things I find really interesting with the work that you and, you know, people like Paul [W.K.] Rothemund enjoin, I mean, the idea of just thinking about DNA as something you build with as opposed to thinking about it strictly as a biological molecule.

SEEMAN: Right.

MCCRAY: And . . .

SEEMAN: [. . .] We're exploiting an aspect of DNA that to the best of our knowledge is not used by biology. That doesn't mean it isn't used by biology. It just means we don't know about it. I don't know about it. You know, except in relatively simplistic forms like in the Holliday junction. I mean, we're still very ignorant about [. . .] all this junk DNA. Could it be doing something? Could it be folding itself into interesting ways? I don't know. Could DNA and single stranded [. . . staple strands].

MCCRAY: Staples. Okay.

SEEMAN: Yeah. In the presence of RNA staples, could we be making structures? Could biology be making structures of one sort or another? Possibly ephemeral ones, because I don't know. It's not known yet. Probably won't be known in my lifetime definitively that it doesn't happen. Anything can be discovered at any time, of course.

I don't posit this kind of stuff. Let me take a bio-break.

MCCRAY: Yeah. Sure.

SEEMAN: And I'll [. . .] tell you the story [. . .] of the NIH's response to all this.

MCCRAY: Okay.

[. . .]

SEEMAN: You know, [William J.] Clinton announces a national nanotech initiative . . .

MCCRAY: Yeah. In 2000.

SEEMAN: . . . in about 2000. And at the time I'm on a study section, and . . .

MCCRAY: Which section?

SEEMAN: Sorry, this is NIH. And—they changed all the names since then—my program manager [. . .] at the NIH, says to me, "Well, you know, you're kind of nano-y. Why don't you help us organize this thing?" **<T: 120 min>** [. . .] The NIH wanted to see how they should participate in nanotech and get their piece of the action and all that. So the upshot of this thing is there's a one-day session [. . .] in Bethesda, and [. . .] there's like a plenary talk or two, [and] eight breakout sessions. We all come back. The breakout session [representatives] address the rest of the group, maybe another plenary talk, end of day.

The message from every one of the breakout sessions is [that] NIH is not going to be a presence in nano until they get rid of the hypothesis-driven study section. Which is how [. . .] the study section [. . .] evaluates grants, hypothesis-driven means you can't say, "Well, we're going to try and make this because maybe it would be neat." All right? It means hypothesis-driven, [which] means, "We [. . .] are exploring a biological problem and we are going to test the following hypotheses to . . . " whatever.

And at the end of this, up stands the head of the Inter-Institute Bioengineering whatever, and he says, "Oh, NIH understands that if they're going to do something with nano, it has to be done differently." Great. About a year later, maybe six months, maybe 18 months, because it was in wintertime, I'm the head of what's called a NIRT, Nanoscale Interdisciplinary Research Team, and I have to go to NSF and do the dog and pony show for them. And I get up there, I give my talk about nano motors and nano machines, and I go back to the coffee machine to get a cup of coffee and there's this head of the Interdisciplinary whatever, and I say, "Hey, how you doing?" He says, "Fine. You know, Ned, [if] you propose that stuff to the NIH, you'll never get funded." I told him, "Listen, I'm not stupid. I never proposed this kind of stuff to the NIH. No way." So that's sort of, you know . . .

MCCRAY: So what kinds of stuff do you propose to the NIH versus . . . ?

SEEMAN: Well, [. . .] for many years it was [. . .] molecular biophysics of branched DNA. And then coming out of all this, there was a structure that we sort of derived in a kind of backhanded way from the nanotech, and we realized that, in fact, it might act as a way in which double helical DNA can recognize homologous sequences of double helical DNA. And we have data that supports that notion. And we published a paper to that effect last year,[9] and we're doing more experiments on that now. That doesn't mean that it does happen that way, but it happens in supercoiled DNA, it doesn't happen [in our hands] if your DNA is not supercoiled. [. . .] There are a number of these different motifs [. . .] that DNA can assume to relax the stress of supercoiling as a function of sequence. So we talked about cruciforms and extruding a cruciform in the case of a palindrome. You can also . . . do you know what Z-DNA is?

[9] X. Wang, X. Zhang, C. Mao, and N.C. Seeman, "Double-Stranded DNA Homology Produces a Physical Signature," *Proceedings of the National Academy of Sciences (USA)* 107 (2010): 12547-52.

MCCRAY: B is the right-[handed helix] and Z . . .

SEEMAN: Z is the left hand . . .

MCCRAY: . . . is the left-[handed helix].

SEEMAN: Right. So [. . .] if you have a supercoiled molecule, you can relax the stress on that if you have the right sequence, typically CGCGCG, although [certain] others are okay. You can make left-handed DNA, and then that will relax [DNA because] you're basically underlinked, [and] you're changing the character of the DNA. There are other things that DNA can [use] to relax it as a function of sequence, and homology is one of those.

MCCRAY: Okay.

SEEMAN: So . . . for what that's worth.

MCCRAY: Yeah. Tell me a little bit about the funding. So, I mean, if you sort of look at the funding that you **<T: 125 min>** received over the last 25 or 30 years, what percent is NIH, [Department of] Defense . . .

SEEMAN: And the . . .

MCCRAY: . . . NSF? How would you break it down?

SEEMAN: NIH was all of it until '89. In '89 I [. . .] received a small amount of Navy funding that stayed relatively small, [. . .] so I was basically one-third Navy, two-thirds NIH, until the end of the nineties. Then the [United States] Air Force chimed in for a couple of years. Then the Navy dropped me. I had a huge amount of DARPA [Defense Advanced Research Projects Agency] money for about a year and a half that they then sent [it] to Iraq. [. . .] NSF has been a relatively minor contributor to my work except [. . .] the NIRT is like a hundred [thousand] a year. I mean, we're not talking about a lot of money. Or was a hundred a year when I had the NIRT. Maybe it was a hundred and twenty—of that order.

And I also have NSF funding for DNA-based computation. So each of them was, you know, smallish amounts of money. So [. . .] then the military [plus NSF] has been in recent

years, [. . .] more than the NIH. Part of that is just self-defense, no pun intended here, that if I have one NIH grant and the NIH has become very much more iffy, I've never been zapped by the NIH, but I'm a little scared of it, as everybody is. So I'm sort of [. . .] building up my Defense money in case the NIH does zap me when I go in for renewal next year.

MCCRAY: So the Defense projects that you're doing, I mean, what do they . . .

SEEMAN: Well . . .

MCCRAY: . . . what do they want to get out of this?

SEEMAN: They sort of tilt towards nanoelectronics.

MCCRAY: Yeah. That's what I thought. Okay.

SEEMAN: I mean, that's sort . . . they want smaller, faster computation, so forth.

MCCRAY: Sure. So the DNA nanocomputing would be attractive to them?

SEEMAN: Yes. Exactly. I mean, not so much DNA computing. Using DNA to organize nanoscale components. That's different from the kind of DNA-based computation that [. . .] that whole community . . .

MCCRAY: Like [Erik] Winfree and [Leonard M.] Adleman and those . . .

SEEMAN: Yeah. Yeah. That's totally different.

MCCRAY: Okay. Thanks. So . . . yeah.

SEEMAN: That's . . . yeah. That's more interesting material than . . .

MCCRAY: Okay. But that's a much more computation-oriented one, where you're talking more about a physical approach to building . . .

SEEMAN: Yeah. Yeah. I mean, both . . .

MCCRAY: . . . structures.

SEEMAN: You know, [. . .] many of the . . . people who experimentally participate in one experimentally participate in the other.

MCCRAY: Okay. So let's go back a bit to the Escher and the '82 image. And I guess I just want to walk forward to that, to when you come to NYU. So you have your . . . again, I'm going to call it your Escher epiphany. And you have the nucleic junctions paper coming out. So what's your next, you know, four or five years spent developing?

SEEMAN: Okay. So the next four or five years is spent, you know, learning how to work with DNA in solution. Trying to keep the NIH happy enough with my [. . .] results. So it was in '83 that we published the first branched junction,[10] that we made it from synthetic oligos. Then in a slightly different thrust, you know, in the thrust involving this work, Bruce Robinson and I, not related to our previous work, we just ran into each other at a biophysics meeting, and he said, "I'm thinking of making some kind of bio chip." And I said, "Gee, I've been thinking about that." And so in early '85, I went out and visited Bruce in Washington and we worked together for about a week and put together something that.

MCCRAY: University of Washington?

SEEMAN: Yeah, yeah, yeah. University of Washington. And [he'd] been on the faculty there since '80. And maybe '81, but '80, I think. And he and I put together a paper, I don't know if you've seen it or not, but . . . [11]

MCCRAY: I read it this morning. I've read at least the introduction.

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[10] N.R. Kallenbach, R.-I. Ma, and N.C. Seeman, "An Immobile Nucleic Acid Junction Constructed from Oligonucleotides," *Nature* 305 (1983): 829-31.

[11] B.H. Robinson and N.C. Seeman, "The Design of a Biochip: A Self-assembling Molecular-Scale Memory Device," *Protein Engineering* 1(4): 295–300.

SEEMAN: Okay. All right.

MCCRAY: And I was curious about it. I mean, I think the paper came out in eighty . . .

SEEMAN: Seven.

MCCRAY: . . . seven?

SEEMAN: Yeah. [. . .] We tried to get into *PNAS* and some asshole said no.

MCCRAY: Okay.

SEEMAN: And then we didn't know you couldn't resubmit it to a different member. So it took till '87 to get it out in *Protein Engineering*.

MCCRAY: But there was a lot of talk in the early eighties through the mid-eighties, I mean, people like Forrest [L.] Carter and maybe even Kevin [M.] Ulmer a little bit, talking about molecular electronics. Was your work . . .

SEEMAN: That's right.

MCCRAY: . . . kind of part of that whole . . . ?

SEEMAN: [. . .] I think so, except they were [. . .] thinking in terms of proteins and there's no **<T: 130 min>** control for proteins.

[. . .] DNA has structural information, or you can use the information in DNA to direct structure. Someday, obviously, we'll be able to do that with proteins. But [. . .] I don't plan to wait till I'm 127 to try to do that.

MCCRAY: Okay. So tell me about the biochip work, then. I mean, what . . . ?

SEEMAN: So we just, you know, it was very straightforward, in the sense that we [. . .] knew nothing at that time about structure of any of the components we were proposing. I mean, Bruce had done some work about [. . .] using polyacetylene, I guess, as a potential molecular wire. He didn't know whether then, and I don't know whether now—I mean, maybe he knows now—whether whatever transport happens there happens along the molecule or in the interstices between molecules. He only knew, you know, because he had a [macroscopic sample], at least not a single molecule thing there, over which he was sending or through which he was sending whatever he was sending. And I think it was [. . .] electrons. It may have been spins. I don't know. And I just organized a DNA lattice that would accommodate it in the smallest thing possible.

MCCRAY: Okay. Did you go to any of Forrest Carter's Multronics . . .

SEEMAN: No. I was an unknown in those days. I wasn't invited to anything of importance. [. . .] A major meeting/[book] or something like that came out about '84 or '85 about unusual conformations of DNA and I wasn't invited, and fuck them very much, you know?

MCCRAY: [laughter] So with the work you're doing with Bruce, I mean, I guess . . .

SEEMAN: So that was theoretical, and that was sort of the last thing we did together.

MCCRAY: So this was just imagining what you could possibly do?

SEEMAN: Well, it was sort of a blueprint for how to do it. And other people have told me that was the first thing that they'd read that didn't seem to be total bullshit. Whether it was or wasn't [. . .], in the end obviously we would do things differently today. We know things today we [. . .] didn't know then. But [. . .] the basics as to how we were thinking about and approaching nanoelectronics doesn't differ very much from what was in that paper.

MCCRAY: Okay. I mean, Forrest Carter always struck me as an . . . just sort of an interesting, charismatic figure that, you know . . .

SEEMAN: Yeah. I never met him. He died relatively young . . .

MCCRAY: He died like '86, '87, somewhere . . .

SEEMAN: Yeah. But I mean, he . . . yeah, he died relatively soon after that got going. I never met Ulmer, either.

MCCRAY: I've talked to him on the phone. I haven't met him, so . . .

SEEMAN: Yeah. And . . . but, you know, all these people talked. They didn't actually do anything.

MCCRAY: Yeah. And it was heavily protein and . . .

SEEMAN: And it was all protein-oriented.

MCCRAY: . . . organic-polymer-oriented, I guess.

SEEMAN: Well, I mean, we were of course starting, you have to use organic polymers if you're going to get any kind of conduction. I don't know whether the transmission of electrons or photons or any other damn thing through DNA is ever going to be successful, and, in fact, on one of the grants in which I'm involved now is exploring some of the features of that. But I am not going to bet the farm on that, [. . .] so our idea is you use the architectural properties of DNA to organize things whose electronic and other properties are appropriate for the task.

MCCRAY: Okay. So I had a question.

SEEMAN: Sure.

MCCRAY: You know, in doing background research to prepare for this interview, I think Paul [W.K. Rothemund] actually told me to look at George [M.] Church's webpage, where he has some lab notebooks from 1997, where he's talking about DNA lattices. And Paul said to ask you what's the connection between . . .

SEEMAN: Okay. I presented an early version of that '82 paper at an '81 Gordon [Research] Conference.

MCCRAY: What was the . . . the theme of . . .

SEEMAN: Nucleic [. . .] Acids [Gordon Conference]. And Sung-Hou Kim, whom I mentioned earlier, was there. George worked for Sung-Hou, and Sung-Hou said, "You should talk to George Church. He's got the same idea." So I gave George a call and he got back to me, and we had a few chit-chats back and forth, and I continued to pursue it, and George had other fish to fry. I didn't get any ideas from George. The one **<T: 135 min>** time I suggested something to him, he said he didn't think that was a very good idea. And that was my only contact with George in this regard. I mean, I've obviously run into George over the years. And if George had chosen in 19 whatever it was, '77, to pursue that, well, he'd have got [where I am]. I mean, he didn't spend his life in what I can euphemistically call middle-level institutions. He'd have got wherever I've got [. . .] wherever I got till 2000, at any rate, because now there are people at good institutions doing it, one hell of a lot faster than I would have. And he would have just swamped me. But George didn't pursue it and I did. It's that simple.

And again, I mean, I didn't know very much about what George was doing, and maybe I'm just incompetent and it took me twenty-nine years to get that crystal, and it isn't the right crystal, and we're still looking to [. . .] make better crystals and so forth. But the only thing I can say is, certainly in the [. . .] 3,000 days since I had the idea at Albany [until I left Albany. And] then in the succeeding say [twelve] years, till 2000, I had to sweat everything out and bootleg everything up off of other stuff. I don't know if George ever got funded for this or not. I never saw any . . .

MCCRAY: Yeah. I don't . . .

SEEMAN: . . . applications from him. And if George didn't have a webpage, nobody would know about it at all because he never published it.

MCCRAY: Yeah. I only know about it because, you know, in talking to, you know, Paul down at CalTech . . .

SEEMAN: And talking to Paul or whatever. Yeah.

MCCRAY: . . . he said, "Oh, you know, take a look at George's webpage."

SEEMAN: Yeah. George has one. And I looked at the webpage, too. It's kind of primitive and it's old, and he's . . . you know, I mean, I was . . .

MCCRAY: It's just . . . it's just a jpeg of a lab notebook, so it's . . .

SEEMAN: Yeah. I mean, so what? I went to a meeting . . . it was a symposium in honor of Gobind Khorana. Do you know who . . .

MCCRAY: Yeah. He just passed away.

SEEMAN: He just died. And this was in the summer I think of two thousand and . . . it may have been '09, it may have been '10. And George was also an invited speaker there, and George gets up there and he talks about how, well, he did the [3D] structure of tRNA, but you're hearing about [things relevant to] that from Uttam RajBhandary or Olke Uhlenbeck or whoever else was there.

So, [. . .] I was a spear carrier in tRNA, [but George] carried the spear for a spear carrier on tRNA.

MCCRAY: Okay. [laughter]

SEEMAN: He did absolutely nothing [significant of which I'm aware] on tRNA . . . I mean, he was [an] undergraduate in Sung-Hou's lab at Duke [University]. Okay?

MCCRAY: Okay.

SEEMAN: [. . .] Then he flashes up his webpage, [. . .] this jpeg, [. . .] so he says, "So you'll hear about, tRNA from whoever else is here. You've heard about it already from them. And tRNA structure from them. And then [. . .] you're going to hear about DNA nanotech from Ned Seeman. So I'm going to talk to you about the DNA nanotech that I, you know, originally proposed. And you're going to hear about how Ned picked up on that," or, whatever. [laughter]

And so [. . .] my guess is George probably regrets that he didn't push that quite as hard as [I] did. I mean, George went from Sung-Hou as an undergraduate to Wally [Walter] Gilbert as a graduate student to some I guess more or less permanent position at the Harvard Medical School. And if he wanted to push that, it was his right, and it's his privilege, and he certainly would have been able to obtain the resources. I had to bootleg it for years and years and years, and in the end, you know [. . .], I didn't have many options. Either I was going to be a failed crystallographer or I was going to do this. And I was going to do some other experiments for the NIH on branched DNA. I never really knew what was going to come out to be most important.

[In my drawers is a file named 'Nu-Prots'. It's an idea I had in the 1980s, with peptide backbones and bases coming off them. This was PNA. I had a 3-bond backbone, not the 6-bond backbone the Peter Nielsen came up with. It was based on the Astbury notion of 3.4 Å base stacking and 3.4 Å beta-sheet spacing. I realized that such a system might not be dominated by the base pairing, but by backbone-backbone interactions, not to mention that I was technically ill-equipped to pursue the idea, so I didn't. All the credit goes to Peter and all the credit deservedly belongs to Peter. I just had the idea earlier, and didn't pursue it, just like George didn't pursue DNA nanotech].

Then from 2000 on, I'm still in a middle-level institution, let's be honest. In recent years they're trying to make this slightly better, but it's still a middle-level institution. [. . .] NYU is not Harvard. It's not MIT. It's not CalTech. It's not Stanford [University] **<T: 140 min>** or Berkeley or any of the others. But [. . .] some of those places, CalTech and Harvard in particular, are now hiring young people to do this. I mean, I'm too old for any of this. The last time I tested the waters several years ago, they told me I was too old. So it goes. I mean, I'm perfectly happy living in New York [City, New York], for the rest of my life, [although it is annoying when potential postdocs with their own salary money say to me, "You know, you're nice guy and a smart guy, but William Shih is at Harvard."]

[. . .] So powerful institutions are now in this field that I certainly originated experimentally [. . .].

MCCRAY: So be it.

SEEMAN: . . . so be it. Yeah. Good ideas are a dime a dozen. You know, [. . .] if you don't pursue them, and it takes a certain amount of *cojones*, to be honest, to pursue them.

