SCIENCE HISTORY INSTITUTE

MARTIN KARPLUS

Transcript of an Interview
Conducted by

David J. Caruso and Roger Eardley-Pryor

at

Harvard University
Cambridge, Massachusetts

on

9 December 2015 and 4 March and 25 May 2016

(With Subsequent Corrections and Additions)

Martin Karplus, interview by David J. Caruso and Roger Eardley-Pryor at Harvard University, Cambridge, Massachusetts, 9 December 2015 and 4 March and 25 May 2016 (Philadelphia: Science History Institute, Oral History Transcript #0962).

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MARTIN KARPLUS

1930	Born in Vienna, Austria, on 15 March

Education

1950	BA, Harvard University, Physics and Chemistry
1953	PhD, California Institute of Technology, Chemistry

Professional Experience

	Oxford University
1954-1955	Postdoctoral Fellowship, with C.A. Coulson
	University of Illinois
1955-1957	Instructor
1957-1960	Assistant Professor
1960	Associate Professor
	Columbia University
1960-1963	Associate Professor
1963-1966	Professor
	Harvard University
1966-1979	Professor
1979-1999	Theodore William Richards Professor of Chemistry
1999-2004	Theodore William Richards Research Professor
2004-present	T.W. Richards Professor Emeritus of Chemistry
	Université de Paris-Sud
1972-1973	Professeur Associé
1980-1981	Professeur Associé
	Université de Paris VII
1974-75	Professeur
	Collège de France, Paris
1980-1981	Professeur
1987-1988	Professeur

	Université Louis Pasteur (now Université de Strasbourg), Strasbourg, France
1992, 1994-95	Professeur Associé
1995-present	Professeur Conventionné
	Oxford University
1999-2000	Eastman Professor

Honors

1947	Westinghouse Science Talent Search Scholarship
1965	Fresenius Award of Phi Lambda Epsilon
1966	American Academy of Arts & Sciences
1967	National Academy of Sciences
1967	International Academy of Quantum Molecular Science
1967	Harrison Howe Award, Rochester Section, American Chemical Society
1979	Award for Outstanding Contribution to Quantum Biology, International Society for Quantum Biology
1986	Distinguished Alumni Award, California Insitute of Technology
1987	Irving Langmuir Award, American Physical Society
1991	Foreign Member, Royal Netherlands Academy of Arts and Sciences
1991	National Lecturer, Biophysical Society
1993	Theoretical Chemistry Award, American Chemical Society, Innagural Recipient
1995	Joseph O. Hirschfelder Prize in Theoretical Chemistry, University of Wisconsin
1998	Doctor Honoris Causa, Université de Sherbrooke
1999	Master of Arts (Honorary), Oxford University
2000	Foreign Member of the Royal Society, UK
2001	Computers in Chemical & Pharmaceutical Research Award, ACS
2001	Anfisnen Award, Protein Society
2004	Linus Pauling Award, Northwest Section, American Chemical Society
2006	Ehrendoktorat, Universität Zürich
2007	David L. Weaver Lecturer in Biophysics and Computational Biology, (first recipient)
2008	Lifetime Achievement Award in Theoretical Biophysics (IASIA)
2009	G.N. Ramachandran Award Lecture, Indian Biophysical Society
2010	Russell Varian Prize
2011	Antonio Feltrinelli International Prize for Chemistry from Accademia Nazionale dei Lincei
2013	Foreign Fellowof the Royal Society of Chemistry
2013	Nobel Prize in Chemistry
2014	Commandeur de la Legion d'Honneur
2014	Doctor Honoris Causa, Bar-Ilan University

ABSTRACT

Martin Karplus was born in Vienna, Austria, one of two sons. Karplus' father was in banking; his mother was a dietician at the family's Fango-Heilanstalt Clinic. During the Nazi occupation of Austria, the family moved first to Switzerland, then to the Boston, Massachusetts, area. Always competing with his older brother, Martin used a microscope to study rotifers in drain water, the beginning of his interest in observing many aspects of nature. He began birdwatching, eventually attending the Lowell lectures and joining the Audubon and Brooklyn Bird Clubs. He won the Westinghouse Talent Search with his research on hybrid gulls, which presented the opportunity to meet President Truman.

Following his brother, a physicist, Karplus entered Harvard University to study physics and chemistry. He spent a summer at Cornell University studying bats with Robert Galambos and took a trip to Alaska to study plovers' migration patterns, adding his own study of robins' feeding patterns. During his time in Alaska, Karplus began a lifelong hobby and passion for photography. He worked on retinal with George Wald and Ruth Hubbard, wanting to know how things work rather than to go into medicine. His last class at Wood's Hole Oceanographic Institute convinced him he was not an experimentalist.

