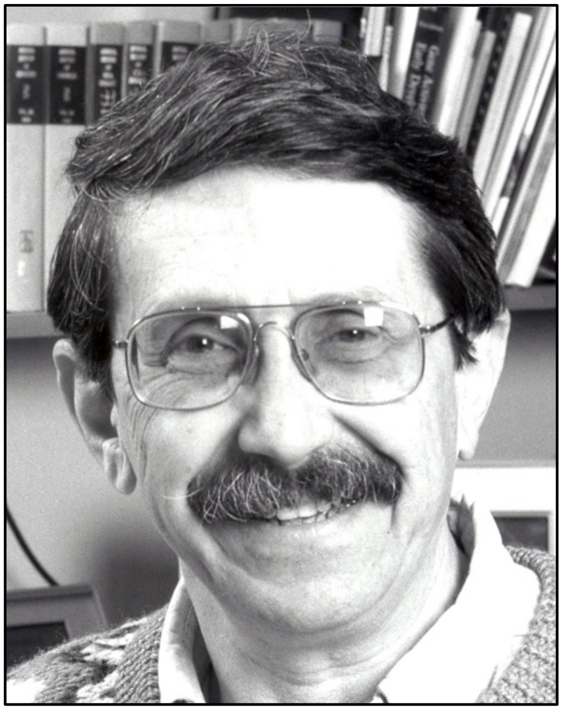

Melvin I. Simon

MELVIN I. SIMON
(b. 1937)

INTERVIEWED BY
SHIRLEY K. COHEN

May 24 and June 5, 2005

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CALIFORNIA INSTITUTE OF TECHNOLOGY
Pasadena, California

Subject area

Biology

Abstract

Interview in two sessions, May 24 and June 5, 2005, with Melvin I. Simon, Anne P. and Benjamin F. Biaggini Professor of Biological Sciences, emeritus, in the Division of Biology.

Dr. Simon received his BS from City College of New York in 1959 and his PhD in biochemistry from Brandeis in 1963. After receiving his degree, he was a postdoctoral fellow with Arthur Pardee at Princeton for a year and a half and then joined the faculty of the University of California at San Diego. In 1978, Dr. Simon and his UCSD colleague John Abelson established the Agouron Institute in San Diego, focusing on problems in molecular biology. He (along with Abelson) joined the faculty of Caltech as a full professor in 1982, and he served as chair of the Biology Division from 1995 to 2000.

In this interview, he discusses his education in Manhattan's Yeshiva High School (where science courses were taught by teachers from the Bronx High School of Science), at CCNY, and as a Brandeis graduate student working working with Helen Van Vunakis on bacteriophage. Recalls his unsatisfactory postdoc experience at Princeton and his delight at arriving at UC San Diego, where molecular biology was just getting started. Discusses his work on bacterial organelles; recalls his and Abelson's vain efforts to get UCSD to back a full-scale initiative in molecular biology and their subsequent founding of their own institute. Recalls his early years at Caltech and the domination of the Biology Division by Leroy E. Hood, who was developing molecular sequencing machines. Recalls the establishment of the Beckman Institute. Discusses his growing interest in genomics and his involvement with the Human Genome Project. Discusses the departure of division chairman Lee Hood, the subsequent chairmanship of Abelson, and his own stint as chairman. Recalls the recruiting and arrival of David Baltimore as Caltech's president (1997-2007) and assesses his presidency.

Administrative information

Access

The interview is unrestricted.

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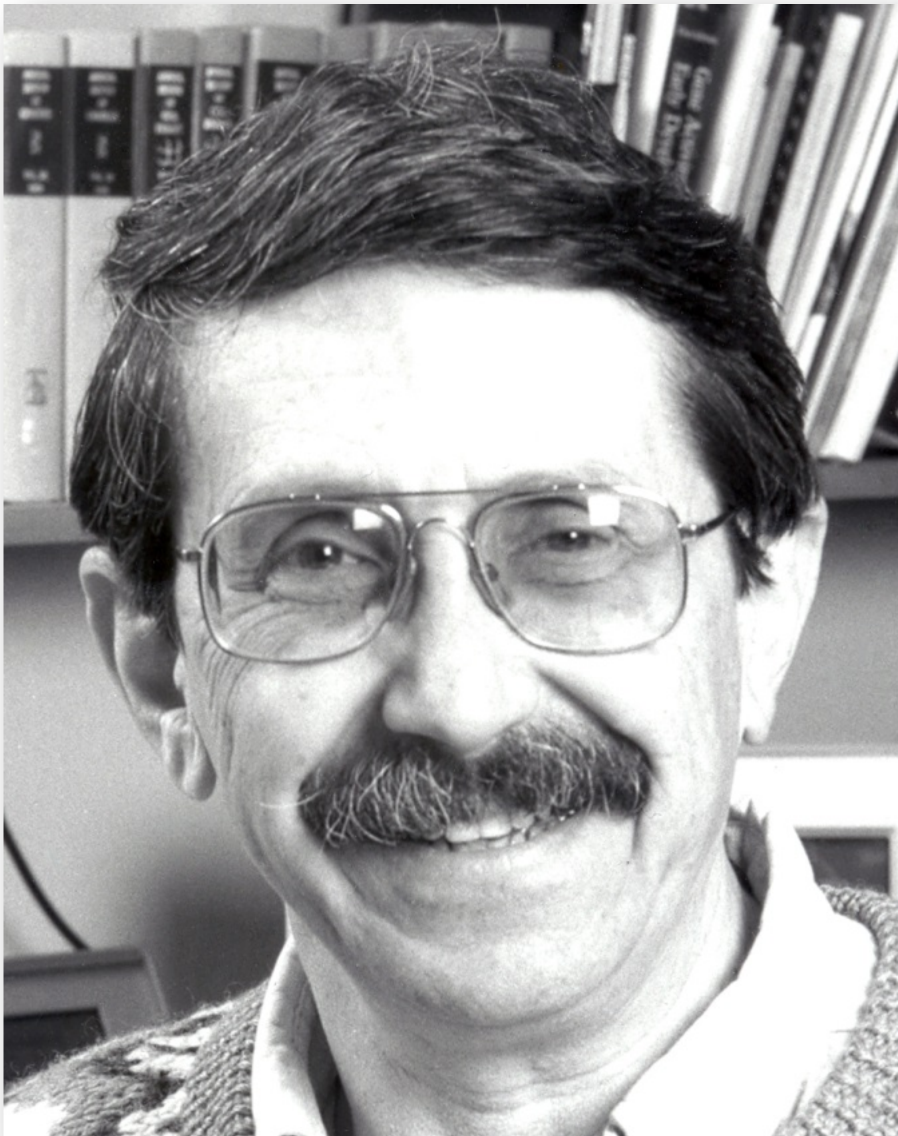
Contact information

Archives, California Institute of Technology
Mail Code 015A-74
Pasadena, CA 91125
Phone: (626)395-2704 Fax: (626)793-8756
Email: archives@caltech.edu



Melvin I. Simon

CALIFORNIA INSTITUTE OF TECHNOLOGY ARCHIVES

ORAL HISTORY PROJECT

INTERVIEW WITH MELVIN I. SIMON

BY SHIRLEY K. COHEN

PASADENA, CALIFORNIA

CALIFORNIA INSTITUTE OF TECHNOLOGY ARCHIVES
ORAL HISTORY PROJECT

Interview with Melvin I. Simon **by Shirley K. Cohen**
Pasadena, California

Session 1 May 24, 2005
Session 2 June 5, 2005

Begin Tape 1, Side 1
COHEN: Tell us a little bit about your parents and your early years.

SIMON: Well, I was born in the Bronx in New York in 1937. My parents were immigrants who came to the United States in the 1920s. They both came here when they were early teenagers; my father was about fourteen, my mother about twelve. They both finished elementary school; neither of them went to high school. They became, essentially, Orthodox Jews, and I have the feeling that they were much freer before they were married, but after marrying they decided they needed to adopt religion, and they kept an Orthodox kosher home and spoke Yiddish to each other when they didn't want my brothers or me to understand what they were saying. So we, of course, learned Yiddish. [Laughter]

COHEN: Were they from Russia?

SIMON: No. My father was from the Polish-German border, and my mother was also born in Poland—both of them were from small towns. My father's father died when my father was very young, and his mother brought him up. My mother's father came to America and made enough money to bring the family over. My mother's mother died in the great influenza epidemic right after World War I, so she came to the United States as an orphan—probably the biggest thing in her life was the loss of her mother when she was that young. She arrived in America, and her father had remarried, and this was all very difficult for her—and she carried that with her for the rest of her life. My father went to yeshiva in Europe, and was apparently quite a good student, but when he came to America all of that pretty much ended, and he went to work when he was fourteen or fifteen. And that continued until World War II; during the war, he was exempt and had to go back to school to be trained to work in a defense industry. He began to learn engineering drawing, and he loved that kind of learning.

I grew up in the Bronx, and my parents decided that the kind of education I should get would be a Jewish education. So I was sent to yeshiva, where we spent the mornings learning in Hebrew and the afternoons doing secular studies.

COHEN: No science, I would guess?

SIMON: Well, actually, very early on, we were fascinated by science, but most of the scientific investigations were primarily done by the students themselves. We investigated areas like making explosives and developing stink bombs. [Laughter] We found the magic of chemistry very, very early. But we didn't have very much basic schooling in chemistry, although we began algebra in the seventh or eighth grade, so we did get some early introduction to math.

COHEN: So, when you finished this, were those essentially your high school years?