MCCRAY: Mm-hmm. So tell me . . . okay, before I sort of move you forward in time to when you come to NYU, do you want to say more about the bootstrapping that you were doing while you were still in Albany?

SEEMAN: Well, you know, during that time we didn't publish an awful lot on this stuff. More of it was on the just biophysics of branched DNA. We [. . .] did a ligation experiment on a three-armed branch junction. I'm not sure ligation experiments are really great experiments for branched junctions.

MCCRAY: Why?

SEEMAN: Because our conclusion was that the [. . .] three-armed branched junction was flexible. But, you know, there is some ATP involved there, and that may be distorting the essence of the system. A simple three-armed branched junction probably is somewhat floppy. That was our conclusion. We made a square that was sort of published by the time we got to NYU, around the time we got to NYU.

MCCRAY: This is the cube paper with the . . .

SEEMAN: No, the square.[12]

MCCRAY: Square. Okay.

SEEMAN: So that's not listed as one of my major things. And then we were involved a lot in sort of working out the structure of the Holliday junction in solution. There was a collaboration there with Tom [Thomas D.] Tullius, and we had a couple of papers with him using his hydroxyl radical attack method, and we kind of made a variation on the theme. He was doing hydroxyl radical footprinting. So a footprint is you have a piece of DNA and you want to know where a protein binds. So you bind a protein to it and you throw hydroxyl radicals [at it; they] are probably the best way to do it. You put iron complexed with EDTA [ethylenediaminetetraacetic acid] in there, [in the presence of] hydrogen peroxide, and that in turn generates hydroxyl radicals [. . .]. And then that attacks the DNA, and you can see where is it broken and where is it not broken.

MCCRAY: So it sort of eats it away and leaves the . . .

SEEMAN: Yeah. Well, it . . . I mean, it's single-hit kinetics, right? So you . . . so it cuts here, and then you've got a label up here, so you run it out on a gel and you say, okay, we cut here, here's . . . so this is a fragment this long. That's that position. And then there's that position, that position. But in this position, so where my wristwatch is, well, it couldn't attack because it's protected there.

MCCRAY: Okay.

[12] J.-H. Chen, N.R. Kallenbach, and N.C. Seeman, "A Specific Quadrilateral Synthesized from DNA Branched Junctions," *Journal of the American Chemical Society* 111 (1989): 6402-7.

SEEMAN: [. . .] So that's a straight-up footprint. So we made a variation on that theme, sort of auto footprint, where you take a motif like the Holliday junction and you hit it with hydroxyl radicals, and then you take each of those same strands and you put them up against the Watson-Crick complement and you see what's different. [Fig. 3]

And so that was what we did in that era. We [. . .] showed that it was the bases next to the Holliday junction to determine [the structure]. Well, first we showed that it's not that sort of intersection, but in fact that you have two domains, and secondly we showed that it's the bases flanking the domain that actually affect whether it's going to be arm one stacked on arm two, arm three stacked on arm four, or one stacked on four and two stacked on three.

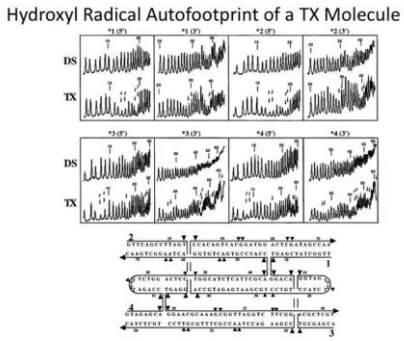

Figure 3.

MCCRAY: On three. Okay.

SEEMAN: There are two possibilities there. And we also showed [. . .] for one of the enzymes [. . .] that it cuts the crossover [strands] or the non-crossover strands in that structure. And then we left Albany.

MCCRAY: Okay. Before you leave Albany, I wanted to ask you, one of . . . one of the things that was interesting to me about reading . . . looking through your biochip paper this morning was you and Bruce cited Drexler's '81 *PNAS* paper . . . [13]

SEEMAN: Yeah.

MCCRAY: . . . and I know in his **<T: 145 min>** work following, you are one of the few scientists that he has consistently cited through his work. And I was just kind of curious about the interactions.

[13] K. Eric Drexler, "Molecular engineering: An approach to the development of general capabilities for molecular manipulation," *Proceedings of the National Academy of Sciences, U.S.A.* 78(9): 5275-8.

SEEMAN: Okay. I first met Eric in ’89.

MCCRAY: Eighty-nine? Okay.

SEEMAN: I was newly at NYU, it was like February. I went to the biophysics meeting in Cincinnati, [Ohio].

[. . .]

MCCRAY: You were at a biophysics meeting, ’89 . . .

SEEMAN: [. . .] Nanotech oscillated back and forth for a while, after Eric wrote his book, between sort of science and sort of cult.

MCCRAY: Yeah. You and I had emailed a little bit about this, which was really helpful for me. But I know I’m kind of going over ground that you and I have gone over, but people reading this ten years from now won’t know that.

SEEMAN: Honest to goodness, I don’t necessarily remember everything . . . . I . . . well, I have it on here, but I don’t remember everything I . . .

MCCRAY: Fair enough.

SEEMAN: Because I’ve written many of these same things to many other people.

MCCRAY: I understand.

SEEMAN: Okay. So it was partly cult and partly science. So . . . anyway, so from the biophysics meeting, I flew to [. . .] Seattle, because . . .

MCCRAY: This was the NanoCon meeting [17-19 February 1989] that they were having out there?

SEEMAN: Yeah. In Seattle, and I [. . .] don't remember how much I told you about that meeting.

MCCRAY: Not much.

SEEMAN: Okay. So that was where I met Eric for the first time. And what it was is, you know, since Bruce [was] in Seattle and he knew about this, he and I were invited to talk about the biochip paper, basically.

MCCRAY: Okay. Okay.

SEEMAN: And Erik Drexler talked about, you know, Eric Drexler-ism, or whatever—nanotech as he saw it, and [. . .] to be honest, I've never heard Eric say anything that I knew was wrong or stupid. The problem is that [. . .] one of the things he does do, of course, is take credit for anything that happens and say, "Well, that's sort of what we predicted." You know, [. . .] he's a little on the Jeane [L.] Dixon-esque side. Am I going back too far for you?

MCCRAY: No, I know who Jeane Dixon is. [laughter]

SEEMAN: Okay. Okay. I don't even know if she still lives, but . . . you know . . .

MCCRAY: She may have moved on to a higher plane, but . . .

SEEMAN: Yeah. Yes. But the point is he [. . .] and the other [. . .] Foresight {Institute] people were sort of willing to take credit for anything that happened that was sort of, you know . . . there will be a great tidal wave and deaths happen, and then, you know, sometime in the 2000s, and sure enough there's a tsunami in South India and there's [Hurricane] Katrina. And, well, gee, you know, what was the probability that that would happen in that decade? [laughter] So it's a little of that there. [. . .] Eric himself doesn't tend to [. . .] do much of that, but the people who kind of followed Eric tended to. Anyway, so that was the first time I met him [. . .]; did I tell you about this party I went to? Okay. So between the first and the second day of this thing, there's a party at one of the organizers' houses, and I'm there, and, you know, I'm talking up some young thing there, and she says, "Gee, isn't it a pity that we're the last generation to die?"

And I say, "Huh?" And she says, "Yeah, well, I mean, you know, once nanotech comes, we'll all be able to live forever." And I said, "Oh, isn't that interesting? Excuse me. I need another beer." [laughter] And, it was . . .

MCCRAY: Yeah. So that would be that cultish . . .

SEEMAN: Yeah, that was sort of the cultish aspect of it. And then the following morning . . . so the first morning is Eric talks about an hour and a half. Bruce and I talked for maybe a total of an hour and a half. And that's the end of the scientists. That afternoon and the next day is a combination of software people and science fiction writers, some of whom were very well-known science fiction writers. You know, Benham, whatever his first name is.

MCCRAY: Benford.

SEEMAN: Benford. Yeah. Greg [Gregory] Benford. [Gregory D.] Bear. Well-known people. **<T: 150 min>** And the last morning, it's sort of a wrap-up, and Eric himself saying, "Cut out the bullshit," right? That, you know, he doesn't want all of this stuff to be a cult, he wants it be something that's going to be pursued technologically. Even if he's not going to do it. I mean, he [. . .] published paper after [paper] or at least book after book. I've never seen any papers since that first *PNAS* –not that I'd look for them—on his stuff. But it's all theoretical stuff of, "Well, if we had this, we could do that. If we had this, we could do that." All of us draw the line between speculation and extrapolation in different places, and he and I probably don't draw it in the same place.

But that's okay. We all have our personal choices. [. . .] There are only about forty or fifty people at this meeting, and it's taking place in some, you know, moderate-sized room in a hotel somewhere. And in the end, somebody says, "Well, everybody that was invited has had their chance to talk. Does anybody else want to get up and say something?" And one guy stands up and he says, "Well, mine is the first [. . .] entire family in the state of Washington to arrange to have ourselves frozen. Does anybody want my phone number?" And all of these notebooks come out and people start scribbling down.

MCCRAY: Yeah. Because nano had a lot of [. . .] interest from the cryonics community.

SEEMAN: Yeah. Yeah. Very much.

MCCRAY: Which is weird, I mean, because it's . . . you have that, but you also had a lot of early interest from the computer science/computer programming people.

SEEMAN: Right. Yeah. Well, see, all of that was a problem in many regards.

MCCRAY: The cryonics or the computer science?

SEEMAN: [With] computer science, because with the exception of certain computability issues, which we can forget about, if you ask me to write a program to do XYZ, I can do it. It may be clunky. It may be a shitty piece of code. It may not [. . .] do what you want done nearly as well as you would like it done. But no matter what, I can write a program to do it. That is the perspective of software people. That is not the perspective of a laboratory scientist. Sometimes you just get into the lab and damn it, it should all work, and it doesn't, damn it. I mean, I can't tell you how many times that's happened to me. Every time I think I know what I'm doing, [. . .] I mean, these days, I don't do anything with my own paws anymore, but, you know, so I give it to a student. But whatever, there's a reasonably small chance even on guaranteed stuff that it's actually going to work out the way I expect it to. And often things just don't work at all. And that's the difference between somebody who does experiments and somebody who writes code. Not everything works. Now there may be reasons why it doesn't work, and, you know, good scientists try to figure out why it didn't work either so that they can get it to work or so that they can learn some new principle or whatever. And, of course, we do that, too. But I think you'll find that a laboratory scientist, and I'll include, you know, theoretical, hardcore scientists in that group, people who work closely with experimentalists, probably draw that line between extrapolation and speculation [. . .] closer to the experiment than do say software people or others of that sort.

MCCRAY: So do you think that accounts for some of the animosity that chemists had for Drexler's ideas versus the . . . you know, the fact that the computer science people seem to be more willing to go with it?

SEEMAN: That's entirely possible. I mean, I never had any problem with any of Eric's suggestions about things to do. A lot of my better-known work is, in fact, stuff that was originated with Eric, but which we didn't do [. . .] with carbon and whatever, but did in fact [. . .] on the nanoscale rather than the angstrom scale, with nucleic acids. A year ago we published this assembly **<T: 155 min>** line, right?

MCCRAY: Which is really kind of interesting to read about, because it seems in some ways a . . .

SEEMAN: It was certainly inspired by some of the stuff that Eric talked about.

MCCRAY: Okay. I mean, that's a fair question, then. I mean, and that was actually my next question, which was would you see as work as having any influence . . . or his ideas as having any influence on your . . . on your own work?

SEEMAN: In the sense of what can be made, yes. [. . . Not] on the scale that we work. You know, when I started off, I was kind of embarrassed to be working on the "nanoscale," [. . .] because all [. . .] the organic chemists in this department, they work on the angstrom scale, right?

MCCRAY: Sure.

SEEMAN: You know, a bond is an angstrom and a half, right? Plus or minus in organic compound. And my fundamental width is the width of DNA, two nanometers.

MCCRAY: A couple of nanometers. Yeah.

SEEMAN: And, you know, that repeats three and a half. I don't have to go a full repeat to do things. But we're basically . . . our basic quantized unit is of the order of, you know, a few nanometers, and it's basically ten times as large as the others. And I was really pleased when nano came along because [. . .] nano was in fact my domain.

MCCRAY: Huh. Okay. So finally you had a name for what you were doing?

SEEMAN: Yeah. After a fashion. [. . .] There are a lot of people who do things with DNA that I don't call structural DNA nanotech. I mean, I've been calling what we do structural DNA nanotech, [but] the name's kind of been usurped a bit by the origami people. But you know, for me, origami is one of many techniques that we use. [We use] it when we need it, but we do lots of things that don't have to do with origami. [. . . Or] that involve origami but [. . .] that's not the key feature. The essence of what we do is that the structure—and when I say structure, I mean 3D structure—of the DNA or the construct, whatever it's going to be, is central. Or at least the topology is central to the nature of what it is we're constructing. So for instance, the kind of stuff where you take let's say a nano particle and put a lot of DNA on it, and then you take another nano particle with complementary or whatever DNA on it, and you throw them together, and you get some kind of schmutz, that's not what [. . .] I call structural DNA nanotech. It's certainly DNA-based nanotech, you know, of one sort or another, but, [. . .] for us that wouldn't really fall [directly] into the purview of what we do.

So when I talk about fifty or sixty labs doing what we do, or maybe more than sixty now, I'm talking about people who [. . .] actually care about the fact that, [. . .] these two helices are one next to the other, and there's a third one over here, or maybe there's an arrangement, [of] the sort of things that my students have done with Hao Yan's vases and Chengde Mao's star polyhedra and so forth.

MCCRAY: So, I mean, if you have to give the elevator description of what structural DNA is . . . structural DNA nanotechnology is, what do you say?

SEEMAN: I say it's using the chemical information in DNA to control the three-dimensional structure of objects, lattices, and [nanomechanical] devices.

MCCRAY: Okay.

SEEMAN: Nanomechanical devices.

MCCRAY: Yeah. That's certainly an elevator description.

SEEMAN: Yeah.

MCCRAY: Okay. So the move to NYU.

SEEMAN: Okay. So that happened . . .

MCCRAY: [. . .] How does that happen?

SEEMAN: It happened because Neville Kallenbach became chair here, and he and I had been working together for a long time, and he brought me in to be a guy he could talk to, and a guy who was doing stuff similar to what he was doing and so forth.

MCCRAY: What was the state of the chemistry department like when you showed up here?

SEEMAN: Well, Neville was improving it from what it had been enormously. But then [. . .] they stopped giving money. So what happened was [that] including himself [he brought]—in four relatively senior PIs [. . .]—well, three were senior, one was just very strong. He was junior, but he'd already been nominated for a Nobel Prize. Okay?

MCCRAY: Who's this?

SEEMAN: David [C.] Schwartz.

MCCRAY: Okay.

SEEMAN: I don't know if you know the name.

MCCRAY: The name's familiar. I can't . . .

SEEMAN: Okay. You may have heard of Schwartz and Cantor pulsed-field gel electrophoresis. It was a really big deal in the late eighties, early nineties. I don't think it's a big deal anymore. It **<T: 160 min>** was a major technique then, and Schwartz was an extremely bright guy.

MCCRAY: Okay.

SEEMAN: Anyway, so the 11th, the 10th, which is where I normally live, the 9th floor, and this 8th floor, were given respectively . . . were designed for Kallenbach, Schwartz was on 8, I was on 10, and 9 was a guy named Joel [M.] Friedman who came from Bell [Laboratories]. So Joel's a guy, you know, roughly my age, a couple of years younger, and for Schwartz they wrote a huge grant to set up his lab. For me, they gave me kind of minimal [setup], because they knew I'd practically pay them to get my ass out of Albany. And for Friedman, they gave away the store.

MCCRAY: What . . .

SEEMAN: Friedman . . .

MCCRAY: What was his work?

SEEMAN: Friedman was a spectroscopist of one flavor or another, and he came from Bell, and he's a pretty bright guy, but he had no academic background at all. I mean, yes, he got his PhD, and an MD, in fact. And . . .

MCCRAY: But he was used to working with the Bell system?

SEEMAN: He was used to working with the Bell system, and he didn't understand how to operate in a university in any regard. So he got this huge setup, he spent it all on toys rather than on postdocs so that he could get the data to get the grants. So he got one small grant. He was given a kingly salary, as Neville described it. I never found out how much it was. But, you know, part of that kingly salary was [he] assumed he was going to get a full-sized summer salary, which he wasn't able to drag down at that point. And this was [. . .] 1990 [that] I guess he came.

And they gave him $600,000, which in those days was a fortune. I mean, today you can't get an average assistant professor for that, but we're going back almost twenty-five years now.

And [thus] the negotiations started. I mean, I got like two hundred [thousand], and I was damned glad to get it. [. . .] Friedman had no idea how to operate, so he didn't get the preliminary data for his grants. He picked up whatever garbage was floating around the department for his graduate students, and he didn't get anybody any good. He spent all of his time being a renaissance thinker at home in South Orange, [New Jersey], which is across the river. So he was almost never here. And then he teaches one quarter of the freshman course in which he quizzes our pre-meds about things having to do with some of the fundamental paradoxes of quantum mechanics. And these kids don't get it. [If] these kids don't get As, they don't get to medical school. They don't get to medical school, they don't stay at NYU. Because NYU charges just like anybody else, any better school.

And he said he was giving them grades according to their understanding, which you can't do. I mean, all right, the kids all fuck up the exam, all right. So you say a thirty is an A and a ten is a B. You do what [you've] got to do to keep these pre-meds happy. They're the fucking customers.

So he did everything wrong. And then in the fall of 1991—I could be off a year here but I think I've got it right—he goes up to Einstein [Albert Einstein College of Medicine].

MCCRAY: The medical?

SEEMAN: Yeah. Where they made him a chair, so he had a guaranteed twelve-month salary. Everybody else is six months, but the chair is twelve months. And so he didn't have to worry about getting his big salary. And they gave him even more toy money. They made him a chair and they gave him more money to bring in colleagues, and I don't know how well he's done [. . .] as chairman there. He's no longer the chair, I believe. But it doesn't matter one way or the other. I mean, Neville lost all the confidence of the higher-ups when that happened. I mean, nobody was really all that sorry to see Friedman go, because he didn't know what he was doing [. . .], from the point of view of those of us in the trenches, but from the point of view of those who just paid $600,000 and [. . .] they'd given another $400,000 guarantee [. . .] that was [. . .] against [a] grant that actually did come in.

But, you know, they just saw it as, "Here's a megabuck [. . .] and we just lost it," basically.

MCCRAY: So for you personally, I mean, I know, you know, it's abundantly clear that Albany did not suit you, but, I mean, what did it mean just professionally to come here? I mean, what did it . . .

SEEMAN: It meant I had a labor force.