For graduate school Karplus worked with Linus Pauling at California Institute of Technology (Caltech), where he realized importance of intuition. He discovered the molecular mechanics of bovine pancreatic trypsin inhibitor (BPTI), though he never published his dissertation. From California he went to Charles Coulson's lab at the University of Oxford. There he wrote his first chemistry publication. He was among the earliest nuclear magnetic resonance (NMR) scientists, having to use homemade equipment. His first faculty position was at University of Illinois, where he developed the Karplus equation, dealing with spin-spin coupling, and wrote a paper on the quadrupole moment of hydrogen. Karplus then went to Columbia's IBM Watson Laboratory, where he and Richard Porter developed the Porter-Karplus surface. Continuing his five-year plan, he took a job at Harvard and returned to biology. He began the CHARMM program to study molecular dynamics simulations. He, Michael Levitt, and Arieh Warshel were awarded the Nobel Prize for the development of multiscale modeling for complex chemical systems, which Karplus says could not have happened except for their work using the mixture of quantum and classical mechanics.

In his interview Karplus discusses his ability to visualize things; his love of birds; his gift for photography; his appreciation of European culture. He describes the Weaver lecture he gave, his "Marsupial talk." He says some of his work did not advance science until later; that it is important to avoid dead ends, that understanding the essential elements of a problem is crucial. Karplus acknowledges the influence on his work of the ever-increasing power of computers; the largest user of National Energy Research Scientific Computing Center (NERSC) computers is molecular dynamics simulations. He shares memories of the Nobel Prize ceremony and reception, as well as the impact the Prize has had on opportunities for himself and for others. He decries some aspects of academic research, but he maintains that it is still preferable to industry research.

INTERVIEWERS

David J. Caruso earned a BA in the history of science, medicine, and technology from Johns Hopkins University in 2001 and a PhD in science and technology studies from Cornell University in 2008. Caruso is the director of the Science History Institute's Center for Oral History, president of Oral History in the Mid-Atlantic Region, and the book review editor for the *Oral History Review*. In addition to overseeing all oral history research at the Institute, he also holds an annual training institute that focuses on conducting interviews with scientists and engineers, he consults on various oral history projects, like at the San Diego Technology Archives, and is adjunct faculty at the University of Pennsylvania, teaching courses on the history of military medicine and technology and on oral history. His current research interests are the discipline formation of biomedical science in 20th-century America and the organizational structures that have contributed to such formation.

Roger Eardley-Pryor earned his PhD in 2014 from the University of California, Santa Barbara (UCSB). At UCSB, he became a National Science Foundation graduate fellow in the Center for Nanotechnology in Society. Prior to that, Roger earned his B.Phil. in Interdisciplinary Studies from Miami University in Ohio. As a historian of science, technology, and the environment, Roger taught courses at Portland State University, at Linfield College in Oregon, and at Washington State University in Vancouver, Washington. From 2015-2018, Roger held a postdoctoral Research Fellowship in the Center for Oral History at the Science History Institute (formerly Chemical Heritage Foundation). His work explored ways that twentieth and twenty-first-century scientists and engineers, culture-makers, and political actors have imagined, confronted, or cohered with nature at various scales, from the atomic to the planetary. In 2018, Roger joined the Oral History Center in the Bancroft Library at the University of California, Berkeley.

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INTERVIEWERS: **David J. Caruso**
Roger Eardley-Pryor

LOCATION: **Harvard University**
Cambridge, Massachusetts

DATE: **9 December 2015**

CARUSO: Today is the ninth of December, 2015. This is David Caruso. I'm here with Roger Eardley-Pryor. We're interviewing Dr. Martin Karplus for an oral history interview at his office at Harvard University. Thank you again for agreeing to take time—take the time to sit down with us. As Roger mentioned, you know, we want to start at the very beginning, so we'd like to hear a little bit about—we know that you were born in Vienna, Austria, in October of 1930.

KARPLUS: Actually, I was born on March 15, 1930.

CARUSO: Oh.

KARPLUS: Which plays a role. We came to the US [United States of America] in October of 1938.

CARUSO: Okay.

KARPLUS: Maybe that's what—

CARUSO: A little confusion there. Okay.

KARPLUS: Yeah.

EARDLEY-PRYOR: Yeah. Thank you.

CARUSO: So can you tell us a little bit about your early life, your family, what your parents did, grandparents did, in Austria?

KARPLUS: Maybe beginning with my grandparents. On my mother's [Lucie Isabella Karplus] and my father's [Hans Karplus] side, actually, both of them were physicians. They—on my mother's side—came from Odessa [Ukraine] to Austria, and on my father's side, they came from what used to be Czechoslovakia, [from Hotzenplotz] a small town where there are still people with the same name, actually, living there.

And my grandfather [Samuel Goldstern] on my mother's side came to Vienna, [Austria] from Odessa at the time—which was a big port in Russia. It was one of the biggest ports. And his family had handled export/import there for the Russians. And at various times there were pogroms that occurred there. And it was actually before one of them, just before one of them, that they became aware—it was at the time of the Battleship Potemkin Revolt, that they managed to leave very shortly before anything happened.[1] So he and his family, actually, there were thirteen living children, which was very unusual for those days, that they—I think two died, and all the rest survived. And it was a wealthy Jewish family, which was completely accepted at that time, though there were these pogroms at various times.

And they managed to leave, most of them, and come to Vienna. And in a way, they left just before something happened, the way I left Vienna, again, just before things really got very bad for Jews. He came to Vienna, and finished his medical studies at the University of Vienna—I don't know whether you want me to go into this much detail . . .

CARUSO: Sure.

EARDLEY-PRYOR: Yes, please.