SIMON: Well, then I went from elementary school to Yeshiva High School, which was at Yeshiva University, in Manhattan, and that was a very different experience. I was a commuter; I would commute by bus. There was a very large group of high school students who were residents, and there were two sections of the Hebrew part of the school. One was much more directed toward rabbinical studies and the other was more directed toward secular Hebrew studies—you studied Hebrew and Hebrew literature and the Bible more from the point of view of literature than from the religious point of view.

There was a school in the Bronx called the Bronx High School of Science—very famous—and many of the people who taught at Bronx High School of Science hadn't had a chance to get an advanced degree, because the Depression came along and they ended up becoming high school teachers. Yeshiva University offered them a chance to pick up an advanced degree, so many of them would come in the afternoons, after they had taught at Bronx High School of Science, and they would teach at our high school and take courses at the university so they could get advanced degrees. So because of that, two of the math teachers I had both taught at Bronx High School of Science and then in the afternoons at Yeshiva. Our biology teachers were also from Bronx High School of Science. These guys were very good and I found science to be very exhilarating.

COHEN: That must really have been an exceptional opportunity.

SIMON: Right.

COHEN: But let me go back a minute. How did you get to the high school? Was it on scholarship? I mean, it must have been expensive.

SIMON: I think we—my brother and I—did get there on scholarship, because I don't remember us paying tuition. There was an exam; we passed the exam. And there was some tuition, but it was minimal. But the nice thing, again, was experiencing lots of students who came from all over the country and all over the world; most of them lived in the dormitory. I would be going to school from—I'd get up about 7:30 in the morning and school finished about 5:30 in the afternoon. So we were busy all day long.

COHEN: No time for sports?

SIMON: Well, there were sports; sports programs were built into the school. My brother ended up on the basketball team, but I was not very much into sports. I was into politics; I ended up becoming president of a student organization and leading a student revolt, and I got thrown out my senior year. [Laughter]

COHEN: Didn't you graduate?

SIMON: I did graduate, but they expelled me for one month for leading the revolution.

COHEN: [Laughter] And you probably don't even remember what you were objecting to.

SIMON: I'm not quite sure. It had something to do with the dress code or something. I don't remember, but it was great fun—I really loved it.

COHEN: And you've been with the opposition ever since. [Laughter]

SIMON: That's exactly right. Part of it was the feeling that one had the power to confront the Establishment, confront established notions and ideas, and in fact that was a lot of fun. It was really interesting.

COHEN: So then you went from there to—

SIMON: I went to the City College of New York.

COHEN: A famous place also.

SIMON: Yes, it was a wonderful place. I really liked it very much. I started out in engineering, because my father said that I should do something practical and that engineering was a field just opening up to Jews. It had been pretty much closed, but after the war [World War II] there was a tremendous need for engineers. But I didn't like engineering. I *loved* physics. I had a wonderful physics teacher, and I loved physics. But I didn't like engineering drawing. I had a terrible time in engineering—it was the only course in my college career that I got a D in. I couldn't draw a straight line, and my pencils would keep breaking, and I would smudge the papers. It was just a *terrible* experience—I *hated* it.

I took a year off from college and went to Israel and traveled. I think that's when I got the feeling that I had to do something serious. Being away from this country and realizing what a tremendous thing it was to be able to get a free college education in a first-rate institution, when you saw that people around the world.... I mean, in Europe, of course, it was possible to go to university; but even there, it was much more of a class system, in places like England. If you fell off the track when you were eleven years old, you never made it, and in the United States there was this tremendous opportunity to make it. I came back after a year with very much the feeling that I had to get in gear and do something serious.

COHEN: That's when you went on to graduate school?

SIMON: Well, I went back to City College—I met my wife at that time—and decided that at the end of City College, I'd get a job. I had no idea of going to graduate school. Nobody in my family went to graduate school. The only tradition I'd had of higher learning was the rabbinical tradition. And there, when you went to yeshiva, the way things worked was that you would decide what area you wanted to study—what part of the Talmud, for example. And then you would find yourself a mentor, who was usually at the level of a graduate student, and you would sit with that person and you would study. That person would devote some fraction of his day—an hour or two—to work with you. And then, if you moved up, you would move to a higher-level graduate student, and finally you would go to the rabbi's lectures—you would be allowed into that. I loved that atmosphere of being able to move at your own pace, to demonstrate that you could master something, and then to move on to the next level. But I didn't think I would be going to graduate school.

I took biochemistry in City College. I took a class in animal behavior with a man named Daniel [N.] Lehrman, and Lehrman was a *fantastic* character. He taught at City College, but his main position was at Rutgers University. He was a real pioneer in animal behavior. He knew [Niko] Tinbergen, he knew Konrad Lorenz—he knew the people in animal behavior, and he would tell us what academic life was like. And I got a taste for that—it sounded pretty much like the yeshiva—and I thought I could do that kind of thing. But the notion of doing a soft science, like psychology, seemed to me like a waste of time, when I should be doing something I couldn't learn by myself.

So I majored in chemistry. I liked chemistry a lot, and my biochemistry teacher seemed to see some promise in me. I don't know what he saw, because I wasn't a really outstanding student. I was working nights in the Post Office at the time, and I was barely awake during the class. [Laughter] But in any event, he came to me and said that some of his colleagues were leaving the University of St. Louis and going to California to start a new biochemistry department at Stanford, and they had written to him to ask for promising students. Some of them were City College graduates—like Arthur Kornberg, who went on to win the Nobel Prize [in physiology or medicine, 1959]. Kornberg actually, at that point, did start one of the stellar departments of biochemistry at Stanford University. And my biochemistry teacher said, "I could get you into that department. But do you want to do that?" And I said, "It's in California." I had never been west of New Jersey, and California sounded like an absurd place to go to. I mean, why would I want to do that? But my wife had been to Brandeis for a year, so I said, "Well, how about Brandeis?"

"Well, that's not a bad choice. Nate [Nathan O.] Kaplan is going there, and he's starting a new department there, and there's a bunch of young assistant professors. He's hired a bunch of really wonderful young assistant professors. That might be a good department for you."

I said, "Good. Get me into Brandeis," [laughter] but I thought it was nonsense. So he did. He wrote some sort of letter, and I went for an interview, and every time one of these guys would look at my file, they would break out laughing. I still to this day have no idea what he wrote. [Laughter] But I got into graduate school [1959], and I loved it, I just loved it.

COHEN: Was Kaplan your professor?

SIMON: Kaplan was the head of the department. My professor was a woman named Helen Van Vunakis. I worked for Nate for a little while. They had a rotation program, and I worked a little bit in Nate's lab. And what I loved about the place—the first day I got there, they said, "You're now in graduate school. Your courses are unimportant. We want you to work in the laboratory. We expect you to work at least twelve to fifteen hours every day, seven days a week. This is your life. This is not a job; this is not a degree that you're here to get. You're here to get a life."

COHEN: [Laughter] Yes, but you'd tend to not *have* a life!

SIMON: Yes, but I loved it. I thought this was just the kind of thing I was looking for—something I could put myself into, a hundred percent. They gave me a complete fellowship—I think it was about $4,000 a year at that time, which was pretty good money—but I still felt I had to work, because I had no income.

COHEN: And you were married already.

SIMON: I was married, yes. So I got, in the evenings, a job selling magazine subscriptions on the telephone. And somehow they found out I was doing that, and they told me, "No way! You can't do anything but biochemistry. We'll raise your stipend if you need it, but we don't want you to do anything but biochemistry." So they raised my stipend, and it was great, it was just wonderful. I don't think it was wonderful for my wife, and it was terrible for my babies, who were born at that time. [Laughter] We moved to a house about six blocks from the lab, and I spent all my time doing science.

COHEN: Those were hard years for families—most people had families then.

SIMON: It was very hard! My wife really suffered through a lot of difficulty at the time. I remember one day she called me at the lab. She was clearly crying, and she said, "Get home, NOW!" I ran home and saw her sitting on the kitchen floor. What had happened was, she had brought home a bag full of groceries, and one of the kids started crying, so she ran into the other room, and the other kid grabbed the tablecloth, pulled it down, and a bottle of juice and a dozen eggs smashed all over the floor. And the kid was sitting there, in the midst of this mess. And she simply couldn't face it. [Laughter] It was traumatic.

On the other hand, it was great; we had a wonderful time—it was a great time in biology. We made discoveries. It was just a *tremendous* time in biology! I started working with Helen Van Vunakis, who at the time was working with bacteriophage. The bacteriophage system was just coming on, and Helen was really very good. She just let me do what I wanted to do. She would critique my stuff, but she gave me pretty much a free hand in the lab. I was collaborating with three other labs and running experiments on different floors of the building, and it was just a very exciting time. Julius Marmur came to Brandeis at the time and brought DNA technology, which was all very, very new. And we had journal clubs, where we'd talk about stuff that was really at the cutting edge. Exciting things were going on at Harvard and at MIT, and we would go to joint seminars with people from other places. It was a terrific time.

Nate Kaplan ran a wonderful department. He and Martin Kamen came there and anchored the biochemistry department, and they went out and hired a bunch of assistant professors, who included the people who would become the leaders in a lot of these areas.

COHEN: So this was really the birth of modern biology.

SIMON: Yes. It was a wave that I surfed for the next forty years. I mean, it's only now beginning to subside a bit. [Laughter] I think. But it's been just a tremendous time in biology. I got there in '59, and I guess Watson and Crick were'53, and it really started hitting. From 1959 to 1963, when I got my degree, it was the beginning of attempts to decode—to find the letters of the code for amino acids and proteins, the understanding of DNA as the genetic material and understanding the basis of mutation. All of the experiments that Seymour Benzer did in '56, '57—all of those experiments were coming into the literature and becoming part of what people were doing. Marshall Nirenberg did the first experiments on setting up systems to find the code. We were working with DNA and working on problems in mutagenesis. Every few months, there would be a huge breakthrough. Questions were clearly posed and then approached experimentally and answered. It was wonderful, and the bacteriophage field was very exciting. So that was a great place to be.