MCCRAY: Okay. **<T: 165 min>**

SEEMAN: I mean, that was what I did not have in Albany. [. . .] Every department has a sort of curator, manager, whatever, and this was a good guy up there. [I mean, when I was in Albany, I was somewhat friendly with ours]. He [John Elliott] had a master's in bio and [. . .] I used to call him the department proctologist. You had a pain in the ass, you saw him, right?

MCCRAY: Okay.

SEEMAN: [. . .] One time he got really pissed off at the chair who was complaining about the administrators—including himself—in some generally broadcast memo that he [. . .] had no right to send out, but [. . .] Lerman was Lerman. [. . .] So he complained to me about it. He said, "Doesn't this guy understand, we read books about what we do, too? We try to improve ourselves, just like you guys read your journals." So one day I went up to him and I said, "You know, these undergraduates don't work out for me. Can you give me one of these books of yours about management?" He said, "Sure." And so he lent me [. . .] a couple. I read them, and there [were] 400 pages there [. . .] but you could boil it down to one key principle that I didn't have working for me there, which is that if somebody works for you, their tomorrow has to depend on their today with you. If they're going off to medical school, [and] it doesn't matter

what they do in your laboratory, then they're no use to you. Right? [. . .] For me, that was the breakdown.

People will not do anything for you unless they're going to get something out of it, more than just my recommendation letter [saying], "Yes, this kid worked in my lab." Right? Which was why nobody was ever doing anything for me. And I understood that principle. And they weren't graduate students. For graduate students, what they do in the lab today is going to affect where they go tomorrow and what their whole future is going to be, because that's where they're going. They're going into science. They're not going into medicine. And, I mean, their going into science [is at least] somewhat influenced by what they're doing with me, right? And I didn't have that in Albany and I did have it here. I mean, [. . .] I had a total of six student years of labor in Albany, including one bozo year. Here, within the first year, I had that every year, and now I have about nearly double that.

And, you know, science is [. . .] not a matter of monkeys and typewriters, because the people running the typewriters have to have some sense of grammar, if you know what I mean, and some sense of spelling. I mean, the typewriter is now a word processor. But [. . .] nevertheless they have to have brains, but you [do] need enough people to try enough things. And I couldn't do that before. So nothing much happened in Albany. I mean, I had the idea. I fumbled along a little bit, basically living off of my collaboration with Neville. And that was it. End of what I could do in Albany. I mean, I had more ideas. I had plenty more ideas when I was up there, some of which I'm still executing, some of which I executed over the course of my first decade or so here. And, of course, I still have ideas and I'm still executing ideas.

MCCRAY: Yeah.

SEEMAN: But it was all just [. . .] was all ideas up there. There was no [. . .] output to speak of, except the last [four] years, when I had [Junghuei Chen], the guy who became my first PhD student, [Kathleen McDonough, who was] this one master's student for one year [. . . and two years of John Mueller]. And then everything that got done was mostly done in Neville's lab by his technician. And that was the story.

MCCRAY: Could you tell me how you manage and organize your lab? I mean, I guess we could start with, you know, how you did it in 1990 versus how you do it now, but, I mean . . .

SEEMAN: It's not much different.

MCCRAY: Okay. So how do you . . . ?

SEEMAN: Except that I'm not in the lab anymore and I'm not here all the time.

MCCRAY: Yeah. I mean, I know you travel a lot, so . . .

SEEMAN: I travel a lot, so [. . .] the nineties were somewhat different from the aughts. **<T: 170 min>** So in the nineties, I was doing the DNA synthesis myself. That meant I was in the lab about an hour a day doing that. And usually that wasn't an hour when there were too many other people here, but I was available. [. . .] In my [. . .] office, I mean, you know, you can see in. My door is always open. And the place was open for my students to come in anytime. [. . .] My students then were maybe in their middle and late twenties because some of them had got caught up in the cultural revolution and so forth. I mean, virtually all my students, not quite all, but virtually all my students were from the PRC [People's Republic of China]. You've probably heard that . . .

MCCRAY: I want to ask you about that, but I want to come back to that, but yeah.

SEEMAN: Yeah. Okay. So they're . . . and, you know, and I was sort of forty-ish, and I wasn't really old, you know.

Now, of course, they're twenty-two, twenty-three, twenty-four. I'm more than forty years older, and so it's a little harder. I'm not buddies with them anymore. We don't go out drinking together or whatever. If I go out drinking, I go out drinking with faculty. And they don't come in to see me anymore very often from the next room. They'll send me an email. So that's changed. Now the big change that happened in the lab, or a major change that happened in the lab, was toward the end of the nineties when my profile really went up, in the nineties, beginning of this last decade. And I started traveling three times as much [. . .] and I started getting more money.

[That coincided] with the dotcom boom [. . .]. So the way it works in my lab, or worked then in my lab, and to a large extent it still does, the older students teach the younger students, the younger students become older students. In the late nineties, a whole bunch of kids came in and said, "Well, you know, I really want to take this course on systems programming." I said to them, not being stupid, "You want to go into computer science. See ya." [. . .] I said, "Listen, you want to take that course or do you want to stay in this lab?" I mean, one or two I might have let do it, but, I mean, I realized that they were leaving anyway. So they all left. So . . . not quite all. But I had a kind of hiatus there.

And [. . .] at the same time I got some money, so I brought in some postdocs who really didn't know anything, because [. . .] there were no postdocs who knew anything. [. . .] As a rule, I don't bring in a postdoc anymore unless they come on their own money. All my money goes to students, and a postdoc can get their own money, but I can't. A student can't [operate] quite the

same way. The postdocs didn't know anything, and I was on the road. And I divide science up into -- you'll get the one minute version of how I see working in science, all right?

MCCRAY: Okay.

SEEMAN: [There are] three levels. There's the technical, the tactical, and the strategic. The technical level is, how do you run a gel? How do you use an instrument without breaking the instrument, without blowing up the laboratory, whatever? [On the] other end there's [the] strategic level. What projects are we going to pursue? What programs are we going to pursue? What is this lab all about? So the first is the business of the postdocs and the students. I'm totally hopeless with anything in the lab. [. . .] There was a time when the first version of, [any piece of equipment] like the synthesizer, I didn't actually take that one apart, but I took apart everything else. The second version, I don't even know how to turn it on. On the other hand, it's my job to do the strategy. I write the grants. I'm the guy who has to beg the money. I know what has to be done to get [and] to keep the money.

In between is the tactical level, which is basically what [. . .] we teach a graduate student. How do you do research? You can't teach somebody what [research] program [or project to pursue]. They can only guess, and I can only guess. But I can teach them how to do research. I can teach them how to design an experiment; how to debug an experiment; troubleshoot an experiment; how to worry about controls; and how to put together data in such a form that ultimately it will be publishable material. And to think about the things you could be doing wrong. Nobody in the lab could troubleshoot an experiment during that period when there were these three more or less ignorant postdocs, and the graduate students, senior graduate students, had gone. The upshot of that was everything was going to hell.

So what I did was I brought back one of my former [best] students <**T: 175 min**> as laboratory manager, and he's still with me.

MCCRAY: Who is this?

SEEMAN: Ruojie Sha.

MCCRAY: [. . .] Okay.

SEEMAN: And you'll see his name on a lot of my papers. And right now, the lab is very dependent on him, and I'm very dependent on Ruojie[. . .]. [laughter] But [. . .] basically he provides all the knowledge in that direction. So it took a few years to get the kids to understand

that they should go to Ruojie if they wanted to know how to do something. But now they understand that.

MCCRAY: So when you're training graduate students, do you give them all a shared set of problems and techniques that they have to master?

SEEMAN: We have a few trainer exercises.

MCCRAY: That's kind of what I mean.

SEEMAN: Yeah. Yeah. We have trainer exercises, but every student has his or her own problem.

MCCRAY: Mm-hmm. Yeah. That I can understand.

SEEMAN: I don't want any competition in the lab. I want cooperation. If somebody needs to know how to do something and they don't know how to do it and it's too hard for them, and this person knows how to do it, fine. They can be an author on the paper and just do that thing. I've done that a fair amount. But I don't like competition in the lab. I think that's kind of nasty. I've known people [. . .] who've done that, and I've not thought highly of them, despite their Nobel Prizes.

MCCRAY: Okay. Okay. But I . . . I guess where I was going more is, you know, say it's your first . . . you know, your first semester here as a graduate student. You know, by the end of the semester, you know, is there a, you know, set of research protocols, or they should have learned how to use X, Y, and Z piece of equipment, or . . . ? Can you sort of like walk me through what that's . . .

SEEMAN: They [do] three exercises [. . .], because we only have a month [. . .]; we have a rotation system. The rotations used to be longer. Rotation is to choosing an advisor like dating is to choosing a spouse.

MCCRAY: Okay.

SEEMAN: You know, so . . .

MCCRAY: So they don't come in here already working with you?

SEEMAN: No, no.

MCCRAY: Oh, okay.

SEEMAN: Many of them may come in wanting to work with me, but then we get to look at each other, right?

MCCRAY: Oh, okay. Okay.

SEEMAN: And so [. . .], we have four training exercises. We don't do very much of what they learn in the second one anymore, so I'll give you all of them. [For the] first one [. . .], we give them the strands for a four-armed junction, like I showed you [earlier]. They have to purify the strands and they have to learn how to work out the stoichiometry so that they can get a single band on a gel, which means they have to learn how to run the gel, without any crap below it, which means they have to get the stoichiometry sort of one to one to one to one [. . .], which isn't so easy.

MCCRAY: The strands . . . ?

SEEMAN: The four strands that they put together in the pot, and run it on a gel and show that. So that's experiment one. So they learn how to do gel electrophoresis—native gel electrophoresis—and non-denaturing gel electrophoresis, and they learn how to run denaturing gels, because they have to purify the strands . . .

MCCRAY: Denaturing gel? Okay.

SEEMAN: Yeah. So there are two kinds of gels you run. And [on the] denaturing gel, [mobility of DNA is] only a function of the molecular weight, and in the other, it's a function of the surface area and whatever. And the mass. So it's complicated.

The second experiment, which we don't have them do very much anymore, involves learning how to work with radioactivity, how to ligate a three-armed junction that has sticky

ends on it, and then run it on a gel, and the three-armed junction with [sticky ends]; when you ligate it together, you get both linear pieces and cyclic pieces, and then the idea was to run it on the gel, and the counts are all in the [. . .] long pieces that are either cyclic are linear, and you can tell the difference. You do it at different gel concentrations, you'll understand the importance of using different concentrations of gels and so forth.

Then the third experiment is to take ten strands of DNA and you cook them up together and you cool them down and you make a little two-dimensional crystal of DNA that has stripes on it, because there's a little domain of DNA coming out of that two-dimensional crystal. And then you look at that on the atomic force microscope. So they learn how to use the atomic force microscope and they learn how to cook these things up . . . this is a very fast experiment.

And then the last one is they set up some crystals just so they learn what's involved in setting up crystals.

MCCRAY: And this is all within a month?

SEEMAN: Within a month. Well, like I say, that second experiment with the radioactivity, usually we're not doing that anymore, because we hardly ever use radioactivity. Once **<T: 180 min>** in a while we do, but it's very [rare]. I mean, it used to be that everybody in the lab every two weeks got their own shipment of ^{32}P, until we started using the AFM [atomic force microscope], maybe twelve or thirteen years ago, and then we just stopped; [of course] we still do it. I mean, there are times when we need it. But [much of the time] we don't need it, and I don't [want] any more counts in the lab than absolutely necessary.

MCCRAY: [. . .] So the training exercises that you just set out, is that sort of a pretty standard routine that most faculty, you know, do? Or is this . . .

SEEMAN: No, [. . .] these are things that I want somebody in my laboratory to know how to do. If you go to work [here].

MCCRAY: I . . . no, I . . . yeah. I don't mean the specific ones. I mean just the . . . the . . . you know, you come into my lab, you know . . .

SEEMAN: Well, most . . . no, I don't think so.

MCCRAY: Oh, okay.

SEEMAN: Because people come into this lab [. . .]; to a good approximation, they've never done anything like this before.

I mean, nobody works with DNA the way we work with DNA, except for the other sixty labs, who don't seem to be sending me graduate students [. . .]..

So, you know, [. . .] there's a book, the original edition of which was called *Molecular Cloning*,[14] and it was known as 'The Bible' in all the molecular biology labs in the eighties and there was another edition of it came out in the nineties, and so forth. And it was how biologists would clone DNA.

And the first thing I had to teach people was learn the protocols there and then ignore them, because we're not doing biology here, where it's good enough to get one molecule into a cell and you've cloned it up and then you can select for it and whatever. We're chemists. We need 100 percent yields, or high yields, and we have to be able to purify away the crap from the failures, and it's a totally other way of thinking about stuff. And [. . .] that's just the way you have to operate here.

So [. . . for] most of my colleagues, the organic chemists, the physical chemists, whatever, [the] people [who] come into their labs sort of know how to do some of it, because they had an undergraduate degree in chemistry. Nobody has an undergraduate degree in DNA nanotech or, you know, whatever. So, I mean, when I was an undergraduate taking chemistry courses, I mean, if somebody had told me to reflux a solution as an incoming graduate student, I probably would have had some idea, and I'd probably ask the senior graduate student, and I've have got some help. But there wouldn't have been an exercise designed to teach me how to reflux a solution or teach me how to do this, that, or the other in one of the other labs. [. . . For] rotations in other labs, [. . .] they're given a little rotation project. "Here's a little thing we need to know. See if you can just do this." Or, "We need to know or we need you to make," and maybe it's a starter material for something else. "See if you can run an esterification or . . . ."

MCCRAY: Okay. Now I think what got me thinking about this was . . . and looking at your webpage, was looking at the protocols. And I just thought that was really interesting, because I think of my own graduate students, and it's . . . it's a very different . . .

SEEMAN: What are your students . . . ?

MCCRAY: History. They're history students.

[14] *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 1982)

SEEMAN: Yeah. So they don't have protocols of the same sort.

MCCRAY: No, but they have something similar in that they have to learn to work an archive. And they have to learn to work it efficiently. So I will go with them, and we'll pull a box off, and, you know, how do you . . .

SEEMAN: How do you look in it? Yeah.

MCCRAY: Yeah. I mean, this isn't like, you know, some like theoretical historical whatever. It's just you have a bunch of papers. You've got two hours. How do you go through and get some information efficiently? But it's . . . but I think maybe it's because my original training was as a scientist, my way of approaching that is . . . is really different from how my colleagues do, which is more like I think there's an archive over there. Go see what's there and come back and tell me about it. My approach is much more . . . it's different.

SEEMAN: Well, see, that's sort of the difference for me, as the difference between being at a middle-level school and an [. . .] elite school. Because when I went to Pitt, I mean, in a sense I lost a certain amount of big picture there. But boy, did I learn crystallography. I mean, when I went to Columbia there was a [. . .] five years' experience, sixth year graduate student there who didn't know a quarter of what I knew in the laboratory. And then when I went to MIT, there was another sixth year student **<T: 185 min>** who didn't know a quarter of what I had known when I got out of Pitt. And the reason is that in the elite institutions, science is often taught *a la*, "There's the lab. Spend four or five years there. There's the typewriter, word processor, whatever. Spend three or four months there. And come back with a thesis. See ya." Whereas at Pitt and at other middle-level institutions—and what I've continued doing here, because fundamentally this is that kind of place—it's, "We've got to teach you how to do this, we're going to teach you how to do that, and we're going to teach you how to do this, and we're going to teach you how to do that. Now [. . .] we can't teach you how to write a grant. We can't teach you to understand what's important, because that's something that's got to come from [the gut]. It's not going to come from a training exercise."

MCCRAY: When you say come from here, you mean . . .

SEEMAN: From the gut.

MCCRAY: Okay. Okay.

SEEMAN: You know? It's . . . you've got to either have a sense of what's good stuff to do or you don't.

MCCRAY: So how do you help your students pick a good problem?

SEEMAN: I don't [. . .]. They don't pick any problems. I pick the problems.

MCCRAY: Okay. Let me rephrase that, then. Of the problems that . . . I mean, do you just . . . you assign a particular problem to them, or do you say, "Here are the range of ones. Pick one that looks interesting?"

SEEMAN: Well, if I . . . if there's more than one student, I may say, "Well, we're planning to this project and we're planning to do that project, we're planning to do that project. Pick one," that way. But, I mean, we're just completely on top of it. I mean . . .

MCCRAY: And you have some sense of their relative talents, so . . .

SEEMAN: No, not at the beginning. [. . .] Ultimately [. . .] the ideal training, which sometimes happens and sometimes doesn't, is I give a student an easy project that in a year they'll work their way through the project all the way from conception to execution to publication. And then I give them a real problem where they learn the other thing that they have to learn, which is how to live with failure. That's the most important thing for them to learn, how to live with failure, and whether they can, because in the end, you know, good scientists . . . great scientists fail 90 percent of the time. Good [. . .] scientists fail 95 percent of the time, right? And the rest are 100 percent losers. [laughter] I mean, that's . . .

MCCRAY: I actually thought you were going to go a different direction, which was to say great scientists fail 95 percent of the time because they're trying things that are like way out on the edge of do-ability . . .

SEEMAN: Well . . .

MCCRAY: . . . and if you're a so-so scientist, you never really fail because you're never really pushing it.

SEEMAN: Well, there's . . . there may be that, too. I don't know.

MCCRAY: Okay. Yeah.

SEEMAN: But, I mean, you know, we've . . . I mean, I wish we failed only 90 percent of the time, actually. [laughter]

MCCRAY: [laughter] Okay.

SEEMAN: But at any rate, you know, and the one thing I didn't mention about the tactical part is in the beginning, that's 90 percent me or me and Ruojie, and in the end, it's 100 percent the student. That means we've taught them how to do research. We haven't taught them, you know, how to plan a research program. Hopefully they'll learn that in their postdoc, if they're going to do that, or maybe it doesn't matter, because they're going to an industrial job. I only have three PIs, at least in America, as part of my products right now. I have a ton of kids out there [as] postdocs [. . .], some of whom will become PIs, but . . .

MCCRAY: Okay. Before we wrap up for the day, you said something a little bit ago about having a lot of Chinese students. And I just wanted to come back to that before we finish up.

SEEMAN: I mean, it's very simple. This is a mediocre university, and there is a dearth of American students going into science. There are enough American students going into science such that the very top ones will fill up MIT and CalTech and Stanford and whoever else is out there.

[. . .] I was involved with graduate student recruitment for many years here. And, you know, you'd see somebody who was even of middle-to sort of-acceptable talent, and they would be going to the sort of Penns of the world. [. . .] We don't have a good tie line to Europe. The [rare] **<T: 190 min>** Europeans we get are okay. Even the Latin Americans we get are okay, Peruvians, that sort of thing.