KARPLUS: At the University of Vienna. And then he began working at a clinic, a private clinic, which he took over after a number of years, and that was called the Fango-Heilanstalt. And it basically dealt with rheumatic diseases, and used the radioactive mud, which was called Fango—I knew that it was called the Fango and that they used this, but I didn't realize that the word was actually Italian and just meant mud.

He took it over, and two of their children, actually, my mother worked there as a dietician, and one of my aunts [Lene Goldstern], who was a physician, worked there as a sort of in-house physician. And then there was another daughter, Claire, and a brother, Alex, who

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[1] The Battleship Potemkin Revolt occurred in June 1905 when the crew, refusing to eat rotten food, turned on the ship's officers, killed the captain and seized control of the ship. The crew spent the next eleven days in an attempt to spark a rebellion against Czar Nicholas II.

actually studied chemistry. And so there was this intellectual atmosphere. **<T: 05 min>** There was a sister, Eugénie Goldstern, who became a relatively famous ethnologist, and was one of the few close members of my family who were deported and died in one of the concentration camps. My Uncle Alex, when the Nazis came in, he was put into a concentration camp, and somebody came to my grandfather and said, "Look, if you sign the Fango over to me, the Nazis will release him." And my grandfather did, of course, and—it was signed over—fortunately whoever the person was, I don't know his name, kept his word. The only thing he said was, "Well, your uncle has to leave Austria within a week," which made it impossible for him to get a visa to come to the United States, which was rather complicated. He went to New Zealand, where he lived during the war, and then he came back [to Vienna] after the war. He got the Fango back, and administered it until he died. Then it became part of the Viennese hospital system. It still exists, and it still functions, and I visited recently.

As an aside, somebody's making a film about me, about my life, and so we went there and visited it. My other grandfather [Johann Paul Karplus] was a professor of neurology at the University of Vienna, and he is well known for discovering the function of the hypothalamus. He did experiments in which he took a cat and anesthetized it, and removed all the nerves that came out of the hypothalamus, and observed when he stimulated it, the cat still reacted, with its eyes either open or closed. I don't remember which.

He deduced that it wasn't nervous excitation from the nervous system, but rather that it was some sort of fluid that did this. More recently people have studied this [reflex], and apparently, the hypothalamus is the only part of the brain that actually has cells that can synthesize hormones, confirming everything he found.

And his wife, Valerie Karplus, came from the [von] Lieben family, which was a very well-known family in Vienna. And one of her cousins, I think—I would have to check—Robert von Lieben is the person who invented the diode, according to European standards. Here, it's Lee de Forest who invented it. And there was actually a long patent fight, which the family lost. But they were still relatively well off on both sides, when we lived [in Vienna]. And he is on an Austrian postage stamp. [. . .] Anna Lieben [my great-grandmother], was actually one of Freud's first patients, and—because many intelligent women were not allowed to do anything, they became "neurotic," which isn't surprising. And also—well, maybe that's enough of this, there are lots of things to be able to say.

CARUSO: Do you know what brought your grandparents to Austria to begin with? I mean, you mentioned that they were fleeing—but why Austria?

KARPLUS: Well, Austria was very close. Of course, this was the Austro-Hungarian Empire, **<T: 10 min>** of which much of this area was part of at the time. And it was a place where Jews were accepted at the time. Vienna has two million people. It was a major capital of a very large empire. And it was just the area where there was a lot of intellectual ferment there. One can go through all the people who lived there in the late 1800s, early 1900s, when this all happened.

The medical school was known to be a very good school, and so it was the attraction of having—they had to leave, and it was was very close. It was really just going across the border to get to Vienna, so that it was easy to get there.

As far as my paternal grandfather's side is concerned, I don't know exactly why they left Czechoslovakia, and I'm still looking into this, in terms of I am writing—so there's a film being made about me, which this is an aside. In addition, I'm trying to flesh the "Spinach" article into an autobiography and so I'm looking up all these things.[2] One of the reasons I accepted to do this, to be honest, is I thought it would be helpful to have this opportunity and get some insight, in terms of what was of interest to you. [. . .]

EARDLEY-PRYOR: How did those two sides of the family come together, between—how did your mother and father meet?

KARPLUS: Well, the sort of relatively wealthy, intellectual families were a relatively small group, and they were interacting. And actually, both of them, my mother and father, went to study physics at the University of Vienna. My mother worked as a dietician after they both stopped their studies. I think it was partly because we were very well off, and there wasn't sort of any pressure to do anything. I'm not absolutely sure whether they met when they were students, or—but their large families, and cousins and such, were related, so they met one way or another. It's an interesting question, but I don't know the answer.

EARDLEY-PRYOR: How long after they met did you and your brother arrive?

KARPLUS: After they were married [in 1923], it was, you know, my brother was born in '27, and I was born in 1930. [. . .]

EARDLEY-PRYOR: So do you have other siblings, aside from you and Robert?

KARPLUS: No, there's just the two of us.

EARDLEY-PRYOR: The two brothers?

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[2] Martin Karplus, "Spinach on the Ceiling: A Theoretical Chemist's Return to Biology," *Annu. Rev. Biophys. Biomol. Struct.*, 35 (2006): 1-47.