COHEN: Now, did you get to California during those years?

SIMON: No. I finished at Brandeis. I had a choice at that point to go to England, which was what all the bright people were doing. But, again, by that time I had two babies and the thought of transplanting everybody was too difficult. So I looked for somebody who I thought was really a cutting-edge professor, and I chose to go with Arthur Pardee, who was then at Princeton.

So I postdoc'd with Pardee. And I found Princeton to be a miserable place; I *hated* the place—which is just the opposite of the excitement and openness that there was at Brandeis. There were conflicts between the chemistry department and the biology department, between old-style biologists and new-style biologists. Pardee was just feeling his way. He had done a great experiment with [François] Jacob and [Jacques] Monod in Paris. And he had a personal tragedy when he was in Paris. He came back and was trying to live through all of this, and at the same time he made a major discovery. And again, the French school found the regulatory process that occurs, where a regulatory molecule binds to a protein, changes its shape, and regulates the function of the protein. And that was astutely named, by the French, *l'allostérie*. In France, he did a great experiment discovering gene repression. He essentially lost claim to that as well, and the Nobel Prize [in physiology or medicine, 1965] went to Jacob, Monod, and [André] Lwoff—instead of Jacob, Monod, and Pardee. So it was a hard time for him. He was a very bright guy, but the problem he gave me to work on was not a very good problem, not very tractable. So I used to work on that problem during the day, and I'd come in at night and work on other things that were more interesting. [Laughter] I was able to actually eke out a couple of publications while I was there.

But I wanted to get out of Princeton as quickly as I could. Princeton was pretty dismal. Year after year, they would hire some of the brightest people, and year after year they would all leave. People like Marc [W.] Kirschner, who went to UCSF and is now at Harvard, was there for five or six years, and he left. There was a whole coterie of such people—

COHEN: Was it the atmosphere of the town or the atmosphere of the university itself?

SIMON: At that time, they hadn't made a commitment to modern biology—it was only years later. Bruce Alberts was there and a bunch of people, and they all left for San Francisco, and finally it dawned on Princeton that they had to make a major commitment to biology—that biology was not a minor science. Their notion had been that physics was real science.

COHEN: So they thought the name was enough to keep good people there.

SIMON: Right. So eventually they did that. But in any event, I wanted to get out. I got a phone call from my old boss, Helen Van Vunakis, and she said there were some job openings and if I was interested I could go and interview. I knew if I stayed at Princeton, my stuff would get old, and the only things I was doing were based on my thesis work. So I went on two job interviews: One was at the University of Chicago and one was in California.

COHEN: Now, was this in San Diego?

SIMON: San Diego, yes. I went to the University of Chicago in the spring of 1964, and they had had riots there the previous winter. They had to stamp your hand before they let you into the building, because they were holding back the hordes. [Laughter] And it was freezing cold! And then I came to San Diego, and they hadn't established the campus yet. Actually, the guy who was the moving force had just died—that was David Bonner, who had brought a whole group from Yale out to UCSD to start a department there. But he passed away and they weren't quite sure what to do with me, because it was Bonner who had decided I should interview. There were only six people in the department when I came there.

COHEN: What year was that?

SIMON: This was in 1964. I came in spring of ’64 to interview, and they were all down on the beach. So here I came from Chicago, where it was dark and freezing cold, and I walk into this place, and there are people running down the hall half-naked, throwing off their clothes—“Volleyball time!” [Laughter] And there were palm trees, which I had never seen before. It was like landing on Mars for me. I just had no concept of what could be happening there, but I got the sense that they really wanted to build something new. They were looking for something new and interesting and important to happen. They really understood that something was happening in biology and that they needed to focus in on that, and they were going to hire young people.

So I gave a seminar, and they offered me a job. And I came home and I told my wife that this would be a great adventure, this would be wonderful, and we’d get out of Princeton. In Princeton, the kids were sick all the time. In the winter, they were sick because it was winter; in the spring they were sick because it was spring; in the summer they would get colds from the other kids who were around. Princeton was an interesting place, but it was just difficult. And our third kid was born, so now we had three kids. So we decided to move to California; we wanted to get out of Princeton as quickly as possible. [Laughter]

COHEN: How long did you spend at Princeton?

SIMON: We were there eighteen months—not even two years. We came to California in December 1964. And it was wild. It was just so different from anything we’d known. It was sort of like “God is dead, and everything is possible.” [Laughter] There was no infrastructure; there was no family; there were no relatives. Everything was open.

COHEN: So you were on the beach. What college were you in?

SIMON: It was Revelle College, and it had just started. They had just built Bonner Hall [1964], the first biology building. There was one physics building—which was later called Urey Hall—

and the physicists had just moved in. In Bonner Hall, mine was the first laboratory, and I spent the first year designing my laboratory and trying to get an experiment done, which was just impossible. And writing grants. And going down to the beach.

COHEN: Did you have to teach?

SIMON: There was nobody to teach. No, no, teaching didn't come for years. It was wonderful! [Laughter] And that was the notion—the notion was to start with graduate students, so we did start with a class of graduate students. And we had some interesting graduate students—Susumu Tonegawa, who went on to win a Nobel Prize [in physiology or medicine, 1987], was one of our graduate students. We had really hotshot kids—because the feeling was that we were at the edge and something new and interesting was happening. It was much harder to hire good faculty, though, because no one was sure how this new University of California campus would develop. Anyway, it was an interesting time; it was great being there at the very beginning.

COHEN: So you pursued the problems you had been doing in the East?

SIMON: Well, when I was at Princeton, I decided I needed to do something different. There was a guy at Princeton by the name of Noboru Sueoka, who had in fact been here at Caltech as a graduate student and had done some very interesting things. I taught his class with him, and I started teaching about sort of unsolved problems in biology. One of the questions was, Since we could use bacterial viruses as model systems to learn a lot about the basic molecular biology that was going on, could we go to a higher level with these systems—could we use them to try to understand development and differentiation? So the question was: What kind of system could you use where you could look at how a bacterium differentiated, how it made an organelle? So I started collecting questions I thought could be answered in bacterial systems using molecular biology and molecular genetic techniques. By that time, I'd become quite adept at moving genes around with the techniques available at that time. One of the organelles that these bacteria made was a flagellum. And it looked like it was complicated enough; at that time, we thought that these flagella beat to make the bacteria move along. And as I started reading the literature, there were all sorts of anomalies that people had not explained—genetic anomalies. These things behaved genetically in a very peculiar way. They seemed to be genetically highly complex, because even then, when you could just begin to enumerate the genes involved in making the flagellum, there seemed to be a lot of them. The control of the apparatus seemed to be complicated. If you grew the bacteria in the presence of glucose, they didn't make flagella, but if you grew them in media that were much less rich, then they made these organelles. So there's clearly some way they control making them or not making them.

Then I began to look further, and as I read the literature it seemed to me that this was going to be a very interesting area to work in and one I could take as my own. At that time, I realized that the way you became a prominent biologist was to find a little area you could take as your own—become the world's expert in that little area and deduce general principles from an understanding of it. So that's what I was going to do. And at the first meeting I went to when I came to California I was devastated, because at that meeting there was another guy, from UCLA, who was doing the same thing. [Laughter]

COHEN: [Laughter] So much for originality!

SIMON: [Laughter] Yes, right.

COHEN: So you did something else?

SIMON: No, I decided to go on with that, and it turned out that just like everything else in biology, it was much bigger than you thought in the beginning. It wasn't a one-person type of thing—there was plenty to do for everybody, and then it began to open up. There was another man, named Julius Adler, who came from Wisconsin, who started studying behavior in bacteria—chemotaxis. And this turned out to be something that had been studied for hundreds of years, going back to Leeuwenhoek and what he saw when he looked through his microscope—that these things were moving around and it looked like their movements made sense. Some of the early people in Germany had begun to study the movements of bacteria. It was clear that they moved to areas where there were higher levels of nutrients. So here was a chance to study how they developed their organelle and how they used their organelle in a concerted way to move toward things.

COHEN: You had your own lab at UCSD?

SIMON: I had my own lab, and I picked this subject to study, and I started getting graduate students. And I was also trying to figure out how to live in California, which meant adapting to a whole new culture and a whole new way of life, where the sun always shines. Very strange! Raising a family, trying to do all that sort of stuff.

COHEN: So you watched UCSD grow into a major institution.

SIMON: Yes—oh, yes. UCSD was growing, and it was a very interesting time in terms of the institution itself. When I got there, there were six other people in the biology department. When I left, in ’82, I think there were eighty faculty members.

COHEN: How much did you have to do with Salk [Institute for Biological Studies]? Was that established by the time you were there?

SIMON: Salk was established in the early ’60s—there were some very good people at Salk. There was a guy there named David Baltimore, who we thought—the young people thought—was terrific and should be hired in biology. But some of the older people in biology objected, because they thought he was too arrogant. And we said, “Arrogant, schmarrogant! This guy’s a great biologist. We’ve got to have him here.” And we had this big fight, after which we decided—the young faculty—that we didn’t want to come to faculty meetings anymore, because we felt that if someone like David Baltimore wasn’t good enough for our division, then none of us would ever get tenure. [Laughter]

COHEN: Did it make any difference? They still didn’t offer him a job.

SIMON: They never offered him a job, no. He went back to MIT [1968].