I had an Argentinian student one time. But the American [applicants] suck. I mean, to a pretty good first approximation. Once in a while you get a good one. I mean, I've had one or two good Americans, but statistically they're not much good. And it's a choice when you're sitting there on the admissions committee, are you going to take dumb Americans or smart Chinese?

MCCRAY: This just goes off in a totally, you know, whatever, political direction, but why are the American students so bad?

SEEMAN: Because there are very few highly talented people who want to go [. . .]. I'll tell you a story about when I was in charge of admissions and the graduate program and all that. This is an older story. It's like maybe '95. One of these Chinese students comes up to me and he says, "How come we're all Chinese?" And I say, "Well, American students, the good American students, they go to law school, business school, medical school." He said, "I understand. Law school, business school, medical school, you have to pay tuition. We don't have any money." This is back when the Chinese had no money. "So we have to go to graduate school so our children can go to law school, business school, medical school. [laughter] And damned if that [isn't] what's going on now. [. . .] I have some students who are from twenty years before.

MCCRAY: Are their kids . . .

SEEMAN: Their kids are, you know, going to things like that. Yeah.

MCCRAY: That's funny. I mean, the standard story that, you know, I always hear is that, you know, American students just . . . I mean, yeah, partly they want a professional degree because they, you know, will make more money. Part of it is a just lack of aptitude and patience for, you know . . .

SEEMAN: Well, and partly there's a generation sort of in between mine and the current generation that saw what happened to my generation. You climbed over the rainbow and at the end of it was a pot of shit, where the jobs weren't there. I mean, this shitty job that I complain about at Albany, there were a hundred of us competing for academic jobs that year, and I nominally got the best one. There were about six total [who got any job], some of which were like not really tenure track or whatever.

MCCRAY: Yeah. So there's a sense of, "Why should I put myself through all of this?"

SEEMAN: "Why should I put . . . ." Yeah. I mean, you know, when you're my age, what's four years, five years? Who cares? You know? But when you're twenty-one, twenty-two, four years, five years, six years, or better yet, when you're eighteen, you know, or sixteen or seventeen, you mean, to spend six years as a graduate student? Which was standard at MIT in biology.

MCCRAY: Yeah. With no guarantee of . . .

SEEMAN: Yeah. Or actually, if you're coming through at MIT, actually, you probably would; it was almost a guarantee. If you came through Pitt, I guarantee you it wasn't. So there was that generation didn't go into science, and their kids don't even consider it an option. [. . .] When we recruited a bunch of physicists a few years ago, and many of them talked to me on the way here, and they said, "Well, what do you do about training grants?" I said, "Listen, there are two ways you can support graduate students. Either you can get training grants if you have talented Americans"—in fact, I mean, I told this to a guy who came here from [University of California], Santa Barbara—"Or you can get enough research grants that you don't have to worry about where they're from." And we've chosen the latter path because they're good students. We can't get good American students.

MCCRAY: Yeah. Okay. Hey, let's pause there for now [. . .].

[END OF AUDIO, FILE 1.1]

[END OF INTERVIEW]

INTERVIEWEE: **Nadrian C. Seeman**

INTERVIEWER: **W. Patrick McCray**

LOCATION: **New York University**
New York City, New York

DATE: **6 December 2011**

MCCRAY: All right. Well, this is working, and it worked well yesterday, so we're good.

SEEMAN: Good.

MCCRAY: I also want to be mindful of time. You've got to be finished by 1 o'clock, I'm guessing, for your class.

SEEMAN: Pretty close to one. There's an hour leeway in there, you know, so if the shit totally hits the fan, it's okay.

MCCRAY: Okay. [laughter] All right. I kind of wanted to start maybe with a broader set of questions . . .

SEEMAN: Sure.

MCCRAY: . . . and then come back more specifically to you.

SEEMAN: I have one piece of paper here for me to review.

MCCRAY: Okay.

SEEMAN: Yes, I do. Okay. I'm all set.

MCCRAY: Okay. So I thought maybe we could talk more generally about how your work relates to . . . to nanotechnology, and I guess maybe we'll start with the question of do you think of yourself as a nanotechnologist?

SEEMAN: Not really. I don't [. . .], 98 percent of people working in nanotech are working either with nanoparticles or carbon nanotubes or bucky balls or whatever. And I'm not. I use those things because there seems to be some interest in being able to organize them, but my thing is using the architectural [. . .] properties of DNA to organize either it or other stuff. So [. . .] most people are interested in the other stuff. I get the table of contents at *Nano Letters* and *ACS Nano*—I'm on both those boards—online on a weekly basis, and I look through there, and, you know, they're perfect journals for me because there's rarely more than one article in each issue, out of maybe fifty, that's actually of any importance to me, and the others I can ignore. That's also true of *JACS*, so the . . .

MCCRAY: *JACS* is the *Journal of the American Chemical Society*?

SEEMAN: . . . *Chemical Society*. I mean, for me a perfect journal is a journal where I only have to really worry about one article in it and I can forget about the other fifty, and if I have to worry about all fifty of them, then I'm going a little bit too low on the food chain, because, you know, you can't deal with fifty articles. You can deal with one.

MCCRAY: With one. Okay. So you don't think of yourself as a nanotechnologist, yet you're doing structural DNA nanotechnology?

SEEMAN: Yeah. That's the word we're using. People always want to put a label on you, but, I mean, I'm doing what I'm doing. It's whatever it is that kind of strikes my fancy, and which keeps the funding agencies happy. [. . .] As long as they're happy and I'm happy, I don't have any need to put myself in this bucket or that bucket or that bucket. My poor late mother was continually confused because [. . .] my label kept changing. She's say, "Oh, you're a biochemist." "Well, not exactly, Mom. I'm closer to a crystallographer." "Oh, so you're a crystallographer." "Well, I'm actually these days closer to a biophysicist." "Oh, so you're a biophysicist." "Well, actually, people are telling me that what I do is nanotech." I mean, you've seen that line because I've published it enough times, that my response to being told I was doing nanotech was the same as Monsieur Jourdain [Molière's *Bourgeois Gentilhomme*]. "Oh, [. . .] I speak prose. How wonderful." "I do nanotech. How wonderful." But in fact I do what I do and other people tell me what they call it.

MCCRAY: So do you think that's typical for a lot of people in your field?

SEEMAN: I don't know. [. . .] I mean, let's [say] my field is kind of "what Ned does." [laughter] I think [. . .] most people are more tightly bucketed. They want to be more tightly bucketed because everybody in this business tends to [. . .] rise or fall [. . .], to some extent, with the popularity of the field, the area, the discipline, whatever you want to call it. And so you want to [. . .] have a home somewhere—everybody wants to have a home. By which I mean scientifically [. . . an] intellectual/scientific home. Because that way [. . .] you'll run into people [. . .] who do the same thing [or] do related things, and a) you can collaborate; b) you can band together and reap the rewards of such combinations. That's one of the reasons that I was involved in the founding of [the] ISNSCE [International Society for Nanoscale Science, Computation, and Engineering].

MCCRAY: I have a set of questions . . . I'll come back to that. But before we get to that, I wanted to also . . . you touched a little bit on Drexler yesterday and Foresight . . .

MCCRAY: . . . and I know you received a prize from then in '95.

SEEMAN: Correct.

MCCRAY: But I kind of wanted to get your assessment of what you think maybe Drexler or Foresight did for nano that was both positive or negative.

SEEMAN: Well, I think that, on the positive side, the word certainly exists [. . .]. So the word is in front of the public. If I say to somebody, "I do nanotech," they kind of know what that is, or at least they've heard the word, and [. . .] to some extent you can credit Foresight with that. The negative side is that to get anything to actually be accepted is very hard. I mean, any new endeavor . . . damn near any paper. I mean, my papers are still rejected at an enormous rate, often by the editors themselves. Sometimes the referees don't like it, whatever. Since I won this [. . .] Kavli Prize, the rejection rate has really gone up, because I'm a better target now. You know, everybody is resentful of everybody else to some extent.

MCCRAY: So they're holding you to a higher standard?

SEEMAN: No, [. . .] I mean, these were editors; these weren't reviewers [. . .] I sent off three papers to three baby *Natures*, and I'm sure they hate being called baby *Natures*, within about a month or so of winning the award, before I even left for Norway. All three of them were bounced editorially. You know: no review.

MCCRAY: Did they give a reason for why?

SEEMAN: They always give the same bullshit reason. For our broad readership this is too specialized. So, like, we made the first crystals of DNA origami, and [an incompetent] editor at *Nature Nanotech* used exactly that line. "This [. . .] is for a more specialized audience." I mean, from other interactions I know this guy happens to be a jerk. It's as simple as that. [. . .] And I don't send to *Nature Nanotech* anymore because of him, because [. . .] the first time [. . .] I got a paper in there through him, he delayed it so I had a later publication year. And [. . . then] he went off for Christmas. Fuck you very much. I wrote this paper back in October. All you're doing is jerking around. They publish about five papers a week or something, or an issue. [. . .] In fact, big *Nature* [is far more reasonable]. I wound up publishing [that paper] in *Angewandte Chemie*.

And big *Nature* actually had, you know, as one of their "things that happened this week," they had, you know, a short paragraph about this paper that *Nature Nanotech* wouldn't consider.

MCCRAY: Okay. So thinking back to Foresight, did you go to a lot of conferences? I mean, they have them . . .

SEEMAN: I didn't go to a lot of [them], I don't go to conferences [. . .] unless I'm invited. The exception to that used to be the Biophysical Society, because there were people there [. . .] were people there that I felt I should see, sort of, once a year. They kept me honest. They were serious biophysicists. [. . .] Here I am flying all over, you know, doing stuff that some people say is a little on the light side or whatever. And these people kept me honest, I felt. But they started getting old and retiring or changing their interests, and so I [. . .] no longer saw them at Biophysics, I didn't see them there. So [. . .] the scheduled meetings that I attend that are not, sort of, invitation-only meetings, or invitation [. . .] to speakers, and applications for those meetings are....

MCCRAY: So the Foresight meetings of the nineties were by invitations . . .

SEEMAN: No, they weren't.

MCCRAY: Oh, okay.

SEEMAN: What I was saying is I don't attend such meetings unless I'm invited. I don't go to a meeting to sit at somebody else's feet and listen to their words of wisdom. And that's been my policy for a very long time. At least fifteen years. And so the only standard meetings I go to are the two that are sponsored by ISNSCE, because that group has kind of become my community. And, you know, [. . .] one group probably a little more than the other group, but I go to both meetings.

MCCRAY: Okay. Before we talk about that . . . oh, I'm sorry.

SEEMAN: The third meeting is there's a nucleic acid physical chemistry meeting in Albany [The Conversation in Biomolecular Stereodynamics] that I was involved with. [. . .] It's run by a friend of mine [Ramaswamy Sarma] from my Albanian period, and it's [. . .] cheap for me to take my entire group there. [. . .] It's an every other year meeting, [. . .] and I believe my group should experience a meeting every couple of years.

MCCRAY: Yeah. So that's one of the few things that'll get you back to Albany?

SEEMAN: Yeah. [. . .] I'll go anywhere **<T: 10 min>** for invitations, as long as I can escape. [. . .] The people in Pittsburgh were very nice to me, but I really didn't like the town very much, in that era, in the late sixties. But I go back to Pittsburgh, I see my friends, those who are still around, and I have a good time. I mean, it's the indefinite sentence that gets you, particularly in Albany, where it was really an indefinite sentence.

MCCRAY: I wanted to also ask you some questions about the National Nanotech Initiative. I mean, we talked about that a little bit yesterday, and you referenced Clinton's speech, but I kind of wanted to get your sense of . . . your own perspective of how and why it came about and what it's done . . .

SEEMAN: I've no idea why it came about. [. . .] There are movers and shakers in the nanotech area. I'm not one of them . . . relative to the government. [. . .] I've run into people from various companies or government people, who say, "Oh, yes, well, at this White House meeting," da dum da dum da dum, well, you know, nobody invited me to that meeting. I don't know shit about it. All right? And that's sort of where I've been for a very long time, [. . .] partly because I'm not at an elite institution, or in the private sector equivalent thereof, or whatever, or connected. I'm not a member of the National Academy. Nobody includes me in any of these kind of deliberations. So I . . .

MCCRAY: But as an outsider, just sort of seeing how this . . .

SEEMAN: As an outsider, I thought it was very poorly organized.

MCCRAY: Because?

SEEMAN: Because [. . .] they had basically two kinds of [. . .] grants. They had these NIRTs, which were about a four person grant, or the money for four people, at any rate, and then they had these NSECs [National Science and Engineering Center]. Well, NSEC . . . you know, I was totally out of competition for an NSEC. I mean, [. . .] I look at funding opportunities very chauvinistically. Can I get my piece of that action or not? So I was eligible for a NIRT, and I was not eligible for [an] NSEC, because you couldn't put together an NSEC at a place like NYU. I mean, Columbia got one; other schools of that caliber got one. We're not that caliber. And [. . .] to be frank, I [have] felt that class difference [relative to] the elite institutions, your Ivies, your super-schools in the middle west and the west, very [strongly during] my entire career. [. . .] It was very evident when I was a postdoc that, you know, things happened for people at MIT, which was obviously such an institution, that didn't happen for people at middle-level institutions.

MCCRAY: Yeah. It's just funny for me to hear you say that, because for history, NYU is considered an elite institution.

SEEMAN: Yeah. But for the sciences it's not. It's mediocre. It's getting . . . it's probably getting better. I mean, certainly the physicists are better than they were when I got here 20 years ago. Chemistry may or may not be better. It's very hard to judge rankings of institutions.

MCCRAY: Yeah. I mean, I know the National Academy does these rankings every so often, but they seem to be . . . .

SEEMAN: Yeah. I don't know if it's the National Academy or . . .

MCCRAY: Or the NRC [National Research Council].

SEEMAN: . . . the NRC, or something does these rankings. We've never ranked above fifty, I think, in chemistry. In fact, we were in the seventies for most of the time I've been here. And, you know, it's not so much whether you're [. . .] anywhere between seventy, one hundred, and say twenty, twenty-five, [. . .] it's not the same as being in between twenty-five and one. There

are elite monies that [. . .] at least used to be available to the top schools, and people are listened to. [. . .] There are a fair number of German postdocs who have visited this laboratory, at least two I can think of, [like Tim Liedl] [as graduate students, and] they come here and they learn stuff and whatever, and they go back and they finish their degrees. And I say to them, "So what are you doing for postdoc?" And they say, "Well, I'm going to apply for DFG,[. . .] and, Ned, you're a really great guy and you do really great stuff, [but] William Shih is at Harvard . . . ."

MCCRAY: Hmm. Okay.

SEEMAN: So guess what?

MCCRAY: They go to Harvard.

SEEMAN: They go to Harvard. And you know something? I did that too when I was a postdoc. I mean, I went to MIT. [. . .] I didn't realize how crappy [the lab at] Columbia was, but I went to the elite because the next step after being at an elite institution is a professorship, and who wants to come <**T: 15 min**> out of a dump? Nobody's going to take you seriously no matter how good your science seems to be.

MCCRAY: Mm-hmm. Okay. Why don't we talk a little bit about the International Society for Nanoscale Science, Computation, and Engineering?

SEEMAN: All right. [. . .] So there are two meetings that take place under its auspices. There's the DNA X, I think we're about to go . . .

MCCRAY: So we just had DNA 17 at CalTech.

SEEMAN: We just had 17, and 18's going to be in Aarhus, [Denmark].

MCCRAY: Oh, okay.

SEEMAN: And . . . so that meeting goes North America, Europe, North America, Asia, and repeat. So [. . .] half of them are in [. . .] the Western Hemisphere. One [. . .] quarter each in Asia and in Europe. [. . .] I wrote a sort of document to get it off the ground because there'd been discussions at DNA 7.

MCCRAY: Well, roughly when is this happening?

SEEMAN: Two thousand one.

MCCRAY: Two thousand one. Okay. So this is a fairly recent group, then?

SEEMAN: Well, yeah. I mean, we just had 18, right? And the FNANO meetings are more . . . that's the other group.

MCCRAY: That's . . . yeah.

SEEMAN: Those are more recent. They began in the last decade. I . . .

MCCRAY: What's the F stand for?

SEEMAN: Foundations of Nanoscience. And they both have their strengths and weaknesses. [. . .] DNA-1 was a meeting on DNA-based computation that took place at Princeton, and it was my program director at the Navy—so that was '95—my program director at the Navy said, "Ned, I think you should go to this." This was like right after Len Adleman had done his.

MCCRAY: Yeah. Who was your program director?

SEEMAN: It was [. . .] a guy name of Mike [Michael] Marron, [. . .] to whom I give a huge amount of credit for having recognized that this stuff could happen, and for giving me the first money directly to do it, as opposed to stuff I had to bootleg. And Mike called me up or sent me an email or something in '95, and he said, "Ned, you should go to this meeting." And [. . .] in eighteen years of teaching classes, that was the first time that I cancelled a class on short notice. I mean, I cancelled classes all the time, but these are for meetings that I [knew] about on the first day of the semester. And that was the first time I just said, "No class tomorrow," or whatever, and I went down there for that. That's where I met Erik Winfree and Paul Rothemund and Len Adleman, for that matter. And Winfree started talking about using our systems as [. . .]—I mean, the term he was using then was cellular automata [. . .]—Wang tiles was a term that came out later, when he tried to formalize that a little bit. And then Erik and I started collaborating. I mean, he was a graduate student, right? And . . .

MCCRAY: He was at CalTech at that point?

SEEMAN: He was at CalTech then, and . . . he's been at CalTech, except for a year at Princeton, and [. . .] much less [than] a year, I think [. . .] at MIT.

MCCRAY: Yeah. Whereas Paul did his doctoral work with Adleman at USC [University of Southern California].

SEEMAN: Yeah. At USC. That's right.

And so Erik and I started collaborating on that, and Paul, I think, [. . .] may still have been an undergraduate then, in '95. I'm not quite sure. And that was my first contact with that community, and I was their first contact, except for Len, who'd just sort of done it kind of on his own, I think, with an experimentalist. So [. . .] for the second meeting, which I think also took place at Princeton, I was part of the meeting, whatever. And then I've worked for many years with Natasha Jonoska, University of South Florida, and she and I wound up being the people in charge of the 2001 meeting that took place in Tampa, [Florida], there.

And at that meeting and perhaps earlier, somebody else, Anne Condon, who [. . .] at some point moved from Wisconsin to Vancouver, [British Columbia, Canada], UBC [University of British Columbia], and I'm not quite sure when (she's also a computer scientist), was saying, "This is a very scary thing," to run one of these meetings, "because there's no institutional infrastructure behind us. If there's a snowstorm and nobody shows up and you're **<T: 20 min>** guaranteeing a motel or whatever, it's coming out of your pocket." So she was concerned about that. And also [. . .] here we have a group of people using the information in DNA either to make stuff or to do computation or to do whatever. And it's a kind of new community, and, you know, we're not going to get recognized, particularly our young people. I mean, by 2001 I was already on the same side of fifty that I am now. Not the same side of sixty, but same side of fifty. And, you know, young people need recognition. They need awards. Old people need recognition and awards, too. We're expected to get those. And [. . .] people are constantly saying that, "Oh, well, you know, you're not one of us." I mean, I've had discussions with numerous people about potential nomination to the Academy, right? And they all say the same thing.