KARPLUS: And he died some years ago. He was actually jogging in Central Park. He was visiting New York [City, New York]. He was a professor at [University of California] Berkeley. And he had a heart attack, and he wasn't found soon enough, that his brain—that he lost blood to his brain. He never really recovered, and lived for a number of years, and I would visit him regularly. He was making a very great effort to recover, but he realized in some sense that he had lost what he had been, an outstanding physicist. And he was very angry often that he just didn't have this anymore. I don't know how much of this you want to put in there, but anyway—

EARDLEY-PRYOR: Maybe we can revisit that—

KARPLUS: [Yes].

EARDLEY-PRYOR: —as we get through. **<T: 15 min>** I'm interested in your experiences as a young child with all these family members, these aunts and uncles from—especially from the Goldstern side of the family. What was it like being a child with having so much family around? Was that the case?

KARPLUS: Well, it was wonderful. We used to get together while we were in Vienna. We used to for various holidays, and, in Vienna, we'd celebrate them together. We were what is often called "Christmas-tree Jews," which meant that we actually had a Christmas tree, Tannenbaum, and so we'd get together for that. And often on weekends, we would be invited to mainly my maternal grandparents' side, the hospital where they lived—actually lived in the hospital—and they'd have all kinds of wonderful pastries, Viennese pastries being well-known. And so it was really a very warm atmosphere.

One thing of interest, I mentioned my aunt [Eugénie Goldstern] who was an ethnologist, and she was very much interested in children's toys, and so she would always be there—she lived also in the Fango; she never married—and bring these toys down and observe us as we played with them. Then in the summers, every summer we would go in large family groups on vacation, either on some of the lakes in Austria—one time we went to Adria, in Italy, always where there were waters, because everybody liked to swim or go out in boats. So I think it was very important for me, particularly, when we had to leave because of the Nazis, that I'd had this background of really having a wonderful circle of people, supportive people.

EARDLEY-PRYOR: Did your mother or father work while in Austria?

KARPLUS: Yes, my mother, after they stopped going to school, my mother worked as a dietician in the Fango, and my father was mainly involved in banking, because particularly on my grandmother's side, the Lieben family, they had large holdings. So he mainly was involved in that.

CARUSO: You mentioned—well, there are two things I'm curious about. Your paternal grandfather, clearly, he was doing medical research. Was he also an active practicing physician?

KARPLUS: I don't think so, actually. I think he was a professor. He was teaching. But he wasn't a clinical professor. I'm not absolutely sure of that, but I think that he was mainly doing research and teaching at the University of Vienna, which—and why were they both doctors? My maternal grandfather—Uncle Samojla as we used to call him, who, according to the people he worked for, was somewhat of a tyrant, but as far as we were concerned, he was a wonderful grandfather—had started to study medicine in Odessa, and then finished his studies [in Vienna]. And what I started to say was that being a doctor or a lawyer were some of the professions that were open to Jews, while many other professions weren't open to Jews. So whether that influenced them I don't really know, but I think it was an important point in what happened.

CARUSO: Part of the reason I asked is I'm also curious to know whether or not your grandparents exposed you to any form of science when you were a child. Did you get to go into a lab with your grandfather, or did you go through the Fango when you were visiting family and see things that were going on? I was just wondering about exposure.

KARPLUS: I think the answer is no, **<T: 20 min>** in the general sense, though as I think I mention in here there was a tradition, particularly on my mother's side, that somebody would become a physician going back quite a few years.[3] I was the only one, unlike my brother and my various cousins, who showed any interest in medicine, and what I think I wrote in there is that I used to go around bandaging chairs and such. But that wasn't really that I was exposed to that. I did have a uncle, Paul Wermer, who was a very good clinician, and his wife was a dentist, and I would visit them, and sometimes he would talk to me about medicine. This continued later on, when they came to the—they managed to come to the United States, and they lived in New York, and I would visit with them, and he would talk to me about the exciting new things that they learned, when I was still in junior high school and high school.

EARDLEY-PRYOR: The being born Jewish and having this history of fleeing, multiple occasions, I'm wondering, the importance of the Jewish religion versus the Jewish culture in your family. Was Sabbath something, and the high holy days, attending—

[3] Karplus, "Spinach on the Ceiling."

KARPLUS: No.

EARDLEY-PRYOR: It was not a part?

KARPLUS: No, there was a certain pride in being Jewish, but it was secular Judaism. We never—the first time I ever was in a Jewish temple was in the United States, when I was invited after winning the Westinghouse scholarship, to give a lecture there. As I remember, my lecture was something about, "Is there a God,"—I was never invited again. [laughter]

EARDLEY-PRYOR: You've written about a nanny that you were fond of. Can you tell us a little about her?

KARPLUS: Mitzi.

EARDLEY-PRYOR: And her name was?

KARPLUS: Mitzi. [. . .] And most children [in well-off families], particularly because both my parents worked, had a nanny in those days. I spent a lot of time with her, and we would play together, and on the weekend my mother would play with us, but during the rest of the week, we mainly either went to kindergarten, or played with her. And she was not at all intellectual or anything. It was just a warm—again, a warm, supportive feeling, that was part of you, like the large family.