COHEN: Right. Well, that’s how it goes—eventually he returned to California [as president of Caltech, 1997-2006]. OK, so things then progressed at UCSD—and what made you want to leave?

SIMON: Well, things progressed—and they went very, very well. And a number of people came to UCSD. The biology department grew; the chemistry department grew. For me, a big event was the arrival of John Abelson [1968]. John got his degree at Johns Hopkins and then went to work with Sydney Brenner, in England. I remember the first day he came in. We didn't have very many colleagues, really. John came into my office, and he looked at me and said, "You're Simon." I said, "Right." And he said, "Listen, I want to tell you about some work I've been doing with phage, because I think you understand phage." And he started on one end of my blackboard and about three-and-a-half hours later he got to the other end of the blackboard. [Laughter] And we were yelling and screaming at each other, and I just *loved* talking with him, and found him very, very exciting. We never collaborated on a scientific project, but we used to talk to each other about science, and that became very important for me—to have somebody around to talk science.

Molecular biology was just exploding. By that time, I had gotten tenure, and John had tenure, and we were beginning to really be able to use molecular biology. So we went to the people who were running the university at the time and said, "Now is the time for UCSD to become a great university by putting a tremendous effort into molecular biology. And what we really need is four or five new appointments in molecular biology and for the university to make a commitment to put more resources and buildings and so on into microbiology." They said, "No, at this time we can't really think about it." So we decided to do it ourselves.

John had a wonderful insight. Marvin Caruthers and people in Colorado had figured out how to synthesize DNA, and it occurred to John that this was something we needed to be able to do, because if we could synthesize pieces of DNA, we could eventually also mutagenize DNA and we could make mutants in any part of a molecule that we wanted. Another person we spoke to a lot at that time was Joe Kraut, who was a crystallographer. The idea was that if we could make mutations any place in the DNA, then we could mutagenize proteins selectively and carefully, and we could determine their crystal structure, and we could find out how proteins really work. This would be a whole tremendous way of designing ligands and understanding catalysis and all that sort of stuff. But we couldn't get the university to get excited about that, so we decided to set up our own institute.

COHEN: Within the university?

SIMON: No. Well, we first talked to the university about letting us set up an organized research unit within the university, because they could do that. But we had no money. So we said we'd put our grants into the organized research unit, and they laughed at us. It turned out that there was this guy named Richard Lerner, who had become a moving force in the Scripps Clinic and Research Foundation, which was down by the ocean, in La Jolla. Richard Lerner realized that biology was changing fast and that it would require enormous resources and much more space, so he worked out a deal whereby he could move the clinic out of the old Scripps building and up to the cliffs—to where it is now, up by Torrey Pines Golf Course—leaving the old Scripps building empty. **[Tape ends]**

Begin Tape 1, Side 2

SIMON: …NIH [National Institutes of Health] money, yes. So it couldn't be used for anything but doing research, and preferably research sponsored by the NIH. I had a friend at the time who was a real character, and he said, "Go for it! Go down there and make them an offer, and tell them you want to set your institute up." He was a lawyer and he said, "I'll write it up for you. No problem! It's boilerplate." So we had a meeting at our house—John and I, and we brought in a couple of other people, and we set up our own institute, the Agouron Institute [1978], and rented space in the old Scripps clinic building. John took his lab out of the university and moved it down there, and Joe Kraut got some of *his* postdocs who were looking for independent jobs, and I had another, mature postdoc in my lab, and we moved them and a bunch of grants down—

COHEN: But how could the university stand for that? I mean, weren't you taking their people?

SIMON: Well, the university was giving us a lot of trouble at the time, but we just moved ahead. I was able to get this very large grant from the navy [Office of Naval Research], because by that time I'd gotten interested in adaptation—how bacteria adapted to environments. The way barnacles and biofouling form on the bottom of ships is by bacteria first sticking to the surface; so, how did they do that and how did they differentiate?

COHEN: Did you resign your position with the university?

SIMON: No, no, god forbid! We were still teaching; we still had our positions at the university, but we set this up as an aside. There were people at the time who were thinking about setting up companies, but we felt that the notion of a company would be mixing commercial stuff with—

COHEN: This was going to be strictly a research institute.

SIMON: Strictly a research institute. So we set that up, and it got going very well. We got a lot of funding, and we kept coming back to the university and saying to them, "Why don't you take us back now? We are an institute. Bring us back as an organized research unit. Help us build a building; we'll raise money for that, and we'll really hit molecular biology hard." We met at that time with [William D.] McElroy [UCSD chancellor, 1972-1980], and Mack was interested, but he was on his way out; the university was pushing him out. [Richard C.] Atkinson came in as chancellor, and because he was new he was reluctant to do anything. By that time, many of the universities around the country were doing molecular biology—this was in!—and both John and I started getting recruiting calls, from Princeton, from Harvard. Harvard was going to set up a separate unit at Mass General [Massachusetts General Hospital], and they wanted us to come there. I got an offer from MIT. And all this while, we were trying to convince UCSD to integrate our institute, and they didn't want to do it.

At that time, we got an offer from Caltech. John was particularly enamored of Caltech. He had a connection through his uncle, Phil Abelson—Phil Abelson was the editor of *Science* magazine. By then, my research was booming; all kinds of stuff had broken open, and we had made some interesting and important discoveries in bacterial systems. We found gene rearrangements that could control gene expression in the flagellar system, and we were able to answer some of these anomalies that had been sitting around in the literature for forty, fifty years. We found that the bacterial flagella rotated; we did some experiments that clearly, unequivocally, showed that. And I had this great experience of being able to give a scientific talk where nobody in the audience believed that what we were showing them was true. So we took movies, and we had to show these movies over and over again to convince people.

COHEN: At this time, you were considering going to Caltech?

SIMON: Yes, this was when we were considering going to Caltech. We met with Lee [Leroy] Hood. Lee had taken over as Biology Division chairman at Caltech [1980], and Caltech was in a difficult time, a real time of transition. The leadership in biology was essentially Lee and Eric Davidson and a few other people, but there weren't very many senior scientists and there wasn't very much leadership—especially in molecular biology.

COHEN: Now, who was president at that time?

SIMON: Murph [Marvin L.] Goldberger [Caltech president 1978-1987]. Lee was moving into developing new instruments and new technology. Lee was on fire. And we were all thinking that the new age had come and things were really exploding, and Caltech provided us with what we wanted. They had an empty building that we could.... The Braun Laboratories had just gotten built [1982]. We looked at the Braun building and said, "This will never do. If you want us, we have to redo the whole second floor." So they worked out a way that we could redo the whole second floor. It was built on the notion of separate labs, and what we wanted was a big interactive floor, where everybody could collaborate and interact.

COHEN: Did you keep the Agouron name?

SIMON: Yes, we kept the Agouron Institute, and the Agouron Institute began to evolve, too. We hired a guy named Peter Johnson to run it. Peter was a terrific administrator and a terrific, very, very bright guy. We started looking around to get funding to support it. We met with [Arnold O.] Beckman at the time—this was before we came to Caltech—and he said, "I never give anything to any institute that's less than sixty years old. [Laughter] How do I know you'll be around when I'm not?" And we met with the people from Salk. We realized that an institute would be very, very difficult to support, so we got this bright idea that we would start a company—since by this time we'd gotten into engineering proteins—start a company that would design drugs. So Peter Johnson started the company [Agouron Pharmaceuticals] within the context of the Agouron Institute. We had another friend who was a lawyer, and he worked out a way of setting up a commercial cooperation agreement with the institute so that the company could get started. And the company then collaborated with the institute and gave the institute and the founders stock. As founders of the institute and of the company, we decided we didn't need a lot of stock. We didn't need a lot to live, if the company really made it; we could get along fine. We wanted the institute to really do well, so all of us put the bulk of our founders' stock into the institute. So the institute controlled a big piece of the company, which helped us later on, when we had to deal with venture capitalists, because we could come to the board representing the Agouron Institute and owning a big piece of the company. That saved our rear ends a couple of times. So the company grew, in the context of the institute, and then it morphed off and went on its own.

COHEN: And that stayed in La Jolla?

SIMON: Yes, that stayed in La Jolla.

COHEN: But you and John came to Caltech.

SIMON: John and I came to Caltech in 1982. **[Tape turned off]**

MELVIN I. SIMON

SESSION 2

June 5, 2005

Begin Tape 2, Side 1

COHEN: So you arrived at Caltech in 1982.

SIMON: We came in 1982. It was in January. John Abelson and I came together; we were hired together. What happened was that the Division of Biology suddenly realized that many of its older members were retiring or were due to retire and the division needed to build itself up, particularly in the area of molecular biology. Lee Hood was the chairman at the time, and he got in touch first with John Abelson and then with me.

COHEN: Did you know him very well before this?

SIMON: No, I didn't know Lee very well. I had known him years before. He came down to UCSD and spent a little time with Russ Doolittle, learning how to make maps of antibody molecules. We didn't know too much about him, except that he was into developing instruments and he was interested in the immune system. But apparently a new building was being built, or had just been built—the Braun Laboratories—and Caltech was looking for two professors to take positions in it. They had approached Abelson first because they didn't have very many people in the RNA field. Abelson and I were both, together, involved in the Agouron Institute, and we decided that if we were going to go someplace, we were going to look for a place to go together. We were both looking at positions at a number of other places—at Harvard and at MIT.

COHEN: And they would have taken your Agouron with you?

SIMON: No. What was going to happen was that we were going to try to become part of some new venture at each of these places. At Harvard, Mass General was going to set up a special molecular biology department, and they were looking for senior scientists to be part of that. I think Howard Goodman ended up doing that. And MIT at the time was also trying to set up the

Whitaker school [Whitaker College of Health Sciences and Technology], which was, again, going to be a separate department that would be joint between Harvard and MIT.