[Somebody] broached it to the biochemists, but they said, "Well, yeah, he's good, but he's not one of us." And the same with the chemists, the same with the [biophysicists]. I've been nominated, I think, in four different divisions now, but nobody wants to go for one of these interdisciplinary nominations because then you're giving something up from your division, sooner or later, and [. . .] who knows what division the person is going to choose to join, because it's apparently your choice, once elected.

And everybody [is the same: The] chemists want chemists. The biochemists want biochemists. People who are clearly one of the boys, or one of the boys and girls these days. But not somebody who's sort of coming in at this discipline from left field, or is only taking a little bit of this discipline and combining it with that [. . .]. I mean, some people think that that's how progress happens. [. . .] Well, nine out of ten of these people are just cranks or whatever. And for all I know I was regarded that way for a while. It's okay. [. . .] That's just the way it works. "This is impossible." "This is ridiculous." "This is obvious." [. . .] That's sort of the trajectory of any idea.

And, in fact, you know, I told you I did [. . .] my main postdoctoral work with Alex Rich, the good postdoctoral work. The stuff I did with the asshole at Columbia is another issue. But, I mean, I did good work [at Columbia], but he and I got along like oil and water, as we say.

But Alex was talking about, at this thing on Friday, this symposium, he was talking about how he had actually invented hybridization, which was true. It was a throwaway paragraph in a paper in 1956, published in *JACS*, and it was coincidental that he was going to talk about that, because I actually had a slide up that had the whole paper on it. It was about [. . .] a column of a relatively short volume, the *Journal* [*of the American Chemical Society*], and there was one paragraph there. "People might find it useful to be able to take [two strands of nucleic acid and hybridize them]." What he had done [was] take poly A and poly U, put them together, and demonstrated [. . . they formed an- A-form helical diffraction pattern [. . .], and that hence RNA could form a double helix, something that wasn't evident beforehand.

[. . .] He said he walked out of his lab and he ran into a guy who was a well-known sort of standard biochemist, and said, "I just got poly A and poly U to come together and form a double helix." And the biochemist said, "What? Without an enzyme? Impossible." That was the paradigm in 1956. And they said, "Listen, you know, these guys are negatively charged? They're going to come together? Ridiculous. They're all coiled up in solution, they're going to uncoil and come together to form a duplex? Ridiculous. I mean, have you thought about the entropic considerations? It's nonsense to get two things to form one thing. Nonsense."

But in fact, of course, it works. And virtually everything that happens in molecular biology is based on [. . .] this notion, not to mention everything that happens in what I regard as my field, happens as a consequence of hybridization. I was told that I couldn't get four strands to come together. I knew that was wrong, because I knew you could get two strands to come together, and sooner or later, with that branch point, you know, the boundary condition had to be right, **<T: 25 min>** that if you made them long enough, who would even know about this fault in the middle? So I knew it was going to work eventually. But Alex had to face that kind of crap for a couple of years. But sooner or later other people repeated the work, and it does seem to work. [. . .] It's always that way. Things go from impossible to obvious [. . .]. I mean, "Of course."

MCCRAY: So tell me more about the . . . I'm sorry. I keep messing up the acronym?

SEEMAN: So the Society?

MCCRAY: The ISN. It's not . . . it doesn't really roll off the tongue, right, but . . .

SEEMAN: No, it doesn't.

MCCRAY: So, I mean, you went . . . it was started in 2001 . . .

SEEMAN: In 2001, I was waiting for a plane [. . . thinking about Anne Condon's concern] that there was no society behind any of this, and hence anybody who was hosting one of the meetings, be it in this country or elsewhere, was up against it for potentially a lot of cash that they might or might not have. And so we decided to put together a society [. . .].

And the other reason of course is to make sure that people can get appropriate recognition. The field can get recognition by giving out prizes, and individuals can get recognition by [. . .] receiving prizes, because the ACS [American Chemical Society] isn't going to give anybody a prize who does this kind of thing. I mean, I did win one ACS award. But I'm not an ACS guy. I'm not a big fan of going to meetings with 20,000 people, you know, whatever. I've gone to ACS meetings [. . .] if invited to speak at some symposium. But as a rule, I don't go to an ACS meeting. And the ACS seems to me to be an organization that exists largely to recognize its own members. I mean, every issue of *C&E News*, you know, here are ten XYZ scholars. Here are our twenty ABC medalists. And then they keep going and going.

MCCRAY: Yeah. The American Physical Society is kind of the same way.

SEEMAN: I'm sure it must be.

And so, when I [joined] the Crystallography Society [American Crystallographic Association], which was my, sort of, original home society, and I'm still a member, they had maybe one, maybe zero awards. Now they've got about half a dozen or something. They all do that, because, you know, there are more and more people gathered under the umbrella of the Society, and they need recognition, and they're not going to get it from the other societies.

MCCRAY: Okay. So this is a way, then, to help nurture a community?

SEEMAN: Yeah. It's a way to help nurture a community. Yeah.

MCCRAY: So what disciplines are people being drawn into? I mean, the word, you know, nanoscale science, computational engineering . . . So who does this bring in?

SEEMAN: [. . .] Well, one of the interesting things about this, one of the things that gives me a small advantage, but only small, is that the people who [. . .] were in [at] the beginning, people [. . .] who were in DNA-based computation, and in other aspects of nanoscience, were largely not chemists. Either they come from physics or computer science for the most part [or] math. And on the other end, some [. . .] some biologists were also involved [at] the beginning, but not so much anymore. I mean, at the first meeting, I was the only experimentalist who showed up, I think.

MCCRAY: This is the Princeton meeting in '95?

SEEMAN: The Princeton meeting in '95. At the second and third meetings, every computer scientist showed up with a tame biochemist in tow. Okay? [laughter]

SEEMAN: And by the fourth or fifth meeting—2001 was the seventh meeting—those people had decided, "Well, this was cute, but I've got to work up my enzyme or I've got to do my thing with DNA repair or I've got to do my whatever thing it is, and this may be cute," and, you know, a couple of very young people were involved in it for a while because it gave them a chance to sort of add credentials and citations and whatever to their career path, but by and large, those tame biochemists had gone the way of the passenger pigeon. They [. . .] weren't there anymore by about the fourth [. . .] or fifth year.

MCCRAY: So where did they migrate to?

SEEMAN: They just went back to biochemistry. One of the things with interdisciplinary sciences [. . . is that] it's very hard to get interdisciplinary stuff to work because everybody has demands from their own primary discipline, right? And **<T: 30 min>** then to get it to be fixed into a university structure is almost impossible.

In my experience, I've only been at two universities, but it's been very clear that in both, particularly up in Albany, the word interdisciplinary is enshrined by deans and provosts, [. . .] A typical provost, such as the one we had up there, I think up there it was called, vice president for academic affairs, will say, "I can take a group from here, let's say the artists, and a group from here, say the scientists, and I can claim that . . . I can make them part of the same

[interdisciplinary unit], artists and science." I've just pulled two things out of [. . .] the air. "So I have the Art and Science Initiative at Albany, and I can keep that going maybe for five years till I can get out of this dump and be a president somewhere else, and [. . .] part of my credentials will be that I will have established an interdisciplinary program for no money, because I'm not giving any [. . .] more money to art, I'm not giving any more money to whatever science it was, that came together." So, free. "It comes free to the administrators. They're going to love it. And at the same time, interdisciplinary. What a buzzword, you know. And I've created it. What a buzzword."

And you just see that all the time. And, of course, it's like two parents who drag their children of roughly the same age and totally different interests together and say, "You and you, play." Right? Maybe it works, maybe it doesn't work. The only thing they have in common is age, so maybe it doesn't. And that's sort of what happens on the faculty level, in my experience, in interdisciplinary: this, that, and the other. So to keep interdisciplinary things going is very hard. Everybody's got to feel like they're getting something out of it. I mean, it's like any other collaboration, in a way[. . .]. I can't tell you how many people have approached me at meetings and said, "Gee, can you send me some of your stuff, or can you make these measurements on stuff I'll send you?," or whatever. And I've said yes, and I've never heard from them again. My response is always, "Sure, send me an email." Ninety percent of those emails don't even arrive.

I mean, it's got to be to both parties' real advantage to do it. And people love to say that they're collaborating with somebody or another, but in fact they're not. [. . .] I don't quite understand why. I mean, if I'm not interested, I tell people straight off the bat, "Look, I mean, it sounds neat, but I've got too many fish to fry," or, "My plate is too full," or whatever. "I just can't do that right now. Why don't you go talk to so and so?"

MCCRAY: So, I mean, one of the things that, you know, in terms of the rhetoric from the National Science Foundation, or just the NNI [National Nanotechnology Initiative] in general, is that, you know, nano is this wonderful interdisciplinary playground where the physicists and the biologists and the chemists are all doing their thing. Is that just talk?

SEEMAN: To me it's just talk.

[. . .] I interact with physicists all the time. I interact much more rarely these days with biologists. I used to interact more with biologists and hardly at all with physicists, but if you look down [. . .] the list of where I give lectures, I give lectures only occasionally to biologists now, [. . .] or to bio-X—biophysicists, biochemists, whatever. And much more frequently either to chemists, or to physicists, or occasionally mathematicians, or whatever, because the biologists aren't all that interested in what I do. So it's becoming more chemical, less biological. And [I've] got to say that what I do in terms of nanotech is frankly far easier than what I do for my NIH projects. That stuff is really hard. And this stuff is, you know, relatively easy. So in fact, [. . .] I like to keep the NIH going, not just because it's the good money, because they give

you twice as much as anybody else does, but also because it's actually harder and it keeps the brain moving, working a little harder to solve the problems.

MCCRAY: Okay. So for the ISNSCE, again, coming back to, you know, when you look at it, what disciplines does it bring together?

SEEMAN: Well, basically it's computer scientists and chemists.

I shouldn't say chemists, really, because there's some of them that really come from physics, and if I don't count my own students, of whom two are relatively prominent in the organization, there are about two other chemists there. **<T: 35 min>** And then [there are] some from biology. [. . .] Some of the people who show up at the meetings, are invited to the meetings, are kind of chemists, kind of biochemists. You know, it's hard to say. But in terms of like real live synthetic chemists or whatever, I could name two. That's it. [. . .] The rest of us can occasionally do a little bit of synthetic chemistry, either by collaborating with a real organic chemist or by following a literature procedure that's pretty straightforward, and we can kind of figure out how to reflux something, with luck. That kind of thing.

MCCRAY: So . . . okay. So this . . . I'll come back to that in a second, but I wanted to also ask you, how does [. . .] structural DNA nanotechnology relate to DNA computing? Because, I mean . . . let me . . . I'm going to back up even further. I went to the CalTech meeting, what was that, a couple of months ago?

SEEMAN: DNA 17.

MCCRAY: Yeah. And I was just really trying to understand how people who were doing . . . you know, looking at the posters, trying to see how the people who were doing structural DNA nanotech are relating to the computer . . . the computing people, and trying to see how they intersected.

SEEMAN: [. . .] One of the things about DNA-based computation is that so far nobody's done anything that's significantly up from a toy, in calculation. And [. . .] a lot of the growth in DNA nanotech—let's not add structural even necessarily—came because, insofar as I can tell, a fair number of the people in DNA-based computation really didn't see that it was going anywhere, and they saw that [what] I was doing was easier. And, [. . .] what they've brought to the party is logic. I don't mean that what I did is illogical. I'm talking about logic in a more formal sense. That [. . .] when I think about making things—or at least up until I became involved with those folks—[. . .] I thought about making things of here's sticky end A and it's going to go to A

prime, and B goes to B prime, and C goes to C prime, and that's it. Whereas they thought in terms of taking our motifs and turning them into logic gates of one sort or another.

So for instance, what Winfree was supposed to do for his thesis, and eventually [. . .] Paul Rothemund wound up doing it in his lab, was to make a so-called Sierpinski triangle. You know what that is?

MCCRAY: I read the paper. Yeah.

SEEMAN: Okay. All right. So [. . .] it's seven tiles that makes a fractal. There's no way I could make that with the initial approach that I had of, you know, A goes to A prime, B goes to B prime. On the other hand, much as I like that approach and much as I appreciate it, I mean, their error rates are just off-scale. You can't do serious computation with a really faulty computer insofar as I can tell. You can get the equivalent of parity checks or whatever, but then the computer hangs up. You're done. But they brought logic to DNA [. . .] nanotech, and that means that we have a broader set of things we can make. They do other things in terms of logic gates. This recent stuff of Erik's, with these successive toehold things and so forth: all of that is good stuff. [. . .] So that's kind of merged the two areas. Basically, [. . .] those people are doing stuff, except for the addition of logic, that we were doing before, because they saw that what we're doing in terms of making stuff, is actually easier. [. . .] They're just not going to compete with silicon [for computation], in terms of speeds or anything else [. . .].

MCCRAY: So what are the potential applications for it, other than the fact that, you know, that some see it as inherently interesting?

SEEMAN: Well, I think the organization of nanoelectronics, nanophotonics, all that kind of stuff [. . .]; what are you going to do with nanoelectronics? You're going to build computers, but you're going to do it from the hardware point of view rather than the software point of view. And I regard what Len Adleman did as using DNA for software. Here's the DNA, and we get the DNA to spew out an answer, but [. . .] I wouldn't call what he did using DNA for hardware, [. . .] for organizing hardware. [. . .] I mean, for a while there were discussions of, well, we could have a swimming pool <**T: 40 min**> full of DNA and all that and work out hard problems. My interest in all of that was that in a way, this mimicked what happens in the cell. A chemist takes two, three, four components, throws something between 10^{12} and 10^{18} copies of them in a pot, stirs them up, and gets out one, two, or three products. The cell has at most 1,000 and often many fewer copies of 10^{8} or 10^{9} different components, not counting the water, and they're all present in very small quantities. [. . .] So what the DNA computation people were talking about in the early days was very much like what happened in a cell. And I figured [. . .] this is an interesting way to emulate the logic that goes on in a cell and so forth, because you have tons of components, and not [. . .] many copies of every one of them. So it may be a different way of looking at what happens, you know, in living systems.

MCCRAY: Is there any parallel with what the DNA computing people were doing versus what you and Robinson had talked about with the biochip?

SEEMAN: No. No.

MCCRAY: Okay. That's what I figured.

SEEMAN: What Robinson and I were talking about was using DNA to organize other stuff.

MCCRAY: So this is another kind of broad question, but, you know, people oftentimes talk about, you know, paradigms for particular fields. You know, what would you say is the, you know, basic paradigm for DNA nanotechnology? You know, like the basic guiding principle, or . . .

SEEMAN: Well, up until a few years ago I would have said it was gain control by trashing symmetry. But in fact Chengde Mao has shown that, in fact, if you maximize symmetry, you often do better than if you minimize symmetry in some regards. And I regard that as a technical triumph for him, but [. . .] he would [. . .] probably say the same thing, because if you only need three strands to do the work of thirty, you only have to purify three strands and you only have to get the stoichiometry right between three strands, rather than between thirty, and [. . .] purifications always suck, and synthetic DNA isn't all that good. I made my career off of synthetic DNA, but there have been at least two occasions when interacting our DNA with enzymes, that we actually had to make the DNA using enzymes, and ATP [adenosine triphosphate] and, you know, NTP [nucleoside triphosphate], rather than on the synthesizer. [. . .] One of them was when we discovered there was an RNA topoisomerase. The way we did that was to transcribe an RNA strand off a piece of DNA, and in principle, you're supposed to get [. . .] fifty to one hundred RNA molecules [for every DNA molecule], and we were getting two.

And when we PCRed [polymerase chain reaction] the stuff up so it was all normal DNA, then we got our one hundred, too. And then in a DNA computing application, published maybe two, three, four years ago, [. . .] it was a toy problem. [. . .] We had a graph, and the question was, is it three-colorable or not? So you have a given graph, and the question is, can you color the vertices with three different colors such that no edge is flanked by the same color? So in order to do that, we worked up a system whereby we restricted the graph that we constructed, and [. . .] those edges that were flanked by the same color—the strands go in from one vertex to the other—wound up being [. . .] restricted. And they had to go to zero, right? Nothing left of that stuff. Then what was left, we [. . .] would [characterize].

And what we found was that, in fact, one of the edges just didn't go to zero no matter how much restrictase we threw in. And finally I had the student just make it biologically, and then it worked okay. So we **<T: 45 min>** had a couple of problems with the synthetic DNA. And . . . I've forgotten the question that started this.

MCCRAY: I was asking about kind of like a paradigm or like a guiding set of ideas . . .

SEEMAN: Oh, paradigm. Yeah. So trash symmetry.

MCCRAY: [. . .] But you're saying now it's . . . you think it's more symmetry rather than less symmetry.

SEEMAN: [. . .] I'm not saying that at all. I'm saying that if we were technically more adept, then the principle would be right. But, you know, there are in science what we call Pauling points, when you [. . .] make one fewer approximations, you go further from the right answer. So, you know, you go like this, then you go like that, then you go like that. [. . .] I mean, experimentally do things more correctly rather than less correctly. And it turns out we happened to be at one of those points where the technical aspects of things are overtaking the logical aspects of things.

So, no, I don't believe that that's [true overall], but it's something we have to do for the time being because we purify our materials so badly or whatever.

MCCRAY: So coming back to the FNANO meetings, we talked a little bit about the people who go to it. But, I mean, how many people show up for these typically?

SEEMAN: Oh, you know, of the order of one hundred to a hundred and fifty.

MCCRAY: So it's a fairly small community, then?

SEEMAN: It's a small community at FNANO, and it's also small . . . well, you saw the size of DNA 17. It was about the same.

MCCRAY: Couple hundred maybe.

SEEMAN: [. . .] FNANO is in one place always. And that's the place where the guy who organizes it has contacts, at Snowbird [Ski and Summer Resort, Little Cottonwood Canyon], in Utah. So, I mean, I'm not a skier, but I've been to the ski resort now about seven or eight times. I guess we've done seven meetings? I'm not quite sure. We started out . . . I think we started in '04, so maybe it's eight meetings now. And it's always there. So this is the [. . .] little less computational, little more physics, chemistry sort of meeting, for whatever reason.

MCCRAY: I wanted to get your thoughts . . . okay. So let me just preface this. So in any of the review articles on DNA nanotech that, you know, *Science* or *Nature* publishes, there's sort of like a standard narrative that shows up. I mean, there . . . it starts with your work where you're referred to as the father of DNA nanotechnology, and I'm curious to know what your own reaction is to that. But then it talks about Adleman's work. It talks about Paul's work a little. Maybe it'll mention Erik's work. But I kind of wanted to get your sense of, you know, what do you think of that sort of overall thumbnail description of how the field developed?