Our Mitzi, we didn't know after the war, but the one who was the equivalent for my cousins, Gus and George, the children of Lene, who was the physician aunt and became a psychiatrist when she came to the US, she continued contact after the war. And we tried to help her but what happened to my Mitzi, or our one—I don't really know. I don't think we had any contact with her after the war.

EARDLEY-PRYOR: Was she involved in both your and Robert's young childhood?

KARPLUS: She was with our family for a long time and was another element of living in an environment where I always felt at home, which I think played a very important role in spite of losing everything when we came to the US.

EARDLEY-PRYOR: When the Nazis came through in ’38, during the Anschluss—before that time, was there a sense of rising anti-Semitism in this cosmopolitan Vienna that you remember as a child?

KARPLUS: **<T: 25 min>** Yes, I didn’t personally realize something until—well, it was before [Adolf] Hitler came in or was welcomed in, and that my parents had this awareness, and my Aunt Claire—who was the youngest one—had been to England, and had learned English, and she gave my brother and me English lessons. And my parents were already thinking about the need to leave, and that something would come up. And we also found that at a certain stage it was fairly late. It was probably just in ’38 that a teacher that I had had—here I don’t know what happened with my brother—who was Jewish—there it is [*looking at “Spinach on the Ceiling” article*]. He was a very good teacher, and also was very popular, because his wife had a candy store, so whenever people did well, he would give them rewards.

And the parents had gotten together—this was when I was in first grade—and suggested that they would like him to continue, basically, that he would teach the next grade to us, which he did, but then before Hitler actually came in, he was dismissed. Then we got another teacher who was very anti-Semitic, and so finally my parents took me out of school, and they worked with me at home. But that wasn’t a very long period. But that was one sign.

The other sign was that we lived at what was at that time the edge of Vienna, and very close to us, there was the—I don’t know quite what it would be called. It was a place where the streetcar [lines] ended, and where [they were] stored—and there were two brothers who were the same ages as I and my brother were. They were our best friends, really, and they were not Jewish, and they were children of somebody who worked there at the—and at a certain stage, it was not very long, but maybe in ’37, they stopped playing with us, and called us dirty Jews and such. And we didn’t really understand why this happened, but we were very upset by it, and . . .

EARDLEY-PRYOR: Do you remember speaking with your parents about that and asking them, or talking with Mitzi about that?

KARPLUS: I don’t really remember. It’s very likely that I did, but I don’t really remember.

EARDLEY-PRYOR: Were your parents—I guess how were your parents in your eyes, as a child, in your memories, responding to some of these transitions? Were they protective of you? Was it . . .

KARPLUS: Well, they tried to somehow have us believe that nothing was really going on, and that everything would be all right. And—but they had also prepared a reservation in Zürich

[Switzerland], where [we were supposedly going on a ski trip] and had gotten me a passport, which I still have somewhere, with the idea that we would leave Austria very shortly, and made train reservations, and basically we left three days after Hitler came into Austria. All of this had been prepared, so this was going on.

But this, of course, is not quite correct. My father was not allowed to leave, because the Nazis—Austrian Nazis in many ways were worse than the German Nazis, at least in the early days. And like there's this story that my grandfather, who had the **<T: 30 min>** Fango, had to come out, and people had written things on the sidewalk about Jews, and he had to get down on his hands and knees and wash this all off, and various degrading experiences. It's not absolutely sure. My cousin Gus, who is a year older than my brother, thinks he knows that this is true, but it's not absolutely sure, but there had been all these things going on. But in terms of my knowing about it, I think my parents were very protective.

As I started to say, even though we had prepared to leave, the family together, my father was not allowed to leave, and he was actually thrown into jail in Vienna. And thanks to the Nobel Prize [in Chemistry, 2013], one of the ministers of the Austrian government stopped in to see me, and so he sort of asked offhand, "Well, what can we do for you?" And I said, "Well, I would be very interested to find out exactly what happened with my father when he was in jail in Vienna." And like good Germans, you know, there was a detailed record of every transaction that had happened, how he had signed over our house, he had signed—we had a little car called a Steyr Baby, which also plays a role in my story. Just everything was recorded. And it was basically only when he had signed over everything that he was allowed to get out of prison.

I know that my Uncle Edu [Eduard Karplus], who was already in the US, and worked for General Radio, and invented the variac, had gotten the head of the company, Mr. Eastham, to give us an affidavit, you may or may not know, to come to the US at that time, you had to have somebody who guaranteed that you wouldn't become a ward of the state. And he guaranteed this. And then once we were in Switzerland, we had to wait for our visa, and it wasn't clear whether my father would get out of jail or not. And the one part of the record that isn't complete is that my Uncle Edu gave five thousand dollars to somebody in the jail, which was instrumental in letting my father get out. Now that isn't recorded anywhere. So who got that money? We don't really know. But anyway, he was able to get out, and then when we finally got the visa and booked passage to the US, miraculously almost, my father joined us, and we came to the US together.

And so, this is really answering your question that—my mother always said, "We will go to the US together," and in my memory, the experience in Switzerland, and then we spent the summer [in a board room in La Baule, France] before we finally got passage to go to the US in October, and I remember all this as being a wonderful time in our life. I wasn't aware that my mother must certainly have been terribly anxious about what would happen to my father.