So we looked at a bunch of those offers; there was a possibility that Princeton was hot. Lee came down; we talked. I came up to Caltech and gave a seminar. John had given a seminar. And the prospect at Caltech was nice, because we were offered a floor of the Braun building with one other professor—there would be three of us—and we could continue our operations in San Diego long distance. The distance was not very far, and I still had a house in San Diego—so did John, at the time. So Caltech's offer looked very good. Lee's operation was very exciting; he had all these wonderful instruments that were going to revolutionize biology. And Caltech was Caltech. I mean, the aura of Caltech.... There was just a wonderful tradition of the place, and it was populated with heroes—people like Seymour Benzer. In my early days of graduate school, I had read Seymour's papers and was just blown away. John had spent some time in Cambridge, England, and there was this connection between Sydney Brenner and some of the people at Caltech, and [James] Watson and [Max] Delbrück. So there was a real feeling that this was a wonderful place to be.

COHEN: And it was in California.

SIMON: And it was in California, only two hours from San Diego. [Laughter] We came and looked at the floor in Braun. John and I wanted to have an interactive operation, and the floor had been terribly designed. We actually went to visit Mr. Braun, who had given the building and apparently had had something to say about its design, and we immediately saw why the building was designed the way it was. C. F. Braun's engineering department was in Alhambra, and it was a series of these long buildings, red-brick buildings. You walked in and there was a long corridor as far as the eye could see, and there were offices on either side of that corridor, each with a glass door. And in each office there was a desk with one piece of paper on the desk—apparently it was company policy that you could not have more than one piece of paper on your desk—and a telephone. And a man behind the desk with a suit and a tie. It was like something out of a Kafka novel. You were overwhelmed by this feeling of modular boredom. [Laughter]

So the deal we made was that we had to have the floor redone to our specifications—that was part of our negotiation. And we did; we ripped everything out. We had Arthur Kornberg's son, who is an architect—he was involved in building the Broad building [the Broad Center for the Biological Sciences], too. We had him work with us, and we redesigned the floor. That was nice, to come into a new space.

COHEN: [Murph] Goldberger was president?

SIMON: Goldberger was president, and Goldberger was very cordial and very supportive. The division was a little bizarre—but then we had come from UCSD, which was also a little bizarre. [Laughter] And Abelson and I both had the feeling that we didn't want to engage in politics—we didn't want to be involved in those kinds of things. We had all the space we needed. It was not hard to get grants at that time, so we had all the money we needed, and we each wanted to just do science. Caltech was wonderful that way; teaching was reasonably minimal. I realized, after the first class I gave, that there was nothing I could do to teach these kids except get out of their way and let them learn. [Laughter] I mean, they were all very, very bright and highly motivated. So teaching was not at all difficult. The last class I taught at UCSD had 420 students in a huge auditorium. Here I had thirty-five students. I'd say to them, "Whenever you like, you can drop by my office," and no one ever came. At UCSD, I was *besieged*. So it was very nice.

I had this very wonderful feeling: I was sitting in my office and I felt so good, and I said, "What *is* this?" And then I realized that I was *thinking*, and I hadn't been doing that for a long, long time. [Laughter] It was wonderful.

COHEN: So you had very little to do with the rest of the Biology Division?

SIMON: We had little to do with the rest of the Biology Division. There were things that irked us, but we would say to each other, "Leave it alone. We're doing just fine." And we were. We got very good postdocs. When we moved from UCSD, somehow the word got out, and we got some really wonderful postdocs—and the graduate students in the Biology Division were not that great, at the time. But we were wailing—John's lab was booming, my lab was booming. Before long, I had fifteen, twenty people in the lab.

COHEN: Were they mostly postdocs, then?

SIMON: Mostly postdocs. I had a couple of graduate students. The first few years—from ’82-’83 to ’86-’87, were just tremendously productive for me. I started a new area of work. All these years I’d been working on bacteria and bacterial systems. I started working on signaling in the eukaryotic systems. And the bacterial stuff was also going very, very well. We made some very interesting discoveries about phosphorylation in proteins and signaling in bacteria.

COHEN: So you didn’t involve yourself in the rest of the division or the rest of the institute in any way?

SIMON: No! Stayed away, as much as I could. I remember talking to some other people at Caltech, and they would say, “Oh, the biologists are all remote. All they do is work; nobody ever comes around to talk about anything. They’re not interested in anything.” And to some extent that was true. But on the other hand, this was just great. [Laughter]

COHEN: So you weren’t called on to do committee work or anything?

SIMON: There wasn’t very much in the way of committees. I had done a lot of that stuff at UCSD; I’d been involved in planning buildings, I’d been involved with the arts department, I’d been on a number of search committees. There was very little of that, and essentially Lee was pretty much building his own group. By the time I got here, he had about fifty, sixty people; three or four years later, it must have been up to a hundred people.

COHEN: Of course, that sort of backfired on him, too.

SIMON: Well, it was getting to be kind of difficult to watch. [Laughter] The other part of it was that it was an interesting time in biology, because people were starting companies. We had started a company at that time in San Diego, and we were doing that by remote control.

COHEN: Was that Agouron?

SIMON: Yes, the Agouron Institute kept going, and we just kept an eye on it. But the man we hired to run the institute realized that it would not be able to perpetuate itself easily, so he started

Agouron Pharmaceuticals, and that began to grow. John and I were on the board, and we'd go down there.

In 1985 I was elected to the National Academy [of Sciences]. Both John and I got in. It was nice. [Laughter] Colleagues, we got to meet and drop in on people in the division. I think I associated more easily with the older guys than with the younger guys, for some reason. And our floor in Braun worked out very well; it was a good place to work.

COHEN: Now, you talked about Lee Hood's machines. How about the gene machine? Was that already built?

SIMON: You mean the [DNA] sequencer? No. When we got here, they were just starting to do the sequencer. [Michael W.] Hunkapiller was still here. In fact, the great promise was that we'd come here and meet guys and we would use all of these wonderful instruments. So I brought these proteins; we had these wonderful chemotaxis proteins and we were able to isolate lots and lots of them. I brought them up to Hunkapiller to help us sequence. There was a guy named [David B.] Teplow here, working these old sequencers that Lee had used. By that time, Lee's company had developed amino-acid sequencing machines. And I think those proteins are probably still in a freezer some place. [Laughter]

COHEN: How about the gene [DNA sequencing] machine?

SIMON: The gene machine was a sequencing machine; and that was, again, going to be a great breakthrough. By that time, the guys to do that had come and Lee had set up a lab down in the basement of Kerckhoff [William G. Kerckhoff Laboratories of the Biological Sciences] and they were doing that. We talked to a lot of those people, and we began to interact with them, because I'd gotten very interested in mouse genetics. The bacterial work was going fine and it didn't require as much attention, so we'd started working with mammalian systems and trying to do mammalian genetics. And I got involved in trying to set up a mouse genetics system here at Caltech, which meant building a mouse house. What we wanted to do was bring in the people and get the money we needed to do mouse genetics, which was just starting at the time.

Lee, of course, was interested in everything. He was interested in genomes, and so we started talking about sequencing genomes. But sequencing pretty quickly transitioned into Applied Biosystems, and there wasn't much sequencing going on at Caltech.

COHEN: This wasn't the project that Lee was doing with Bill [William J.] Dreyer?

SIMON: Lee's notion was that he was going to build five machines that would revolutionize biology. One of them was a protein-sequencing machine. And so, with Bill Dreyer, he built the first protein-sequencing machines. And then Lee—very astutely, I think—realized that there was a big difference between building a breadboard operation that worked in the laboratory and building a commercial instrument. So he started Applied Biosystems to build the commercial instruments, and the company started, if my memory serves correctly, with the protein-sequencing machines. That's what had been done with Bill Dreyer, and there were two old prototypes left here—over in the Dreyer lab, actually—and we tried to get those things to sequence our proteins; they would blow up every few days and it was a real mess.

And then they were trying to develop the DNA sequencer. Lloyd Smith, who's now at Wisconsin, came here, and he was a very smart kid. He realized that fluorescence was the only way to do it, and he started using fluorescent nucleotides. And that was being developed in Lee's lab, but I think as soon as they got a fairly decent prototype, that transitioned over to the company as well.

COHEN: So it wasn't being done here?

SIMON: No. Then they did a DNA-synthesis machine. By that time, I think, Hunkapiller was about ready to leave, or left and moved over to the company [1983], and they built the machine to synthesize polynucleotides. You know, this whole issue of how you invent these things and use them to do research and then transition them so that they can be built to be used by everybody, and then how do you use them for your own research—that never really got resolved. We started out by setting up these facilities, and it was sort of a con game, because what would happen was that we ended up charging people to buy one of these prototype early machines and charging people to have their oligonucleotides made in the facility—have the sequence done in the facility. And the facility would charge more than what it cost to do that. There was a slight operating profit. [Laughter] They were running a little business, kind of. But it wasn't bad, in that we were one of the few places in the early days that could get oligonucleotides made relatively easily.

Meanwhile, Lee's operation here got bigger and more complex and bigger and more complex. It was really almost as if he were the entire division.

COHEN: There must have been a lot of resentment about that.

SIMON: Well, that's when resentment started to build up. But, again, things were going so well with us, and with John, and we didn't want to rock the boat. [Laughter]

COHEN: So you went along with it.