SEEMAN: Well, certainly I was there first. I was there nearly fifteen years before Adleman was. And then [. . .] Adleman sort of dipped in and dipped out of the field. And there were a lot of people who dipped in and dipped out, and he was one of them. I mean, Adleman's a really smart guy, so when he dipped in, [. . .] it wasn't just a 'we got some of his toe fungus in there.' We got . . . it was a substantial . . .

MCCRAY: Whole foot.

SEEMAN: It was . . . well, a substantial contribution, right?

[. . .] Erik is a very smart guy. I don't think his contributions to nanotech have been as much as his contributions to DNA computation. [. . .] Basically what happened was when we agreed to collaborate, he was supposed to make the Sierpinski triangle and we were supposed to make a periodic array, but he realized when he finally got around to doing it that the first thing to do is to make the periodic array, and he was simply better than my graduate student. And so he got there a little bit ahead of my student, so we published together, and it was a nice collaboration there. And he's done other things with it, with that system. I mean, I don't think they've gone very far beyond DX in terms of motifs and so forth. Maybe some TXes.

I would say [. . .] if you want to talk about after me who made the two major contributions, I would say Paul with origami, without question. And the other one who keeps not getting what I feel is appropriate recognition is Bernie [Bernard] Yurke with toeholds, you know, toehold-based isothermal strand displacement. Now I [have] of [. . . the] students in my class [. . .]—present—papers, and one of them just presented a paper where she kept <**T: 50 min**> talking about something that sounded like [isothermal strand displacement], and I downloaded the paper, and I haven't had a chance to read it yet—a paper that talked about [. . .].

She kept talking about a 1981 paper, and maybe Bernie got it from that.[15] I don't know. [. . .] I never heard of the people who wrote that paper and all that.

But [. . .] if somebody said to me, "Ned, all right, you got your Kavli. Who should get the next one?" I would split it between Bernie and Paul. [. . .] The important thing in my opinion about origami is not the part about the smiley faces. It's the part about where he made that map of the Western hemisphere. He's [. . .] shown that you can relatively [easily] put a couple hundred [. . .] individually addressable points together, and that was his main contribution. When you start looking at origami, the first you thing you say is, "Wow, it's so big." The second thing you say is, "Shit, it's so small." [. . .] I wanted to combine nanomechanical devices and 2D arrays before Paul did his work, and we took a TX motif and connected the [TX motifs] one to three like that, so that in a row like this we had four helices worth of thickness. And we had to take four [in one row] and four in the next row, so we had eight different ones, which was a real pain in the ass for the student who was doing it; [we did that] so we could put something in there that would flip back and forth that we could see in the AFM. And [a standard M13] origami [is] big, but it [is] only three times as big as those eight tiles. Eight: that's a lot. And we would never go back to doing that with eight tiles. But, in fact, one of the things that we published not long ago was that we went to making [. . .] 2D origami crystals because at least M13 is pretty small, and [. . .] these are really expensive experiments. You start fucking around with your origamis and you have 200 staple strands or 250 staple strands, and you want any kind of quality from them, so you don't buy them from Bioneer, [Inc.]. You usually get them from IDT [Integrated DNA Technologies]. Man, that's a lot of money. I mean, what do . . .

MCCRAY: The expense is coming from the size of . . . or the length of the . . .

SEEMAN: The number of DNA strands that you have to buy, each at X number of cents per nucleotide, and William Shih [. . .] has sort of pushed his research to do that. [. . .] He and his German postdocs are taking origami as far as it can go, and the Wyss Institute, [they've] got slightly more money than God. I don't know how much more money than God. And he's able to invest in experiments like I would never dream of doing. [. . .] It's the story of my career. You have to be smart rather than rich in order to [. . .] get things to happen. I'm not saying William isn't smart, but [. . .] William is very rich.

MCCRAY: What was your reaction to Paul's paper when you first . . . did you read a pre-print of it, or, I mean . . .

[15] C. Green and C. Tibbetts, "Reassociation rate limited displacement of DNA strands by branch migration," *Nucleic Acids Research* 9 (1981): 1905-18.

SEEMAN: Paul presented the work [. . .] at that summer meeting in Albany. I had just asked him to give a talk at that summer meeting in Albany in 2005. So I was well aware of it eight months beforehand; that it was great stuff. And then I reviewed the paper also. And I asked a couple of questions [. . .], as a reviewer, that he didn't really answer, which is sort of okay. But, I mean, one of the things about origami is [the issue of its quality]. I mean, Paul talks about pixelation. My word is resolution. He never really did answer what's the resolution of an origami; namely, if you take 100 or 100,000 or some appropriate number of them, and you superimpose them by the best algorithm you've got, and then you Fourier transform that pattern, how far out in [. . .] reciprocal space . . . you know what that is?

MCCRAY: I remember. Yes.

SEEMAN: In scattering space. How far out do you get? What's the equivalent of Bragg peaks? That's resolution. So he used the term pixelation, which may be unfair to him, but his pixelation is 60 Ångstroms. I think in terms of four [Å].

So I'm pissed off that I can't do better than four [Å] right now. Maybe we can, and we can get down to 3.5. I don't know. Right now [. . .] we're doing experiments to see if we can do that, having to do with the way we freeze our crystals and [. . . so on]. Paul **<T: 55 min>** is exploiting, as far as I'm concerned, a different size region from what we're exploiting. We use it when we need to. So, for instance, the nanoscale assembly line that we made, that's a *nanoscale* assembly line, and we're taking five nanometer particles and putting [. . .] putting them together on this walker and so forth, which I consider to be like the chassis of a car going through a Detroit, [Michigan], [auto] factory [. . .]. Anyway, I would very much like to be able to shrink the scale of what we're doing there from putting together nanoparticles to putting together [small] molecules.

In principle, we can do that without even protecting groups on [. . .]. One of the key things we showed in that piece of work was that even in solution, and of course, we could always tie them down to a solid support, the origamis almost never talked to each other. So we had less than one percent, at least with three additions, we had less than one percent wrong answers. We had yield problems, like everybody else. It was like 0.75^2 for . . . all the way down there. Part of that had to do with the fact that the origami is so damned small, we couldn't make a bigger walker, so that meant that the walker was a certain size, and then what was on this corner and this corner and this corner [were] starting to talk to one another. [The first two particles if you] would talk to the third guy, [so] you'd have trouble getting him on, and . . . so [there are] steric issues.

Why did we do it with nanoparticles? The answer is we could deal with under a [. . .] femtomole of material, nanomolar concentrations in the TEM [tunneling electron microscope]. To get to a mass spec, at least at the time, we needed maybe as much as a picomole rather than a femtomole of material. So at some point we'd like to goose it all up to the point where we could characterize our products in the thing we're making with mass spec rather than with actually

cherry-picking [. . .] our answers out of the TEM. [. . .] There is a lot of that [going] on in this business, and I'm the first to recognize it, and I'm the first to admit that we do it.

MCCRAY: So some of those . . . some of the TEM data that you're getting is not . . . sometimes it's not rep . . .

SEEMAN: [. . .] Some of the things we do, you know, you're talking about very small numbers that you are actually able to get onto a TEM grid. [. . .] We're hoping it's the average stuff, and not a lucky punch for that sample.

MCCRAY: Tell me a little bit, if you would, about, you know, as you've been part of this field now for, you know, all these years . . .

SEEMAN: Thirty years.

MCCRAY: . . . yeah, you know, what do you see as major controversies or, you know, either technical or personality-wise, well, that you are able to speak about or care to.

SEEMAN: Well, I don't think there really are too many technical controversies yet. We haven't [. . .] really got to that point. I mean, every once in a while you see stuff . . . I see stuff that I think is kind of crappy, and I'm not going to mention any names there. But, you know, stuff that, if I had enough money and enough time and enough resources, I would probably go out and repeat because I don't trust it. That kind of thing. But that's kind of rare, sort of like in the generation after the generation of my students.

MCCRAY: I guess what I'm getting at is, you know, when the FNANO meetings or the DNA-X meetings happen, you know, is there one particular group of people that, you know, is aligned with this particular way of thinking, and this one . . . okay, so it hasn't developed?

SEEMAN: Not so much that way. I mean, [there are] some people who don't think about things the way I think about things. **<T: 60 min>** Probably nobody thinks about things the way I think about things. That's okay. But at a certain point, you've imposed your way of thinking on the field. Most people do think about it that way. I mean, I had the same thing happen in my youth when I was a crystallographer. This so-called paper we mentioned briefly, my most cited

paper until recently, I mean, so now my most cited paper is the 2D array with Winfree,[16] but the one that's number two there is this recognition of nucleic acids by hydrogen bonding from proteins. And a lot of people said that was really poorly written, and I said, "Yeah, it is poorly written, because I was coming up with concepts for the first time." And even in this sort of founding paper of this field, the one in *J. Theor. Biol.* [*Journal of Theoretical Biology*] I put together notations and I used terms that [. . .] I've tried [since] to eliminate. Something somebody young does when they're trying to invent something, and they don't have the words there yet. And then I'm embarrassed now when people use these words from thirty years ago that . . .

MCCRAY: Like what?

SEEMAN: Oh, criton and what not.

MCCRAY: Criton. I don't even recall that. What is a criton?

SEEMAN: That was like the criterion length of how long the piece is when you're choosing your symmetry.

MCCRAY: So sort of like a codon, a criton, was that kind of the same?

SEEMAN: Yeah. Criton was . . . yeah, codon was three. Criton was . . . could be any length, but it was the criterion that you were using to minimize your symmetry.

MCCRAY: What would you call it now? Or what do you call it now?

SEEMAN: Well, [. . .] in the second paper even, when I sort of goosed it up with a better program, I called it just an element or something like that. There were [no] words in the English language [. . .] so I made up a word. There's nothing more pompous than that. But as you get older, you learn some things you shouldn't do, and that was one of them [. . .].

There aren't really that many controversies. I mean, [there are] a lot of questions, you know, to [. . .] where everything should be going and for what purposes. You see that in every

[16] E. Winfree, F. Liu, L. A. Wenzler, and N.C. Seeman, "Design and Self-Assembly of Two-Dimensional DNA Crystals," *Nature* 394 (1998): 539-44.

article about it, when the wider scientific community looks at DNA nanotech. And as far as I'm concerned . . . there are a lot of things that I just want to do, that I want to know whether they can be done, and . . . because they seem to me to be appropriate things to do. I mean, I think we could do automatic weaving with this, these systems, for instance.

MCCRAY: What would that mean?

SEEMAN: Taking . . . well, and it's something we're eventually going to get to. We published a preliminary paper this fall,[17] where just taking DNA strands and having them weave themselves together into a braid. We've done the smallest possible braid at this point, which is a Solomon's knot. I don't know if you quite know . . .

MCCRAY: I remember seeing the pictures of that. Yeah.

SEEMAN: And in that paper we showed pictures of a [. . .] braided mosaic from Conímbriga in Portugal. [. . .] And the work that I did with Jim [James W.] Canary, which I don't know if we talked about that, [. . .] this is an idea [. . .] that he and I have been working on now for fifteen years, and it's hard, Which is to attach polymer components to the two prime position that . . . of, well, effectively RNA, because there is no two prime in DNA. And this is the position where that hydroxyl sits, that makes RNA not DNA. If you look down an RNA helix, maybe you can see it on this A-DNA helix, maybe you can't, because the model's kind of crappy. Now you have . . . see, that's what an RNA helix looks like, and you can see it's different. There's a hole down the middle.[18]

MCCRAY: Where do you . . . where do you see the hole?

SEEMAN: Just look down the helix axis. You can see a hole. [. . .] If you look on a better model than this one, the atom furthest from the helix access is the hydroxyl [. . .]; here's the position, unless they fucked that up. No, I don't think so. Yeah. This is the two prime position. And if you had the hydroxyl out here, [. . .] out here is where the [DNA] hydrogen would be and the oxygen is a little further out. That's the atom furthest from the helix axis. So we've been trying to attach stuff to that for years and years and years. And, of course, we've gotten somewhere. We've made a sort of nylon polymer, and [. . .] now we're trying to do other things [. . .] because there are other chemistries that are actually going to make it a little bit easier to do

[17] T. Ciengshin, R. Sha, N.C. Seeman, "Automatic Molecular Weaving Prototyped Using Single-Stranded DNA," *Angewande Chemie International Edition* 50 (2011): 4419-22.
[18] See, J.M Rosenberg, N.C. Seeman, R.O. Day, and A. Rich, "RNA Double Helices Derived from Studies of Small Fragments," *Biochemical and Biophysical Research Communications* 69 (1976): 979-87, Figures 3 and 4.

that. And the idea is to direct the topology of **<T: 65 min>** some other polymer using the topology of DNA. [. . .] There are circles in which I am known as the father of single-stranded synthetic DNA topology. Right? Rather than the father of the other.

MCCRAY: We haven't talked about that.

SEEMAN: No, we haven't.

MCCRAY: Okay.

SEEMAN: [. . .] We've published a relatively small number of papers. Only one other guy [Andrzej Stasiak] has ever picked up on it, and [. . . he's drawn some conclusions that I wouldn't draw. But] it's there, right?

So in the early nineties, we made a bunch of knots, and [. . .] we stopped making knots because we couldn't characterize our products. If you make a knot with three nodes, it's a trefoil knot, and you can tell, and it migrates like something in a gel, migrates faster than the so-called un-knot, the circle. You can make a knot with four nodes. It'll migrate faster, yet with the same number of nucleotides. And you can demonstrate in other ways that it really has four nodes, because [the third and fourth nodes were] made out of Z-DNA.

And then we could make two domains that had Z-DNA in them and make the [. . .] other-handed version of that first trefoil knot. And we've made the trefoil knot in [. . .] two or three different ways, in any account. But when you get to five-noded knots, it turns out there are two topoisomers [. . .]. They're different, okay?

MCCRAY: But what's a topoisomer?

SEEMAN: It's a topological isomer of something.

MCCRAY: Okay.

SEEMAN: So if my finger's a length like . . . if . . . we talk about catenanes, too, okay?

MCCRAY: Yeah.

SEEMAN: So . . . and this is . . . this would be a catenane of, say, two links of a chain, but if I could wrap my finger all the way around itself and . . . and link twice around here, then . . . then that would be a topoisomer of this same notion. And with the knots, I mean, there's like one kind of [. . . 3]-noded knot, not counting handedness, [and one 4-noded knot], and there are two kinds of 5-noded knot, three kinds of 6-noded knot, forty-nine kinds of 9-noded knot, and by the time you get up to about thirteen you're in the tens of thousands. All just different sort of, you know, intralacings, if you will, of the strand.

And the only way to demonstrate those reliably is by looking at them, by structurally looking at them. And the things that we look at [right now] are too small to see in the AFM. So we would need something else, and crystallography is now [lending] itself to that.

But the weaving is another story altogether. [. . .] If you're doing it on a large scale, even if there's a flaw in the weave . . . so there's a flaw in the weave, who cares? You're doing molecular scale weaving, so you can make . . . I mean, conceivably you could make a stronger version of Kevlar or whatever.

MCCRAY: Okay. So you've mentioned AFM and TEM. I kind of wanted to get a sense of, you know, for people in your community, what are the . . . what are the common instruments that you have to use in order to be competent and . . .

SEEMAN: A gel box [and] AFM. [. . .] We have only used TEM to look at metallic nanoparticles. I guess we've only looked at metallic nanoparticles at this point, but there are others that we're going to look at. And [. . .] other than that, the typical biochemistry lab equivalent. You'd have to have a spectrophotometer and whatever. Fluorometers are useful. [. . .] Chengde [and William Shih look] at constructs in the TEM, [. . .] things without heavy atoms on them in the TEM, using cryo-TEM. [. . .] We're not skilled at that, so we haven't done that.

[. . .] I think we're still the only group doing crystallography. There are other groups that want to do it desperately, but they're not trained in crystallography; until one of them, which is going to happen someday, pulls down enough bucks to hire a crystallographer or gambles on hiring a crystallographer who's much better than I am (and it wouldn't take very much), then we're going to remain the only group doing crystallography.

MCCRAY: So tell me about other . . . the other good groups that are working in the field now. I mean, if, you know . . .

SEEMAN: Well, I'd say my two students, Hao Yan and Chengde Mao, are both strong. William Shih is obviously strong. The Winfree-Pierce-Rothemund axis at CalTech is strong. **<T: 70 min>** [Andrew J.] Turberfield is strong.

MCCRAY: Turberfield's at . . .

SEEMAN: Oxford [University].

MCCRAY: Oxford. Right. Okay.

SEEMAN: Yeah. Fritz [Friedrich C.] Simmel is strong. Bernie Yurke is strong. I'm not quite sure how much he's doing, because he works mostly with undergraduates.

MCCRAY: He's at Idaho.

SEEMAN: Boise State [University]. I just visited him a couple of months ago.

MCCRAY: You know . . .

SEEMAN: He retired from Bell.

MCCRAY: Okay, because I just . . . you know, all the schools that you just mentioned are, you know, the lead schools, and then it's Boise State.

SEEMAN: Right.

MCCRAY: And that always struck me as an outlier.

SEEMAN: Right. Well, that's because he retired [to] there, and he's from there, and his father's there, and old, and whatever.

MCCRAY: Okay. Okay.

SEEMAN: So for . . . so, I mean, for him it's like . . . for them, it's like [Albert] Einstein walking into the middle of the mountains and saying, "Well, we . . . got anything I can do here?"

MCCRAY: Okay. Who's the guy at Duke? Was it . . .

SEEMAN: [John H.] Reif?

MCCRAY: . . . [Thomas H.] LaBean?

SEEMAN: Oh, LaBean is . . .

MCCRAY: LaBean . . .

SEEMAN: . . . has moved to NC State.

MCCRAY: Okay. And Reif is at . . . is at Duke still.

SEEMAN: Is it Duke. Yeah. So LaBean is now starting his own independent . . . I mean, he was sort of independent before.

MCCRAY: Paul suggested I ask you about Reif because I guess . . .

SEEMAN: Why?

MCCRAY: . . . just . . . he seemed like an interesting personality with lots of ideas, and . . .

SEEMAN: Well, yeah, Reif is an interesting guy with some really smart ideas. Some people find him a little on the overaggressive side, and he hasn't taken anything from me that I know of, but he's the kind of guy who [. . . gets a reputation for being a little bit grabby].

MCCRAY: Isn't that viewed as sort of violating a community norm?