[My wife] Marci thinks that I must have had some awareness of this, but in terms of what I remember, we had a fun time at the school we went to in Switzerland, and learned, my brother and I, learned Schweitzerdeutsch, which is relatively hard to understand, [even if one knows German]. And when we were at home, if we didn't want my mother to understand, we would speak that. So I have all these good memories, and **<T: 35 min>** whether I was somehow aware of this, I don't really know.

CARUSO: So you didn't witness your father being arrested? You just knew—

KARPLUS: No, no. He just couldn't come with us.

CARUSO: Okay.

KARPLUS: And so I knew he was in jail, but—one of his attributes, which I think played a very important role in my life, was that he always had a positive view of everything that happened, and when he joined us, he described how he had taught his jailers to play chess, and had chess competitions. And this was true of everything that he did, that he found interesting, positive things, and that I think has played a big role in my life, that I've been able to—when there were problems or whatever—surmount them.

EARDLEY-PRYOR: Do you have memories of—or understanding— what happened to some of this extended family? All of these aunts and uncles and cousins that were on the Goldstern side, or from the Karplus side, that you knew as children?

KARPLUS: I think we were very, very lucky, and except for my great aunt, who was the ethnologist, who stayed in Vienna partly to take care of one of her brothers, who was quite ill, and then when they went walking and disappeared. That's all we know. We know where she was killed, in Sobibor, [Poland], in the concentration camp there. And there's a whole story connected with that, but I don't think it's really germane.

EARDLEY-PRYOR: When around the time did you have a sense of what had happened? When was it at a point where you became older, where your parents told you a little bit more about what you had really gone through?

KARPLUS: That was after we arrived in the US, and so it was probably 1940 or so, when—'40, '41—we moved to Newton, [Massachusetts], and there was this business that we bought this house in Newton, a small house. The person who bought it from my brother and me after my parents had died is still living there. I didn't really know this, but then I gave a talk at BU [Boston University] to some students, that one of my former students asked me to give—one of the things I've done with the Nobel Prize is to give talks to groups of disadvantaged students, to try to inspire them in terms of science—and there somebody came up to me and told me, “Well, you know, I’m the person who bought the house from your parents, and we’re still living there,” and invited us to visit it. When we were there filming my life story, they unfortunately weren’t home. We were probably the first Jewish family in Newton, even though now it’s one of the places where many Jewish families live. It has a whole Jewish culture. Our neighbor—the story is that an FBI person came to our house, and very apologetically said [to our father], “Look, your neighbor has told us that every morning before you go off to work you sort of face the house and do ‘Heil Hitler.’” This was our next-door neighbor. And the FBI agent said, “Well, it doesn’t make any sense to me, but it being during the war and everything, I have to—”

EARDLEY-PRYOR: As refugees?

KARPLUS: **<T: 40 min>** “I have to investigate this.”

EARDLEY-PRYOR: Wow.

KARPLUS: And so that was one of the—you asked when I became aware of things, and then my parents talked about leaving, and how lucky we were in many ways that really our immediate family, except for my great-aunt, managed to get out, and all the other cousins, and most of them [came] to the United States, except my uncle who went to New Zealand.

CARUSO: Did they all come to Boston, or did they go to—

KARPLUS: No, some came to Boston, mainly Boston and New York.

CARUSO: Okay.

KARPLUS: Pretty much. So that we kept a close relationship with them.

EARDLEY-PRYOR: Why was it that Boston became the American hub?

KARPLUS: [It was just our place, as was New York.]

EARDLEY-PRYOR: On the trip from England to the United States?

KARPLUS: We landed in New York and then came to Boston. Boston did have a refugee [arrival] house. It was a large mansion where we were taught what it was like to be an American and such. That was one of the reasons. We personally came here because my uncle who was working at General Radio was here, and he had found an apartment for us, and there was a large group of Jewish families in Boston. Many people had relatives who already were here, and so more I think than Philadelphia [Pennsylvania] or Washington [DC] or further south.

EARDLEY-PRYOR: What are some of your memories of that mansion that was the acculturation training? What was that like?

KARPLUS: [. . .] I think we were able to stay there for several weeks, until we actually had the apartment that our uncle had found. [The mansion] wasn't that different in some ways of the mansions that [some members of] my family had had in Austria. There were relatives. I don't know the exact relationship, but we called many people aunts, even though they weren't really aunts. They were second cousins one time removed, but aunts were sort of [what we called them]. The Motesiczky family, which was another wealthy Austrian family, had a big house in the countryside where we would go sometimes for the weekend to visit. She was actually the mother of Marie-Louise Motesiczky, who became a famous artist and lived in England for many years, and so we have quite a few artists in our family. But again, that's an aside.

I mean, the [mansion] sort of reminded me of the family country house, even though it was in Brighton, [Massachusetts]. It was on the hilltop, and people were very welcoming. Of course, my brother and I, we knew more English than our parents, but that was sort of a special thing, that we already had a connection, and it was a nice—like all these experiences we had living in Zürich, and then in the summer in the beach in La Baule [Escoublac, France]. Again, I have this positive view of things. Marci accuses me of forgetting the negative parts, and it may be true. But no, it was nice, and then we found this apartment and moved in there, and I went to school immediately, and my brother did, too.