SIMON: Yes, we went along with it all. But it began to get egregious, because there was no end to Lee's capacity; his model was sort of like, you know, the old [Ernest O.] Lawrence model—the guys who built the first synchrotron and were building bigger and bigger models at Berkeley, in physics. The notion was to have this *huge* group building instruments, and the instruments would be good for everybody—but it wasn't quite that way. I think that that's when it began to get difficult. Lee essentially had set up kind of a partnership. Lee and Eric Davidson were very good friends, and Eric had quite a large operation. Eric was essentially acting as Lee's deputy in Lee's absence, and Lee was absent a lot. So it was getting to be difficult.

COHEN: Well, they were apart from the rest of biology, too, then, weren't they?

SIMON: They were a lot apart from the rest of biology, yes. They pretty much grew apart from the rest of biology. What was happening was that genomics was getting more and more interesting, and the mouse systems were getting developed, but there wasn't a way of doing that. These were things that required, really, the division's help, and it wasn't forthcoming. Lee was very interested in transgenic mice, but it was pretty much an operation that, in the early days, he was trying to control. Carol Readhead was involved in that, and she was working with him. So I got involved in it, and I tried to go to Amgen to raise the money. And we did in fact get some money from Amgen to help get the transgenic facilities started. That was when I started getting into more and more division stuff.

COHEN: What year was this?

SIMON: Now we've moved to the end of the eighties and the beginning of the nineties. What was happening now was that the possibilities for molecular biology—at least for collecting data on a large scale—began to be very, very clear. People were able to work with bacterial systems and do almost anything they wanted to do. And we were moving very, very rapidly with the chemotaxis system, which had essentially been broken open, and the future there looked very straightforward. It was obvious what we had to do. We had gotten into G proteins, which were the next thing, the signaling systems of mammalian cells, and there we began to use mouse genetics to try to explore those systems. And we were doing a lot of cloning and sequencing. The emphasis at that point was on being able to collect large data sets, because you could begin to do that now, with a lot of instrumentation help, and there were many breakthroughs in a number of areas. So I got more and more interested in mammalian genetics—trying to do on the mammalian systems the kinds of things we'd done with the bacterial systems. The Human Genome Project was getting started at that time, and I began getting involved very, very early in the Genome Project, because we had experience in doing these kinds of things—chromosome mapping and sequencing—with bacteria, and we felt we could do a similar community-wide project with the human genome.

COHEN: So you were in that with Lee, although he was traveling somewhere all the time?

SIMON: Well, we didn't do it with Lee. If you did something with Lee, Lee owned it. It was kind of difficult; it wasn't clear how you did a partnership with Lee. But we were working pretty much in the same area; we have a couple papers together. One of Lee's students did a lot of the work with us later on, when he was doing the mapping of antibody genes. So, we got more and more involved in the Human Genome Project. Lee's lab was interested in the sequencing aspect; we were interested in the mapping aspect.

COHEN: Now, sequencing is all the stuff that's in the gene? But the mapping is the—

SIMON: Mapping goes way, way back, to the early days of Caltech, when [Thomas Hunt] Morgan and [James Holmes] Sturdivant found out where genes sit on the chromosome—what the relationship is between the genes. You want to be able to place a gene in relation to all the other genes and in relation to the chromosomes. So we started doing that with the mouse genome, because it was critical to the kind of stuff we were doing with mice. And it became clear to us that the techniques that people were using for mapping and sequencing weren't going to work. People started thinking that we could do all of this in yeast, where you could keep large pieces of DNA. And what we realized was that you *couldn't* do that, because they would scramble: The recombination system in yeast.... The yeast would take the foreign DNA and scramble it, because it had lots of regions that it could recognize as being similar, and then it would recombine the DNA. So if you isolated a piece of DNA, put it in yeast, and shipped it to your friend on the East Coast, by the time it got to the East Coast, it would be scrambled. So we invented a way of making fairly large pieces of DNA stable and keeping them in bacteria, because we'd had the bacterial genetics background. These were the BAC [bacterial artificial chromosomes] libraries. And that worked out, and people started using that.

COHEN: Now, when you say "we," you're talking about you and your postdocs, or about you and John?

SIMON: No, we never collaborated with John; I meant my postdocs and I. I now had essentially three groups: One was still doing bacterial chemotaxis, another was doing G proteins stuff, and then there was the group doing mammalian genetics and the Genome Project. Then the Genome Project really started to take off; money got poured into it. But our part of it was to lay out.... The idea was, you were going to lay out all these pieces of DNA in a tiling pattern, so you knew which genes were next to which, and then the sequencers would come in and sequence them, one at a time, and then they would know what the continuity was of the genome. So we got involved with the DOE [Department of Energy, which, with the National Institutes of Health, was coordinating the Human Genome Project—ed.]. And now I had two groups: the group that was doing regular research, which was the G-protein group and the chemotaxis group, and the genome group, which worked in the Beckman Institute.

COHEN: Oh, by then the Beckman was built?

SIMON: The Beckman Institute was getting built at the same time that the Genome Project was really beginning to expand, and that was one of the things envisioned for the Beckman Institute. Again, Lee's group kept getting bigger and bigger. The vision for the Beckman Institute was that you would have your group doing your own basic small-scale research, but then a big project would come along and the Beckman Institute would be the place you could expand into: get the money, do the big project, assemble the team, finish the project, and then move out.

COHEN: People don't move out. [Laughter]

SIMON: I know, I know. But that was one of the initial notions; this must have been '85 or '86, when the idea was to approach [Arnold O.] Beckman about building the Beckman Institute [finished 1989]. Lee Hood had had a bad time with Beckman. Lee had offered Beckman the possibility of building his machines and Beckman's guys had pretty much refused, and then Lee went someplace else and set up Applied Biosystems, and then Beckman, of course, got upset when it was successful. So Lee couldn't go ask Beckman for the money to build the Beckman Institute.

COHEN: I thought Harry Gray [Arnold O. Beckman Professor of Chemistry] did a lot of that footwork.

SIMON: Well, Harry Gray was doing the footwork. I didn't know anything about any of this stuff; I didn't know what the relationship was between Hood and Beckman. But they gave me the honor of approaching Beckman to ask him about who could head the Beckman Institute when it was set up, and the guy they thought needed to be the first nominee was, of course, Lee, because Lee was doing all of this stuff and he could easily move in.

COHEN: [Laughter] Expand into the Beckman Institute.

SIMON: He had the perfect model for this kind of thing. So we all went down to see Arnold Beckman, and I was the patsy. I didn't know that there was bad blood between Beckman and Lee, I didn't know any of this stuff. And we came into Beckman's office; and everybody was congenial. Harry was his old self, and everybody was yucking it up, "Ha, Ha, Ha!" And then there was moment of silence, and it was my turn.

COHEN: To propose Lee?

SIMON: Yes. Beckman says, "Oh, this all sounds wonderful! Who would run this institute?" And that was my cue, and I said, "Well, we were thinking that the perfect head for this institute would be Lee Hood." [Pause] Absolute silence! [Laughter] And it was all very embarrassing, with a lot of staring at the ceiling and staring at the floor. And finally we got out of there, and I said, "Harry, what happened?" He said, "Well, you know, Dr. Beckman and Lee don't quite get along." [Laughter] But in any event, it all worked out well. And it may have been a plan of Harry's—or it may have simply worked out that way—that Harry would be in charge. But Lee still got what he wanted and needed; he got plenty of space at the Beckman Institute and it was very productive. But it was getting egregious, more and more.

COHEN: You mean, Lee's taking over more and more of biology?

SIMON: *Everything!* Lee had a lab at the bottom of Kerckhoff. Lee had the top floor of the Braun building. Lee had a whole wing of the Beckman Institute and 120 people he really couldn't possibly have kept track of. I think a number of people realized that it just couldn't go on. As I recall, there was some sort of petition to the provost that something had to be done.

COHEN: That was by many people?

SIMON: Yes.

COHEN: Who was the provost at the time?

SIMON: Paul Jennings. And there was a new president—[Thomas E.] Everhart [Caltech president 1987-1997]. Meanwhile, the Human Genome Project was exploding like mad; things were moving out of the mapping phase and into the sequencing phase. And we realized that there were better ways to sequence the human genome than the BAC tiling approach that this crazy guy [J. Craig] Venter, whom I don't like anymore—

COHEN: Oh, you went to see President Clinton with him once, or something, didn't you?

SIMON: It wasn't Craig Venter, it was a guy named Ham [Hamilton] Smith, who won a Nobel Prize [in physiology or medicine, 1978], who worked with Venter and had come up with another way. Venter is not really much of a scientist, but he has a nose for technology, and he realized that there was another step, a new technology.

COHEN: Where did Venter work?

SIMON: What happened was, he set up his own institute, which was supported by a bunch of venture capitalists, because they realized they could spin a company out of it. And they set up a company. They wanted to capture all of DNA—they thought it had great commercial potential. So they set up a company called Human Genome Sciences, which a man named [William] Haseltine ran. And they set up an institute, TIGR [The Institute for Genomic Research], that Venter was going to run. Initially, the whole thing was supposed to be one operation; Venter was going to do the sequencing for Human Genome Sciences, but they got into a big fight.

What I got a kick out of was that Ham Smith, who was working with Venter, thought of another way of doing the sequencing, which was better than the mapping technique we had developed. It was called shotgun sequencing. By this time, there were a number of camps. Lee Hood was trying to become a major moving force in the Human Genome Project, and on the other side of the country there was a guy named Eric Lander, who was trying to do a similar thing at MIT. And then there was Craig Venter, who was trying to do this as part of a company-type arrangement. So everybody was fighting with everybody else for the dollars and for the arrangement to do this and over how it was going to be done.