SEEMAN: Yeah. It is. There's some people who are less fond of Reif than I am, because he hasn't done that to me. Two other labs that I didn't mention are the two chemists in the business. One is Hanadi Sleiman in Montreal, [Québec, Canada, at] McGill [University], and [. . .] she was a Jean-Marie Lehn product—as a postdoc. And the other is Kurt [V.] Gothelf at Aarhus [University]. And now I'm trying to think is there anybody else. Well, there's William Shih, of course. And then, much more on the DNA computation side of things, there are the Israelis, there's Kobi [Yaakov] Benenson, who I think is back in Israel now. And then there are people [. . .] like Uri Sivan and [. . .] Erez Braun. You know, I think they're both in Haifa, [Israel], but I'm not sure. And depending how far afield you want to go, you can think of people like Roy Bar-Ziv, who are much more biologically tilted. [. . .] There's nobody really in France that I can think of. There are people doing nano and who add DNA to it, but that's not quite the same thing.

And there are other groups where, you know, you see their names, and they come around, and somebody at Brigham Young [University] that I always forget his name [Adam Woolley], and then you see papers to review that are . . . they're just out there, and you're not quite sure who is this guy or this gal, and what are they doing, and I never heard of them, and, you know, what's going on? And for a while I kept a list of those names, some of which you don't see again, and sometimes you do. And yeah, it's like sixty, seventy laboratories that are out there.

[. . .] At the major institutions, there aren't so many other people, but then you've got to ask things like, you know, is what Chad [A.] Mirkin does what we do or not?

MCCRAY: Yeah.

SEEMAN: Is what Oleg Gang does what we do or not?

MCCRAY: What's that name? Oleg?

SEEMAN: Oleg Gang. And he's at Brookhaven [National Laboratory]. [. . .] There's a relatively small-time lab at Brookhaven that was run by Bill [William] Sherman, my former postdoc.[19]

MCCRAY: I think of Mirkin's work as more the dip pen lithography.

[19] William Sherman left BNL at a point after this interview was conducted.

SEEMAN: Well, no, [. . .] his first stuff was taking nanoparticles and putting half of a probe on one and half of a probe on another, and then **<T: 75 min>** if he threw it in the pot, they would be brought together by the DNA or RNA or whatever for some AIDS protein. As you bring these guys together, there's some plasmonic event, and they change color. So that was the first thing Mirkin did.

And [Armand] Paul Alivisatos was I guess the first guy who added the DNA to nanoparticles to try to make stuff with [. . .]. It was DNA plus nanoparticles, and Paul's done things like make an asymmetric tetrahedron, that kind of thing. I mean, Paul is quite a star in his own right, but [. . .] it's a different area. I mean, he's now director of LBL [Lawrence Berkeley National Laboratory], and he was a founder of the Molecular Foundry and all that kind of thing.

MCCRAY: Yeah. I think of . . . yeah, I think of him more for quantum dots, but that's . . .

SEEMAN: Yeah. Well, [. . . but] many of the quantum dots [have] DNA attached to them.

MCCRAY: Oh, I wasn't aware of that. Okay.

SEEMAN: Some of them did, anyway. Oh, and then there's Willner in Israel, too. Itamar Willner [. . .].

MCCRAY: Yeah. Is there a lot of work being done in China or Japan?

SEEMAN: I've seen a lot of papers coming out of China, and I . . . and, yeah, there's work in Japan definitely. In fact, one of my former postdocs [Akinora Kuzuya] is in Japan and he's doing good stuff. And there's other stuff that's related, that Hiroshi Sugiyama, who's doing stuff. I'm actually sending somebody to his lab to do an experiment, because he has this real time AFM. [. . .] One of my former students is now in China, Baoquan Ding. And I see Chinese papers that are somehow or other related to this stuff, and I don't know any of the players. Chunghai Fan I know, and he's doing stuff. There was some Korean activity for a while, but it seems to have disappeared.

MCCRAY: Okay. Geographically what . . .

SEEMAN: Oh, and . . .

MCCRAY: Sorry.

SEEMAN: . . . and Yumana Krishnan is in India doing stuff. And I have an Indian student [Banani Chakraborty] who's going to go back. She's right now in a Humboldt in Aachen, Germany. So right now she's working for somebody else. But [. . .] she worked with Dipankar Sen at Simon Fraser [University]. I mean, she's been kind of following her husband, but she did [. . .] two significant pieces of work in this lab.

And so Dipankar Sen is another person. He and Yumana were both kind of originally tilted toward G4, C4 kinds of things. These are like special motifs for special sequences that came out of [Shankar] Balasubramanian's lab at Cambridge [University], I think.

MCCRAY: Okay. So you've described a pretty big community that's pretty far-flung.

SEEMAN: Yeah. Yeah. And, you know, I haven't hit all the . . . I mean, the experimental community, I've hit most of the high points, but then there's Andy [Andrew] Ellington, and I just sent somebody [Chunhua Liu]to him, in fact. And [. . .] he tends to be more RNA-ish than DNA-ish, but he . . . I mean, one of his students just published on his—student or postdoc, I don't know—just published a paper on his own. Let me see. Who else? I mean, so, as we keep . . . if you keep bringing up names, I'm sure I would say, "Oh, yeah."

And so it hasn't trickled down to too many of the sort of second-level schools yet, and all the top schools aren't saturated. There's [still] nobody [. . .] doing this stuff at Princeton. I've got a former student there [Xing Wang]who's a postdoc, but he's working with somebody who's part of the [. . .] computing community [. . .]; her interest was these various protozoa that have [to] shuffle genomes and they unshuffle and whatever. And so [. . .] he's working for her, but [. . .] I don't think there's too much in the way of DNA nanotech going on there.

Nothing at Princeton, nothing at Brown [University], nothing at Penn that I can think of offhand. Nothing . . . well, I have a former student [Hongzhou Gu]who's a postdoc at Yale, and you never know. You send <**T: 80 min**> a postdoc somewhere, I mean, I sent Hao Yan to Duke and suddenly they were doing experiments down at Duke. There's some guy from the computer science department there, Chris Dwyer, who does stuff with DNA, trying to organize stuff, and to some extent he worked with LaBean.

And so, the community is large. And then, I mean, there are other people that I interact with, and then the question is, well, how much of that is DNA nanotech and how much of it is [other stuff]. I'm interacting with a guy now who works with nanotubes. We've never worked with carbon nanotubes. And I'm interested. I have a grant with somebody else to do things with

carbon nanotubes, and I'm hoping the stuff I do with the first guy will wind up pumping into that grant, and we'll be able to do significant stuff with it.

Oh, and there's also Mike [Michael L.] Norton, I forgot, at Marshall University, who's doing stuff. So the community [. . .] . . . there's at least . . . a list of at least sixty names, when you get down to it, I mean, I'm not even counting . . . oh, and there's Peng Yin, next door to William Shih at the Wyss. And . . . and then there's somebody else there who's not really part of what I regard this community, but she took a postdoc . . . she got a postdoc from Hanadi Sleiman, and they just made some kind of structure that does something inside a cell . . . out of RNA. This . . . this guy will eventually be a superstar, Faisal [A.] Aldaye. I mean, [. . .] Faisal works for Pam [Pamela A.] Silver, but Faisal Aldaye is one of the future superstars [actually, he quit to go to medical school]. And . . .

MCCRAY: Let's talk about . . .

SEEMAN: And then there are all these other people . . . Hao has sent students to William Shih, so that's already like a third generation. And, I mean . . . oh, and yeah, I keep . . . these two Germans who left Shih already and went back to Germany. One's with . . . I mentioned Fritz Simmel, I think. But one's at the same school, and one's at [. . .] Ludwig Maximilian University, LMU, and Tim Liedl is there, and he's doing good stuff already. And Heindrik Dietz is back at TDU, Technical University of . . .

MCCRAY: Mm-hmm. I'll . . .

SEEMAN: . . . Munich.

MCCRAY: . . . have to see if I can get one of my students to map just where all these people are. That would be helpful.

Let's talk about money a little bit. And . . .

SEEMAN: Always happy to talk about money.

MCCRAY: Yeah. So you talked a little bit about funding for research, but I kind of want to get maybe a sense of just, you know, have there been any broad shifts in terms of where your funding has been coming from over time?

SEEMAN: Well, my money [. . .] for this, basically it doesn't come from the NIH. Hao was able to squeeze an NIH grant out of them. There's some kind of nanotech thing, and I think it was some kind of diagnostic thing[. . .]; we don't play in the diagnostic field, because [there are] so many diagnosticians out there, and [. . .] I don't like competing with people very much. [. . .] If I've got my own weird tack on something, I'll dip into a field and dip out, like when we found the RNA topoisomerase. I didn't pursue that. Maybe I should. That was fifteen years ago and nobody has touched it, basically. It's one of my . . . you know what H-numbers are. You know, it's one . . .

MCCRAY: Actually, I don't. I saw that in your CV, and . . .

SEEMAN: Okay. Okay.

MCCRAY: . . . it's not a term I'm familiar with.

SEEMAN: Okay. So it's the way people are judged . . . it's one of the [criteria].

MCCRAY: Okay.

SEEMAN: So . . . and your . . . what you do is you take your papers and you sort them in order of references.

MCCRAY: Okay. So number of citations.

SEEMAN: Number of citations. So your top paper might be 1,000, the second paper might be 500, third paper may be 300. If your fourth paper has 10 and your fifth paper has 10 and all the rest, then your H-number is going to be 10.

MCCRAY: Okay.

SEEMAN: So [. . .] if you have a blockbuster, it kind of ignores that, right? So you sort them in order. The paper that [. . .] as many citations as its rank order, that's your H-number. So that means, if you have a 1,000, and then 100 10s, your H-number is 10. So if you had a blockbuster paper as a postdoc or whatever, it doesn't matter. You have to keep having produced papers that

somebody cited. So my RNA topoisomerase [. . . paper], the number of citations it's received in fifteen years puts it well below my H-number.

MCCRAY: Which is <**T: 85 min**> something like sixty.

SEEMAN: Sixty-five. Yeah.

MCCRAY: Yeah. Okay.

SEEMAN: So that means it's basically been ignored. To the extent that I was at a meeting in Bordeaux, [France], fall a year ago . . . two years ago, I think, now. And some guy [Hervé Isambert] was talking about how complicated the weaving of RNA was in some system he was working on. He was the husband of somebody [Alessandra Carbone] with whom I've published a half a dozen or [so] papers. And I raised my hand and I said, "Well, [. . .] you know, in one of my least cited papers, we show that there is such a thing as an RNA topoisomerase. Have you . . . I assume that would have impact on your system." And he said, "Well, I had never heard of that." You know? So . . .

MCCRAY: Yeah.

SEEMAN: So, I mean, things are often rediscovered because people don't know the literature. And that happens.

MCCRAY: So . . .

SEEMAN: But that wasn't what we were talking about. We were talking about . . .

MCCRAY: About funding, but . . .

SEEMAN: . . . funding.

MCCRAY: . . . in the last couple of days you've . . . as I . . . as I am understanding it, you talk a lot about your NIH work, and then there seems like there's everything else in terms . . .

SEEMAN: That's right.

MCCRAY: Yeah. So . . .

SEEMAN: There's my NIH and my non-NIH.

MCCRAY: Yeah. So I'm trying to understand the . . .

SEEMAN: So the NIH is studying biological phenomena, one way or another. And getting through an NIH study section to be funded, it's much more of a peer review thing . . . it's somewhat peer review at the NSF, but it's . . . I mean, there's a small number of people, and, you know, if they know who you are, often that helps, because you're [. . .] talking about relatively small amounts of money. NIH, you're talking about double the amount of money you're talking anywhere else.

And they want you to be solving a biological problem. I tell people who want NIH funding, I say, "Do not have anything you want to do. Have a problem you want to solve, then work out the [. . .] very best way to solve that problem. If the very best way to solve that problem happens to be what you want to do, you're very lucky. If not, [. . .] propose what is the very best way. And forget what you want to do. Maybe you'll do that if you get the money." But that's how you have to write an NIH proposal. You can't do the backward thinking of, "I want to do this shit, and how am I going to justify it?" It's the easiest thing in the world for a reviewer to pick up, and you just get slaughtered.

So that's the NIH world. The rest is my DNA nanotech world. [. . .] I was spending NIH money to do things like to explore aspects of the branched DNA that I could conceivably justify as being involved in the NIH. I mean, [. . .] the funny story was that when we made the cube . . .

MCCRAY: This was like in '93?

SEEMAN: Ninety-one.

MCCRAY: Ninety-one. Okay.

SEEMAN: Published the cube in ’91. And the United Airlines magazine ran a small article on it, and my program director at the NIH said, “Ned, I want you to write a little something about this.” So I went through all sorts of prevarications about how this [. . .] is showing things about the flexibility of branched junctions, blah blah blah and all sorts of horseshit. And [how] that was relevant to the [. . .] mission of my NIH grant. And then [. . .] one time I was standing behind her boss at the biophysics meeting, and he was saying, “People ask if we’re relevant, and Ned Seeman’s stuff . . . ,” he didn’t know I was there, “Ned Seeman’s stuff is being cited in the United Airlines magazine.” And at that point I realized, as long as people like it, you can maybe get away with a little of it [. . .]; you can get away with it with the administrators, but you can’t get away with it with the study section. Now I can’t even get away with it with the administrators. I mean . . .

MCCRAY: Do you have a copy of that still? The American Airlines . . .

SEEMAN: The United Airlines thing? I have . . . I certainly have the reference to it.[20] I’m not sure if I have the . . .

MCCRAY: Okay. Just curious. Interesting to see.

SEEMAN: The article. I . . . because in those days, I mean, it was . . . it was probably in paper.

MCCRAY: Yeah. I’m just thinking of, you know, millions of people would see it. I mean, all the people sitting, you know, bored on airlines are flipping through the magazines and they’re going to see this thing.

SEEMAN: Yeah, lots of people must have seen it. That’s why the . . . why her boss was so . . .

MCCRAY: Yeah. Did anyone ever write just, you know, “I was flying from New York to Chicago . . . ”

SEEMAN: No.

[20] Lance Frazer, “Through the Looking Glass: Nanotechnology,” *Hemispheres* (May 1993): 79-80.

MCCRAY: Okay.

SEEMAN: No, nobody ever did that. **<T: 90 min>** The only time I've ever been recognized on the street was the afternoon or the evening that the Kavli was announced, some NYU student had seen it [. . .] at this science festival thing, and she said, "Hello, Professor Seeman." I said, "Hi. Do I know you?" And she said, "I saw you on this TV this morning." It's the one time I've ever been recognized, to the best of my knowledge. And . . .

MCCRAY: Okay. So you got the NIH and then you have everything else . . .

SEEMAN: Everything else is the nanotech in one flavor or another. And that's largely military and a little bit NSF.

MCCRAY: So when you applied to NSF, what directorate or division or whatever do you send your . . . would your proposals go to?

SEEMAN: Well, the main NSF division that has supported me is, in fact, computation, because this is usually a joint grant. It's called collaborative research, so it's administratively better than me being the PI or Natasha. But it's a grant with Natasha. So Natasha and I have been getting money from the NSF for, I don't know, we're on about our third or fourth round now. And she takes a small amount of money and supports a student and her summer salary, and I take a not much greater amount of money, but maybe three times as much, but, I mean, like the last round [. . .] may have been 100,000 [dollars]. The round before that was like 75,000 [dollars]. And the [. . .] program director at the time wanted me to go down to Washington and participate in his [. . .] meetings that he was forced to run, for $75,000 a year. I mean, be serious. I mean, the military wants those every year, but, you know, the NSF is kind of moving into that mode.

MCCRAY: Okay. So to think about it, you know, you've got the lab here, you've got your students, your postdocs, your grad students, what does it cost annually, you know, to keep it all going?

SEEMAN: More than . . . right now, I have committed to me but not necessarily in my pocket about $1 million, $1.2 million.

MCCRAY: Per year?

SEEMAN: This year, per this year. I mean, last year I had to spend a lot of time writing stuff because [. . .] I'm not used to this mode of having a whole bunch of small grants. In fact, I let a bunch of them lapse, and I had to get them back. And the financial services at this university, which you can quote me on, are incompetently managed, and I've got about a half a million dollars in so-called account receivables that they're not willing to recognize, money that's going to come in when the Navy gets its money from the [. . .] continuing resolution.

MCCRAY: Looking at the military agencies, I mean, you've had Navy, Air Force, DARPA. Can you give me just a general sense of what those are like relative to work with?

SEEMAN: The Navy and the Army have both been wonderful. DARPA dropped me [. . . quickly]. I'm a subcontractor. [. . .] I don't think I've ever been the prime contractor on anything except that first round of Navy funding, that sort of went on fifteen years and then it stopped, and . . . I was a prime contractor once since then, on a small, like, four-person grant.

But [with] the Navy and the Army, it's always an issue of, "Gee, [. . .] we'll try to get you the money as soon as we can, but it might not be there right away, and you just have to learn to live with that," which NYU doesn't seem capable of doing. DARPA [paid] me six months [late for two years, and] gave me a huge amount of money, and [then] the third time, [. . .] the money was six months late, and then the third year they dropped me like a hot potato. And I'm still suffering from the effects of that, [because I was spending like the money eventually would come in]. Ten years later. They sent the money to Iraq. So I haven't gone back to DARPA. Maybe I should.

MCCRAY: I've heard other people say this about DARPA, which I find interesting, you know. If you just pick up a magazine, you know, DARPA is always portrayed as this, you know, lean . . .

SEEMAN: Really forward . . .

MCCRAY: . . . agile, forward-thinking, but I talked to some scientists who get DARPA money: "Eh."

SEEMAN: It's a lot of money. DARPA's idea is, "We want to produce a baby in a month. Let's get nine women pregnant." [laughter] That's the essence of a DARPA proposal. "We're going to impregnate nine women and you'll get your baby in a month." You know, but [. . .] that's much closer to development than it is to research.

MCCRAY: Because I know they have like their 6.1, 6.2, various divisions.

SEEMAN: Yeah. [. . .] 6.1 is more or less research and 6.2 is kind of development and 6.3 is contractors for supplying munitions and weaponry and what not. And I don't even know what the **<T: 95 min>** 6.1, 6.2 budgets are or whatever. I don't even know what I'm funded out of. I assume it's 6.1. And, you know, in the end they come through with the money, but it's very hard to live on military money at NYU, because it's coming in dribs and drabs. And they don't have a proper buffering system in place, where, all right, here's . . . "You're going to get $200,000 this year. We'll just set aside $200,000 for you and then basically the Navy [. . .] money will pay you back," you know. They don't do that here.

MCCRAY: So they're just waiting for it literally as it comes in the door, then it goes to you.

SEEMAN: They [. . .] wait for it to come in the door and about two months later it gets to me, or about a month later it gets to me, if it gets to me. I mean, so right now [. . .] I have, you know, a half a million dollars, I think. It's either a half a million or 300,000 [dollars]. I think it's half a million, in so-called accounts receivable, that they're not giving me credit for right now. And [. . .] there are various people that I am un-fond of as a consequence, you know.