And we had this feeling that we very much wanted to be real Americans. I mean, we wanted to belong. And at home for a while, we would—again, my brother and I would mainly speak in English. Our parents knew enough so we could talk to them in English, but we tried to sort of **<T: 45 min>** not talk German to them, which I got over after a while, but it was—

EARDLEY-PRYOR: Was that resistance? Was that part of being a rebellious young lad, or was that a part of you trying to help your parents adjust as well?

KARPLUS: Well, I would say—

EARDLEY-PRYOR: All of the above?

KARPLUS: —neither, in a way. It was just that I wanted to belong to the US, and wanted to play with the other children. I just tried to really play—I remember playing marbles on the sidewalk, and things like that, and also, this incident where I was running around with them, and was, quote, "run over by a car." I wasn't really run over by a car, but I slipped off the sidewalk, and the car came, and actually, it stopped on my foot. And the guy got out and said, "What's wrong?" I said, "Would you get off my foot?" Which he did. But then the point of it is that he said, and he was very concerned, "Can I take you home to your parents?" And I said, "No, no, no, I don't want them to know about this." And so he finally went off. [I was scared that my parents might forbid me to play outside,] that they would not happy about it. But it was the idea of belonging, which I think [in my mind] played a very important role.

CARUSO: What was it like for your family generally, adjusting to the different financial circumstance in the United States? Clearly, they had to give up a lot in order to leave Austria. They are taking their knowledge, their skills with them, but just because you have those, that knowledge and skill, it doesn't necessarily mean you're going to become a well-paid physician. I think you mentioned that your aunt became a psychiatrist eventually?

KARPLUS: Right. Right.

CARUSO: So clearly, I mean, they were able to bring those skills and put them to use, but it's not a guarantee that those are going to translate.

KARPLUS: [Yes].

CARUSO: How was it for your family?

KARPLUS: Well, speaking of my immediate family, we did have a certain amount of money, partly because my father had gotten quite a bit of money out by—he was always a stamp collector, and he had some very valuable stamps, or even bought some valuable stamps, and put them on envelopes—may not have been valid anymore—and sent them to the United States. And then we also did have some money in the Netherlands, which we were able to get to the United States. I only discovered this recently [when I went through] lots of papers around from my parents. They also describe that in order to get my grandmother—on my mother's side. My grandfather died just about that time [in 1939]. I don't know whether it was because of the stress or whether he just passed away— to give her an affidavit, we had to show that we had some money. And so it turned out we—in the papers that I found, in connection with making this film—went through all this, and it says that we did have a certain amount of money. And we were able, not immediately, but after a couple of years when it was time for me to go to junior high school, to buy this small house that I mentioned in Newton. I think we sold it for around ten thousand dollars. Nowadays it probably would at least be worth maybe twenty times as much, probably not quite that.

And so we had some money, but—my father took a course at the [Wentworth] Institute [of Technology] in machinery and such, and found, because it was during the war, he very quickly found a job at a pump factory, which made pumps for **<T: 50 min>** airplanes. My mother went to school and got a degree as a dietician, a master's degree, and worked at the Beth Israel Hospital [Boston], and when she was there for quite a few years, the food was much better than it ever had been. I would go over there every so often, because I was interested also in the hospital.

So they both adapted to the fact that we weren't wealthy, but we didn't lack anything, because my father did find this position very quickly, and rose very quickly in the ranks. And again, just the way he described what happened when he was in jail [in Vienna], he would come home and tell us what interesting things, how these pumps worked, or that he'd found a new way of making the pumps. Itwas always this interesting description, both for me and my brother. And I think my brother understood more of it, what was going on at the time, but it was still whatever he was doing, he found something interesting and positive about it, and that I think played a very important role [in my life].

EARDLEY-PRYOR: Sometimes at that age brothers can repel from one another and not want—especially an older brother— having a younger brother tagging along. What was your and Robert's relationship, having gone through these experiences, and then moving and living in Massachusetts?

KARPLUS: I always did try to tag along, as you describe. And when we had first moved to Newton—I don't know really whether my brother asked for it— my parents gave him a chemistry set. And of course, I wanted to play with it also, or do whatever he was doing. And he told me, "Oh, you're too young to do this. You can't come around here." I was very unhappy about that, of course. And so my parents thought that having two people with a chemistry set would be just too much, would be explosive, and so they gave me a microscope, which originally I was very unhappy about. But it had the really nice attribute that father [was interested in when I showed him under the microscope]. He liked to observe nature, which I think had a lot of effect on me. Also I would go [with him] when—he liked to go fishing, but not to fish, not actually to catch fish, but just to watch the fish. This observing of nature really is something that appealed to me.

And having the microscope, he also spent much more time with me. I'd see something in the microscope, and show it to him—than with my brother. He wasn't that interested in the chemistry. And so I think it had this [had a] very positive effect, and I still have the microscope. There was this incident. I used to go out and just collect water flowing in the gutters and such. Of course, when I brought that in, it made smells as bad as my brother's [chemistry set] smells. Then one day I observed the rotifers—I showed my father and my mother—and they're just wonderful little creatures, and also showed them to some of my friends in school. And so then I really was very excited about having the microscope. I think that part of it was that my father showed more interest in this than in what my **<T: 55 min>** brother was doing.