Now we're moving toward the middle of the nineties, and by that time we had been doing lots of mouse-genome and human-genome mapping and building these BAC libraries for other people to map and sequence. By this time, Lee had decided to move to Seattle and take his operation, which was doing lots of sequencing. Lee had been trying to sequence the MHC complex—the major histocompatibility complex. Actually, one of his students worked with us on mapping parts of the MHC. So Lee moved up to Seattle and Norman Davidson took over [in 1989] for a year as a caretaker, as interim chairman of the Biology Division. Lee was still trying to set up his sequencing operation within the University of Washington, which was having a hard job containing him.

COHEN: [Laughter] Well, he had a pipeline to [Bill] Gates, didn't he?

SIMON: The thought was that he had a pipeline to Gates, but apparently it didn't work out—there was a clot in the pipeline. But I don't know—I don't know that story.

The story I did know more about was the business of finishing up the human genome sequence. At that point, Lee had gotten estranged from the company he'd started, Applied Biosystems. Applied Biosystems was bought by another company, and his former postdoc, Mike Hunkapiller, was involved in Applied Biosystems. They were building new instruments, and they built a new sequencing instrument, and Venter realized that it would sequence much, much faster, and bought a whole bunch of them. And then Applied Biosystems and Venter went into cahoots, to finish the sequencing of the human genome, and that's when I got involved with Venter. He set up a company that was part of Applied Biosystems to finish the human genome. We kept advising him that this would never be a business. [Laughter] He might have known that it would never be a business. Then there were all sorts of anomalies in the human genome. The whole thing was a riot! The whole project was a riot!

COHEN: There were rumors about it—that somebody gave their genetic material to the genome. Is there anything to that?

SIMON: Well, what happened was—that was part of the funny business. We had decided that the only way you could make a true representation of the human genome was to use sperm, because sperm had the totipotent capacity to generate a whole organism. I mean, if you used white cells, lymphocytes, we know that lymphocytes rearrange their DNA, so we thought everything would be a mess and it would be rearranged. If you wanted to really be accurate, you'd have to use sperm. We had some fly-by-night operation, in which one of our technicians' husbands contributed the sperm to make these first library sets for sequencing. We kept his name secret, but we hadn't taken out a human-subject-protection policy. We hadn't followed the human-subject procedure because we didn't think of him as a subject—he was just a contributor. And at that time, it became very complicated. People who were contributing their tissues or their cells were suing for possession of their cells, because a company might use their cells to make a diagnostic that would make money. And the Human Genome Project was getting very complicated, because if you sequenced somebody's genome and found that he had a disease or that he had AIDS or something like that, and that person didn't know it—did you have a duty to inform him?

COHEN: I vaguely remember some of this.

SIMON: It got very complicated. We didn't realize that we had stepped into the middle of this until we went to a meeting where we were trying to push our method of sequencing. Eric Lander had another approach that he was trying to use, and he pointed out to us that we had not taken care to follow all the rules about human subjects.

COHEN: So he's the villain in this story?

SIMON: No, he wasn't a villain! He did this, I think, to slow us down, and it worked, because we had to stop everything we were doing. We went to the DOE and they told us what the rules were and how to follow them. So we worked all that out. We made arrangements with a sperm bank at UCLA—the sperm bank is right across the street from UCLA, and they have a multitude of donors. And they gave us donors from random samples of people.

COHEN: So you didn't use the technician's husband anymore?

SIMON: No. Well, we have some libraries from his stuff. Some of the stuff was sequenced from his DNA. But then we got random stuff, and we followed all of these rules, and all of this was set up here, and we were making all these [BAC] libraries. But Venter was moving ahead without having to make libraries, and he was succeeding. And then the NIH finally realized that if they were going to—I think part of it was competing with Venter—that they were going to have to get really serious about what they were doing. And I think to this day that if they hadn't been competing with Venter, the Human Genome Project would never have gotten finished. The notion of competing, the notion of wanting to do it before Venter did it, was really driving a lot of what happened. It finally got organized, and a couple of other people came into the area who were very good. So it was all very exciting.

COHEN: Where were you in all this?

SIMON: We were working away, building our BAC libraries here, doing the stuff for the DOE, sending them to central depositories. The libraries were sent out—mainly through the NIH human-genome group, which was sequencing different libraries. Venter asked me to be on the scientific advisory board of his company; so that's what I did—I ended up being on the advisory board of his company. [Laughter] And that was very funny. At the time, I saw Venter as the underdog—and he *was* the underdog. The NIH had a straight pipeline into Eric Lander's lab and a number of other labs, and the competition was really fierce. And then they finished it, which was nice. Then we went to see President Clinton, and that was nice.

COHEN: So who essentially won? NIH won?

SIMON: No, it ended up roughly a tie. Venter's informatics and systems were much better, I think, than the NIH's. The NIH guys packed together, though, at the last minute, and the publications—theirs and Venter's—came out neck and neck. The guys at the DOE acted as arbiters, and they declared a tie. And Clinton had both of them over, along with the guys from England, from the Wellcome Trust.

It was an interesting experience. You know, one of the things I'd always wanted in science was to be part of a community of scientists doing things together, and I thought the Human Genome Project would be that kind of thing, but it turned out to be dreadful, horrible, more competitive than anything else I'd ever been involved in.

COHEN: Is that because of the character of the people, or just that it was a competition?

SIMON: I don't think—even today—that biologists know how to do big projects. The physicists have figured this all out. Maybe it was because of [E.O.] Lawrence; maybe they had— **[Tape ends]**

Begin Tape 2, Side 2

SIMON: ...data-collecting projects and were able to assign credit; and people would really grow in these projects and do their part. But biologists have still not figured out how to do it. In fact, the latest debacle, after we finished with the Human Genome Project, I got out of that, and we decided to do G proteins, which was another area that I'd been working on, signaling—

COHEN: G proteins?

SIMON: Yes. A lot of the way we sense things in our body is through cell surface receptors. Cells are receiving signals from your bloodstream all the time—chemical substances—and one of the systems they use is called the G-protein system. There's a receptor on the surface of the cell that binds this signal. Your eye works the same way: There are photoreceptors that bind photons, and then they change, and that change is converted into a signal inside your cell, so your cell knows, "Aha! Photon hit the eye," which is converted eventually to an electrical signal to the brain. Or hormones are converted to a metabolic signal, which changes something in your body. We started working on those G-protein systems when I first came to Caltech, and we made quite a bit of progress in that area.

Well, five or six years ago a bunch of us decided we were going to do a project together, because the Genome Project had indicated that people could do large projects together. [Laughter] So we started this project with seven laboratories, and we got a lot of support from the NIH and a lot of support from pharmaceutical companies.

COHEN: Is that where I picked up this word "alliance?"

SIMON: Yes, the Alliance for Cellular Signaling. We put it together with six other laboratories, across the country. Besides the lab here, we had one in Texas, one at UCSD, one at Stanford, one at UCSF, one at Vanderbilt, and one at Berkeley. We were all collaborating and interacting with video, and we got a lot of money from the NIH. But the NIH didn't renew it this year. We're going through a re-convolution phase. Essentially what the NIH said is, "We don't really want to do these big projects. We want to support individual investigative type of stuff."

Biology isn't ready to do this big kind of stuff yet; we don't really have the infrastructure; we don't know how to reward our postdocs who are involved in these things, and this project didn't publish a lot. We published three major papers; one of them is still to come out, and I think it will have a major impact on the field. We have a huge Web site and all our data was made available as it was generated. We had a variety of community services we initiated and made available. We were moving to try to understand the whole network of signaling in the cell—which is much too big a project for any individual. But the reviews that came back said, "No, you haven't published a lot of papers. You haven't done work on the control of transcription"—you know, the usual NIH type of thing, whenever they want to move out of a system and they argue that it's a fishing expedition.

COHEN: I see. So that's in abeyance now?

SIMON: We're going to transition it back into a more conventional form of science, where we'll start keeping secrets. We won't tell our competitors what we're doing; we'll start competing; we'll try to be the first to publish, as quickly as possible. We'll publish a whole load of nonsensical papers. We'll do what we're supposed to do—the traditional way. [Laughter]

COHEN: Oh, too bad! Well, when did you become chair of the Biology Division?

SIMON: Oh, I forgot about that whole chapter, yes. [Laughter] So what happened, when Lee Hood left, Norman Davidson was chair for a little while. Then John Abelson took over and Abelson was chair for five or six years [1990-1995]. When Lee left, I think Eric Davidson thought he should be chairman and should be running the division. But Eric is very, very rigid in his ideas; he has very, very fixed ideas about what is important in science and what's not important. And really, the division couldn't sustain him as chairman. It became clear when people started talking to the provost that that would not work. So John took over, and John immediately got into a clash with Eric. It was difficult, because there was a faction that Eric interacted with and worked with, and there were other people, who were anti-Eric. This kind of thing happened for a while.

John was, I think, a good chairman. But then he had some difficulties in his own life. His marriage broke up, and he had a number of other problems while he was chairman. But he managed to have ideas about building up biology. It was clear that biology needed more space and needed room to grow and required a focus and a lot of new young energy. I was in England at a meeting when I got a call from John—rather, I got a call from my wife, who said, "John wants to talk to you. Your friend John is really going to mess you up. He wants you to be chairman of the division." And John talked to me and said, "You know, at this point, there aren't any young people who can take over the department. It really has to be in the hands of somebody who's going to open it up and not close it to focus it on one area of biology. If you don't do it, it's going to be a mess." I didn't want to be chairman, but I reluctantly agreed.

COHEN: And this would have been in what year?