MCCRAY: Any qualms about military funding?

SEEMAN: I had them in the beginning, but basically I don't think we've done anything that's going to [be dangerous]. I mean, I don't write proposals to say we're going to develop a nerve gas or whatever. I [write] proposals to do what I would do anyway, which is relatively innocuous stuff, I think. You know, building better computers, [. . .] or better, smaller, faster, computers, lighter computers, whatever. The military will certainly take advantage of that if we can do it. So will every other enterprise and endeavor in in the civilian economy. So, I mean, Erik Winfree doesn't take military money . . .

MCCRAY: That's in part why I asked, because . . .

SEEMAN: Erik Winfree's at CalTech.

And if I [. . .] were at CalTech, I could [arguably] afford to have [. . .] those principles. But I can't afford the principles, and the military has actually treated me rather well. [. . .] I make no bones about it. I'm a Vietnam War draft dodger. [. . .] If you read my biography, you saw how I got out of the draft by faking my physical, effectively. I mean, you know, they leave

it open to me, what I'm going to eat; I can eat what I want to, and respond appropriately. But, in fact, I gave a lecture one time at West Point, and I was extraordinary impressed by the teaching going on there. Their undergraduate teaching was in many respects like my graduate teaching. I treat graduate students as younger members of my profession. [. . . I have taught large undergraduate lectures, but fundamentally it is a chore]. They don't really care about what I'm teaching them. They're taking my courses because they have to, not because it's going to have any impact on the rest of their lives, except that if they do well, they can go off and become medical people, or health people of one sort or another. None of them to speak of really [wanting] to go on and become scientists that I'm aware of or anything.

And at Albany, at least they were poor kids who were doing the best they could education-wise, and, yes, they would slit your throat for a point, but [. . .] I understood it. Here, [. . .] I really haven't taught undergraduates in a very long time because they're treated as customers here. And you cannot teach customers. And [. . .] there is an aspect of no pain, no gain, to teaching. And we were kind of instructed, "No pain." So . . .

MCCRAY: How about patents?

SEEMAN: I've got about ten or eleven or something.

MCCRAY: Is this something that the University actively encourages you to pursue?

SEEMAN: Well, the University owns the patents. I don't.

MCCRAY: Yeah. I mean, this . . .

SEEMAN: At one point, the University went out and peddled my goods [. . . and] licensed my patents to a company that brought in a fair amount of cash to my lab. That was part of the patenting deal . . .

MCCRAY: Which . . . what was the patent for?

SEEMAN: Well, it was the set of them. The ten . . . everything, you know, about DNA nanotech. And then that company [Nanoscience Technologies, Inc.] **<T: 100 min>** went belly-up after three years of a five-year contract, and they haven't gone back to trying to do that again, much to my disappointment, because that was real money. You know what I mean? It was the one dollop I've gotten out of the private sector that was there. There have been occasionally

grants, private grants. I've been funded a couple of times, kind of small scale, from the [W.M.] Keck Foundation. I mean, you know, one . . .

MCCRAY: Yeah. I noticed the sign on your door, I think, was a Keck . . .

SEEMAN: That sign on my door. Actually, I was part of that Keck grant, but this was somebody else. This was Schwartz, actually. [. . .] I got like half of a useless instrument out of that grant. And then more recently, along with the physicists, we had some money that enabled our most recent *Nature* paper, about self-reproducing . . . I don't know if you saw that or not.[21]

MCCRAY: With the patents, are you the only . . . are you the sole person, or . . . ?

SEEMAN: No, who . . . no, no. I mean, [if there are] students involved I put the students on there, and some of the patents are with Jim Canary, because it's . . .

MCCRAY: You had mentioned him before. Where is he based?

SEEMAN: He's on the third floor.

MCCRAY: Third floor. Okay.

SEEMAN: He's [an] organic chemist, and we've worked together for fifteen years now. And we share a couple of grants, and, you know, whatever.

MCCRAY: Tell me about the Kavli Prize. I mean, the picture is sitting here behind me with you at the Oval Office with [President Barack H.] Obama and [Donald M.] Eigler wearing I think what might be Eigler's best suit.

SEEMAN: And mine.

[21] T. Wang, R. Sha, R. Dreyfus, M.E. Leunissen, C. Maass, D. Pine, P.M. Chaikin, and N.C. Seeman, "Self-Replication of Information-Bearing Nanoscale Patterns," *Nature* 478 (2011): 225-8.

MCCRAY: Yeah? Okay.

SEEMAN: My only suit.

MCCRAY: Yeah. So just, you know, how'd that all happen?

SEEMAN: The prize?

MCCRAY: Yeah. How'd you find out? Did they call you?

SEEMAN: Oh, [. . .] it's a funny story, actually. In April of 2010, a Norwegian topologist by the name of Nils [A.] Baas gets in touch with me. He's been in the news over the last couple of years, because [. . .] he's come up with sort of hyper structures or one sort of another. So like Borromean rings of Borromean rings . . . this may not mean much to you, but . . .

MCCRAY: No, it doesn't.

SEEMAN: Okay. Borromean rings are three . . . you're probably never heard of the Borromeo family in Milano.

MCCRAY: Sorry. No.

SEEMAN: Okay. So there were three branches of the family, and they had a series of rings . . . also Ballantine Ale had the same symbol. Three rings. But if you look closely at them, they're linked [. . .] together such that if you break one, the other two fall apart. So the idea was that if one branch of the family falls apart, the rest of us fall . . .

MCCRAY: Got you.

SEEMAN: . . . go away. And [. . .] so he's made like Borromean rings of Borromean rings, and he was on sabbatical, and he tried to actually talk to some other chemist who has done topological stuff, and the guy didn't get back to him, so he sent an email to me. And I'm pretty responsive in that regard. And [. . .] so he comes up and we spend the afternoon together. I forget . . . we had lunch or whatever. [. . .] In fact, we have a paper that's now sort of in press

and print—I don't know where it is right now—about how some of these things might be synthesized chemically.[22] And, in fact, [. . .] that's a project I'm going to give one of the newer students I'm planning to take.

And so we said we'll write papers, we'll try to write grants, see if there's some sort of, you know, joint Norwegian-whatever money. So his name was Nils Baas. And then he goes back to Princeton, and [. . .] I don't hear from him again. And he's on sabbatical, and I figure at some point he's going back to Norway; I'll hear from when I hear from him. A lot of these things—I said that sometimes they work out, sometimes they don't. This one actually in the end, [. . .] did work out [. . .].

And then on [. . .] the night of June the 2nd, I'm here till two in the morning working, which is not uncommon for me. That was [. . .] a little later than normal. And I go to bed, and normally I'm here till about midnight, but sometimes [you've] just got to put a push on or you're never going to get something done. And it's harder now that [. . .] the Obama event wound up with my injuring my back [. . .]. But at any rate, I'm in bed. I'm asleep. It's 5:30 in the morning. And the phone rings, and I'm not a morning person anyway. I'm totally incoherent. And I answer the phone, and I can only make out two **<T: 105 min>** words, Nils and Norway. And I say, "Nils, Norway, oh, Nils. How are you? How are you? How are you doing?" And he says, "I don't know who you think you're talking to. This is Nils," somebody else. "I'm the head of the Norwegian Academy of Arts and Letters, and I'm calling to tell you," et cetera.

And he called me at the time of the morning because around the corner from me was some New York science festival, where [Fred] Kavli was, and where some Nobel laureates were, and what not, and I was supposed to go over there, and there was going to be a transmission to the science festival, and I was supposed to stand up and wave at the appropriate moment, [. . .] as the Norwegians announced the prize. And as chance would have it, I had sent off [. . .] my laundry to be done. I had no socks, a tee-shirt, so [. . .] I wandered in there wearing a pair of sandals, a tee-shirt, I had enough sense to put on a blazer or something. And I'm totally dazed, because it's like I've had three and a half hours sleep that night before, and I sit down, so the other NYU people knew about this. The provost knew about it. The PR [public relations] guy knew about it, and so forth. I was instructed to call him, and they said, "Yeah, go around the corner to the science festival," which I otherwise wouldn't have been going to at all, "and [. . .] wave and try not to drool or fall asleep during the ceremonies."

So I did all this and there are photo ops of Kavli and what not. And then [. . .] I get all [these] instructions: you have to have this black suit for the ceremonies, and [. . .] if you don't own a tux, you have to rent a tux, in Oslo, [Norway]. And it turned out [. . .] that about a week or two later I was supposed to be going to Hong Kong anyway for a meeting, so I bought my

[22] N.A. Baas and N. C. Seeman, "On the Chemical Synthesis of New Topological Structures," *Journal of Mathematical Chemistry* 50 (2012): 220-32.

black suit in Hong Kong, because [. . .] I was there, and [. . .] that's where you can buy suits relatively cheaply.

MCCRAY: Yeah. That's true.

SEEMAN: So I did that. And then I did the right thing. I mean, they had the ceremony . . . we were so tightly scheduled in Oslo. We sat down with the people there, and it was at 9 o'clock; [. . .] I don't know, [maybe] ten in the morning. "At three this afternoon you're going to be here and you're going to be wearing this. At 5 o'clock this afternoon you're going to be here and you're going to be wearing that." And you were just totally scheduled in terms of dress and whatever. And at some point we were supposed to be in [the audience at] some symposium, and Don and I had to sneak out to get our tuxes measured.

MCCRAY: This is you and Don Eigler?

SEEMAN: Yeah. Because there was just no [. . .] room on the schedule to get our tuxes measured. So . . .

MCCRAY: Did you two know each other before?

SEEMAN: We had met once. [. . .] By chance, we both wound up at a Gordon Conference about a month later, and I had seen his picture. He recognized me. I didn't actually recognize him, because his pictures are a little younger than he is, and [. . .] the pictures I had seen were taken ten years ago. I didn't quite recognize him. I mean, [. . .] while I was talking to him I realized, "Oh, shit, this is Don." [laughter] We only met once at a CIFAR [Canadian Institute for Advanced Research] meeting.

MCCRAY: I'm sorry. C . . .

SEEMAN: It's Canadian something something something. The R is research. C-I-F-A, whatever that stands for. Advanced research, for advanced research. Somehow he has a connection with them. And all I knew was that he was in the room. I might have heard him say something. I don't think we chatted, really. We [. . .] probably heard each other's talks. But I often forget what people look like and so forth. So I didn't remember. Anyway, we chatted a bit [. . .] at the Gordon Conference in New Hampshire or wherever it was. And then [. . .] we re-encountered each other up in Oslo. Okay? But I didn't really know [him], because we do really quite different things.

MCCRAY: Yeah, you do.

SEEMAN: Yeah. I mean, I think what they were doing was they were simply trying to get rid of a sort of backlog of people who [. . .] had been leaders in nanotech for a while, **<T: 110 min>** and, [. . .] because there were two people the time before, Lou Brus and the [. . .] Japanese guy who discovered the carbon nanotubes.

MCCRAY: Oh, Iijima, Sumio Iijima.

SEEMAN: Iijima. Yeah. Iijima. Right. And, you know, I mean, arguably Iijima could have gone to Stockholm, [Sweden], with Rick [Richard E.] Smalley and whatever, but he didn't. And so this was kind of, you know, his recognition.

MCCRAY: Did you get to meet . . . you met Kavli, then?

SEEMAN: Oh, yeah. I met Kavli here that morning.

MCCRAY: Yeah. So it . . . yeah. What did you think?

SEEMAN: Well, I mean, we didn't really talk then. [. . .] He's always very nice, very cordial.

MCCRAY: Okay.

SEEMAN: And I said, "Well, thank you very much." And he said, "Well, thank you for doing your science," or whatever. He's a very nice guy [. . .] .

MCCRAY: So who do you see . . . I mean, I'm just curious. I mean, the next prize will be announced, you know, in 2012. What's your sense of what areas they might . . . ?

SEEMAN: Well [. . .], for me, it was kind of weird because, like, I disappeared for that and I disappeared for my sabbatical. I am only just coming back now. So I'm not reentered. Were I reentered, I would have had the time to do the nominations of Paul and Bernie [. . .] who I think

deserve [. . .] that prize, if you're going to give a prize to DNA nanotech. I don't think there's anybody else who deserves it, [. . .] DNA nanotech prize at this time. If there are other forms of recognition, somewhere along the line I expect Erik will get some kind of recognition. But for DNA nanotech, [. . .] his contributions haven't really been significant, except through his students or whatever. And you can say that Erik, to some extent, you know, contributed to Paul's work, because Paul was technically working for Erik, but Erik's name's not on the paper, so I don't know what the bottom line story is there. If Erik wants his prizes, he has to put his name on his papers. Okay?

MCCRAY: Fair enough.

SEEMAN: My name goes on all my students' papers, and Alex Rich's name goes on all of his people's papers, and that's the way the game is played in this business. Hopfield's name was not on the paper that Erik and I and my people did, so there may be a different tradition there, and in that area, but that's part of recognition.

MCCRAY: So we're about out of time, and I don't want to, you know, impinge on your getting ready for teaching your class. But is there anything . . . I mean, you know, we can always come back to this. I mean, I come to New York a fair amount. If there are things we haven't talked . . . that we haven't touched on.

SEEMAN: What have . . . what are . . . what are we missing?

MCCRAY: Well, that's what I'm going to ask you. I mean, is there . . . is there something . . . over the things we've talked about the last couple of days, you're sort of wondering, you know, why hasn't he asked me about, you know, X or Y?

SEEMAN: No. I mean, I think it's been pretty thorough in terms of what we've talked about. It's the nature of my being at a place like this, that not too many of my people are going to wind up being PIs [principal investigators]. That's kind of inevitable. If they go to a really super postdoc, then I think they can become PIs. So Chengde Mao was with George [M.] Whitesides at Harvard. Hao did very well with John Reif, and [it] was kind of recognized that it was really him, not Reif, doing much of it. I think Reif may have contributed more than is obvious, but [. . .] it's not clear there. But Hao certainly got them off the ground experimentally. They didn't know what they were doing.

And, like I mentioned, the guy who built the assembly line, he's at Yale. [. . .] He missed getting one of these Wellcome grants, but he was a finalist, so he's obviously going to be a player. I expect him to be a PI, sometime, somewhere. [. . .] I mean, Erik's people jump to

Harvard. I mean, he's got this guy, Peng Yin, who just went to Harvard, which seems to me okay, but I don't know if he walks on water [. . .] or not [. . .].

MCCRAY: What do you do when you're not here?

SEEMAN: When's that?

MCCRAY: Okay. [laughter]

SEEMAN: I mean, <**T: 115 min**> I travel so much.

MCCRAY: Yeah. I mean, I know you're . . . you said you were leaving for another trip tomorrow, so . . .

SEEMAN: Yeah. That's right. I travel so much that I . . . when I'm here, I'm here.

MCCRAY: [. . .] I guess I meant like, you know, hobbies. I'm assuming you don't have kids, so . . .

SEEMAN: I don't have kids. My long-time girlfriend [Nora Lapin] and I just got married because of some fuck-up with her Social Security. So, I mean, otherwise [. . .] we wouldn't have bothered with that. I mean, she was losing . . .

MCCRAY: Well, congratulations.

SEEMAN: I mean, it was in name. It's not a big deal. But it was just a technical thing to get her status.

MCCRAY: You two met here in New York, right?

SEEMAN: Yeah. We met . . .

MCCRAY: Yeah. Okay.

SEEMAN: And then . . . but . . . so I eat dinner with her every night.

MCCRAY: Is she . . . she's a scientist, or . . .

SEEMAN: No, no.

MCCRAY: Okay.

SEEMAN: No, she . . . she writes grants for nonprofits.

MCCRAY: Oh, okay.

SEEMAN: And her business has basically dried up, because [Mayor Michael R.] Bloomberg does not believe in there being money for poor people, so there are no RFPs [request for proposals]. I mean, she writes the grants for people who are competing for [. . . RFPs] to help poor people, but there are no RFPs to help poor people in New York anymore. She has an extraordinary batting average, and I wish I had such a batting average with my science grants.

MCCRAY: Does she ever read any of your grant applications?

SEEMAN: No. No. She can't . . . one time we tried it. I have a close friend [Alex Vologodskii] who came to the U.S. at around . . . in his late forties, early fifties, from Russia, and he . . . he wasn't very good at English at the time, and he said, "Well, maybe Nora could [. . .] read my grant [and fix the English]." It wound up I had to do what he wanted her to do because she didn't know the words. You know, "Topoisomerase? Is [. . .] that a verb or a noun or an adjective?" She just had no clue. So she's not at all scientifically inclined.

MCCRAY: Does she travel with you at all?

SEEMAN: She travels with me often. When we can; when we go to San Francisco, [California], always. She'd rather live there than here. She's a native of there. She actually hates New York now. And . . . that's life. I'm immovable at this point, and I'm simply too old to

move up the food chain, and I'm not about to make a lateral move at this point in my life. I mean, I can't afford to lose a year or two and the infrastructure that I've built up here. She's kind of reconciled herself to that. But she's not happy. So, yeah, she travels with me whenever we can. [. . .] So if I get an invitation to go to some dump, she may or may not . . .

MCCRAY: Fair enough.

SEEMAN: . . . want to come with me, but, like, I got an invitation to go to Bangalore, [Karnataka, India]; she's an Indiaphile, so that's where we're going next week. So we'll be in India for about three weeks. India, Sri Lanka, and then I have to go to Qatar, and so she'll go with me to Qatar.

MCCRAY: Oh, I was there last year.

SEEMAN: Oh, yeah?

MCCRAY: Yeah. I had given . . .

SEEMAN: How . . . how is Qatar?

MCCRAY: Bizarre.

SEEMAN: Yeah?

MCCRAY: I was there to give a . . .

SEEMAN: Bizarre with an i?

MCCRAY: Yeah. [laughter] Yeah. Not a bazaar. No, I was there to give a . . . a couple of talks at the Northwestern campus. And I went with my partner, and it was fantastic. I mean, we were well-taken care of for the whole week and everything, but it's just a weird place.

SEEMAN: Yeah. I'm expecting it to be weird. I mean, it's three days, four days, something like that. We'll cope with it.

MCCRAY: You know, if you get a chance, the Islamic Art Museum [Museum of Islamic Art] is incredible.

SEEMAN: Okay. Islamic art is like my favorite kind of art, so, you know, it's all this geometrical stuff.

MCCRAY: Yeah, yeah, yeah. That's . . . yeah, that's interesting. Yeah. I mean, that's pretty mind-blowing, and just the skyline itself is just this weird, futuristic hodgepodge of whatever. But . . . anyways, yeah, you'll have a good time.

SEEMAN: Yeah.

MCCRAY: Well, we should probably wrap it up so you can get ready for class [. . .].

[END OF AUDIO, FILE 2.1]

[END OF INTERVIEW]

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