SIMON: This was in '95. John had the chairmanship from '90 to '95. It was at the end of his term, and he had to move over. So I decided to do it. And it was important, because we were going to get a new president in a couple of years; there was going to be a search committee for a new president. We really needed to build a new building. There was talk of an initiative for biology, which was going to try to raise some money to give biology a boost, and I felt that that was an important thing to do. So I did it and I think we were pretty successful. Development finally ended up raising $100 million for a new building and for a new initiative in biology, "Beyond the Genome."

COHEN: So you essentially were, not in charge of it but the chair when all this was going on. That must have taken up a fair amount of time.

SIMON: Yes. It really began to eat up my time, and it took me away from a lot of the research we were doing. At the same time, our company was prospering, so that was nice, and the lab was still quite productive during that time.

I think we did OK for Caltech. I was very intent on hiring, because I felt we had no young people. And it's true that some of the people we hired haven't worked out.

COHEN: How many people did you hire?

SIMON: Well, we hired—

COHEN: These were assistant professors?

SIMON: These were assistant professors. I think Raymond Deshaies came before I came aboard. But then we hired, let's see, three assistant professors, and one of them was not going to make it. But the others did fine, are doing fine. Well, mainly I got interested in systems biology at the time. I started talking to people. We were doing the G-protein stuff, and I'd become interested in computational biology. With the bacterial flagella system, a small system, we could begin to develop network models for how that system worked. I started talking to [John J.] Hopfield and some of his students. And we had a sabbatical visitor who took this up.

COHEN: Who was that?

SIMON: Dennis Bray. He was British; he did a lot of stuff on the network modeling. And there were a number of other groups. [Stanislas] Leibler, at Princeton, began to build computational models for bacterial chemotaxis, and I was dying to hire his student, Uri Alon, and I just about got him. I remember he was in my office and I said, "Uri, you've got to come here," and he agreed. We'd raised $1 million to set him up. For an assistant professor at that time, that was a hell of a package—we were competing with the Rockefeller and the Weizmann Institute. And he said, "OK, give me five minutes and I'll tell you what I'm going to do." And when I walked back into the room, he said, "I can't do this. I've got to go back to Israel." And he's done very well. He would have been great here.

But then we got [Michael] Elowitz, who's done very well, too. So we're making some strides in systems biology at Caltech. That's what we had hoped the Broad building would do, but there weren't enough people—that whole area hadn't developed enough to really seed a whole building.

COHEN: So what's going on in the Broad building?

SIMON: Well, there's some systems biology and computational biology going on on the bottom floor. There's a lot of structural biology, structural stuff, going on. And at the time, the neurobiologists said.... You know, we felt that neurobiology was going to be the great future of Caltech—we had a lot of strength in neurobiology. But for some reason, that hasn't happened.

And also, the mouse genetics and mouse behavior was going to go on. But we haven't been able to hire anybody in mouse behavior yet.

COHEN: Were you involved in [David] Baltimore's [Caltech president 1997-2006] coming to the institute? How did that work?

SIMON: That was great. Kip Thorne [Richard P. Feynman Professor of Theoretical Physics] was really wonderful. It was a real coup to get Kip Thorne to run that search committee for the new president.

COHEN: Were you on the search committee?

SIMON: No. I was a division chairman [1995-2000], so I couldn't be on the committee. But I made sure that a couple of people who were good biologists and chemists were on it—David Anderson and Doug [Douglas C.] Rees. When I was chairman, I spent most of my time trying to keep people here. When Lee was here, a lot of people left, and that was continuing. So most of my time was spent not so much recruiting people from outside but making sure that people didn't leave who were really good. There were a lot of young people, like Pamela Bjorkman and Elliot Meyerowitz and David Anderson, for whom I ended up spending most of my time trying to find real estate. [Laughter] And dealing with the provost. But we were able to keep some of these guys, and I think it was critical to have people like Anderson and Doug Rees—Doug Rees was another one we really had to bend over backward to keep here, both chemistry and biology jointly.

There were some really good people on that search committee, and Thorne had a taste for the kind of talent, the kind of intelligence, that would mesh with Caltech. And when they started looking at David, David had just been through this whole terrible thing with Congress, and his friends had thrown him out of the Rockefeller University and he'd gone back to MIT. And everybody said he was looking for something else to do that was big. I knew him from the Salk Institute and he was great. But there were a number of people on our faculty who, if this search had been operated in a different way, would have sabotaged it for sure. But Kip did this wonderful thing. He took the whole search off campus; it was all done on the Westside, in a hotel. The candidates were brought in and interviewed offsite. The trustees were brought in, one at a time, to meet with these people. It was all done wonderfully, with absolute confidentiality, which at Caltech is unheard of.

I called Baltimore a couple of times—Kip asked me to call him and talk to him. And I think one of the things that was a deciding factor in his coming here was that he asked me whether the division would allow him to be a faculty member and maintain a research laboratory while he was president. And I said, "No problem!" [Laughter] He is one of the star performers in the Biology Division. He can be that without any difficulty. And he has.

COHEN: So you don't think he's neglected his presidential duties.

SIMON: Oh, no way! He's a really bright, wonderful guy, in terms of being able to be with it. I don't know how you can rate him as a president, but in terms of being able to do biology, to run the campaign, the presidency.... When he first came in, we were doing this Beyond-the-Genome thing, and it was up to David to close on a donor for the building and the rest of the campaign—this was the small, $100-million campaign. And he made very good friends with [Eli] Broad and brought Broad in as the prime donor. I think he did a very good job of that. At that point, I didn't want to be chairman anymore, and that worked out fine, because Elliot [Meyerowitz] was ready to take over.

COHEN: Did you have any serious problems while you were chair, anything disruptive?

SIMON: Oh, all sorts of things. [Laughter]

COHEN: Any that you'd like to mention?

SIMON: Well, there were a number of problems, nothing out of the ordinary—nothing more than, you know, professors fooling around with their students. The usual type of stuff.

COHEN: OK. So you think Baltimore has been good for the institute?

SIMON: I think David's been good for the institute. I'm not sure how good he's been in terms of the financial status of the institute, and I'm not sure how good he's been in terms of the machinery, of running it. But in terms of representing the institute, and in terms of the ideas, and in terms of the initiatives that have occurred here, I think he's been very good. His sense for what's happening in biology is terrific. I think his sense of science is very good; his ability to grasp science is very great. It would be great if he had a really first-rate COO—chief operating officer.

COHEN: Like a provost or something?

SIMON: Well, more like what a chief operating officer does in a company—to make sure that all the operations are working. And that means drilling down into the nitty-gritty—what the property department is doing, what the investment group is doing—and keeping all of these guys up to snuff. I don't think that that's necessarily the job of a president, and I don't think a provost can do that. I think you really need a chief operating officer.

COHEN: Do other institutions have one?

SIMON: I don't know. Sometimes I think the financial officers do that; I think it's part of the finance department. And we've had these terrible troubles—

COHEN: They seem to come and go.

SIMON: I think [Albert] Horvath was a good one [vice president for business and finance]. But the one before that, the one under Everhart—oh, he was a joke! That was so bad, I just could not believe it. He instituted this whole computerization of the—

COHEN: Oh, that was a disaster.

SIMON: When I first heard it, when I went to this retreat, I said to Everhart, "We're going to waste $35 million; it's just going to be thrown out. Levi, the jeans company, just tried to do this and they lost $100 million." Well, I was wrong; we lost $60 million.

COHEN: [Laughter] So this past year, you decided you'd really had enough, and you became emeritus.

SIMON: Yes, that's nice. I like it, because now all I do is my research, and that's a very nice thing. Caltech lets you sort of glide into emeritus. I'm gliding!

COHEN: So you spend half your week in San Diego now?

SIMON: Yes. I think it's working out well. My biggest problem, in all my career, has been how to end things; I have a very hard time wrapping things up. We're still doing things in bacterial chemotaxis, which I nominally stopped twenty years ago.

COHEN: Do you have graduate students and grants?

SIMON: No graduate students. I have a lot of grants. Even with this Alliance thing, they will continue to fund us for another three years. Probably altogether I have about $1.5 million in direct costs and fourteen or fifteen people working.

COHEN: So you still have plenty of money.

SIMON: Money, people, I even have a few ideas.

COHEN: [Laughter] So has this been a good experience being here at Caltech? How have you found Caltech all of these years?

SIMON: I can't think of a better place to do research in the world. It's been a really wonderful place to do scientific research. I can only be grateful for it—for the opportunity. You know, things happen, and they don't seem to happen continuously; they happen discontinuously. Last week, Ben [Benjamin F.] Biaggini, the guy who donated the money for my chair, passed away. So it's just strange. And then this Alliance thing is ending. A number of things are coming to an end.

COHEN: But then, of course, you've got your business in San Diego you want to devote yourself to, I gather.

SIMON: Well, a little bit of that. What I've been thinking about in the last couple of weeks is seeing if I could just postdoc with somebody in San Diego and get back in the lab. Maybe biology should never be big. Maybe biology isn't like physics; maybe biology should be small.

The other thing that's been really great is that since we did very well with this Agouron Institute, we've been funding all kinds of research all over the world. We're funding a big project in Chile—I was just down in Chile working with oceanographers. And we're going to the Bahamas with a bunch of geologists. And next year, we're going to have a big meeting on oxygen, and we're doing another project in Africa.

COHEN: So you've managed to do all these different things.

SIMON: Yes, it seems like that. If I have to sum up, it seems like I've never had any focus. [Laughter] Or maybe too many foci. I want to thank you for this opportunity. It's really been interesting for me just to sit here and talk about myself. Fortunately, or unfortunately, I don't do that very often.

[Tape turned off]