I think there was also some jealousy that I had that my father used to teach mathematics to my brother; in the morning before going to school, they would sort of chat, or on the weekend, and I would listen, but I didn't really understand what was going on. It was just beyond me. And so I was somewhat jealous. [. . .] This was somewhat later, my brother being very supportive of me, and that played an important role. But there was both some rivalry, and obviously, the fact, like with my father, that I wanted to be able to do the same thing as he did, and there's just no way of my doing that, because I was too young, three years younger, so I was always somewhat behind, which I don't know whether it led to an inferiority complex or whatever.

CARUSO: Thinking about what you mentioned with regard to, you know, the friends that wouldn't play with you in Vienna—

KARPLUS: [Yes].

CARUSO: —because you became this "dirty Jew," and also thinking about your neighbor who said that you were saluting Hitler in the mornings, I'm curious to know how you and your family were received generally when you were in Newton. Did anyone think of you as the Jewish family? Did anyone treat you differently because they knew that you came from Austria? What was it like in terms of those aspects, moving into this sort of—

KARPLUS: I think we really didn't have that much relationship with people in Newton who weren't the immigrants. There was a large immigrant community in Boston, of which I don't think anybody else lived in Newton at the time. I don't know whether we were really the first family, but it just wasn't the way it is nowadays.

CARUSO: Right.

KARPLUS: And so we didn't—I don't know whether if we had been not Jewish, we would have been invited by some neighbors. I don't think this was done that much at the time. Our contact was with other immigrants, mainly Jewish, many of whom we had known from Vienna.

And there was the newspaper, a German newspaper put out [by the Austrian immigrant community], and there was a big community life—some people were more religious, some people were less. Most of the people that I'm aware of weren't really religious. They had a Jewish heritage, which we've always been very proud of. But, if anything happened with my father, he never talked about it.

CARUSO: [Okay].

KARPLUS: Whether there was something like that, where he had contact with non-Jewish people when he was working. And I, as soon as I could, I worked for a while at the equivalent of the Star Market. I don't remember what exactly its name was, but when people had orders, putting whatever had been ordered into boxes to have it delivered. And I was just one of the kids. I'm trying to think about how much of an accent I had. I very quickly didn't have very much of an accent. People tell me when I was talking on the phone to one of my relatives, they would know that I was talking to one of my relatives, or my brother, for example, because our accent would sort of mount up.

But in normal conversation, I don't think it was really obvious to people who were [not] sensitive to things. So I never felt it—well, I mean, **<T: 60 min>** you asked about my parents, and I think there it was mainly that they were in the Jewish community, and I don't think they really felt anything. They never mentioned anything from their work. I don't think it really had any effect, but there were instances where the fact that I was Jewish had an effect on what happened. The clearest case was that in the chemistry department in [the University of] Illinois [Urbana-Champaign], where there had never been any Jews hired because of Roger Adams, who ran it—I don't know whether he's somebody you have an oral history [with] him?

CARUSO: No.

KARPLUS: He was a well-known organic chemist. There were no Jews in the chemistry department. And then he retired, and Herbert Carter, who was an organic chemist, became the head of the department. And Illinois was one of the places where department heads were really department heads, and did a lot of the hiring, rather than at Harvard [University], you know, where the department head—or chair is called now—he doesn't have that much power. He does a lot of the dirty work of making things work, but it's really the whole department that nowadays hires [new faculty].

And when he retired, there were four Jewish faculty members who were hired in the same year, of which I was one. So in that sense, I guess that was one time where being Jewish had an effect. It just happened to work out well, just to be at the right time, and that's, of course, much later in the story, how I got the job there. [Actually, it is likely that our being Jewish had nothing to do with our being hired—it just happened, though it is clear that under Roger Adams we would have not have been hired.]

EARDLEY-PRYOR: Will you tell us a little bit about your summer memories in the United States? As a child, you had gone to the mountains, to the beaches across Europe and Austria and Italy. What were summers like in the United States?

KARPLUS: Well,—again, thanks to my parents—in order to make summers nice for us, in the first summer they worked. My father worked as a gardener, and my mother worked as a cook with a family in Holderness, New Hampshire, which had a nice summer place, and we could be there during the summer. And another time, they worked at a boys' camp, and we were admitted to this camp. They did everything to make it possible for us to have a nice time. Shortly after that I joined the Boy Scouts, and I had done a lot of nature study. When I was quite young, I must have been fifteen or sixteen, I became nature counselor at one of these camps, independently of my parents. But the initial thing was that they did everything to make our life as close to what it had been in Austria. This may not be the right term, but just to give us a really nice summer, because they couldn't afford to send us to the camp. So that's a case where the limited income really played a role, but they did their best to make it a nice summer. And I remember these summers as really being wonderful.

EARDLEY-PRYOR: Can you talk a little bit about the experience with the Boy Scouts?

KARPLUS: I was a very active Boy Scout, and accumulated merit badges. Of course, we haven't talked about my interest in birds yet, but I got all kinds of nature merit badges, and then I think I became the youngest Eagle Scout in the history at least of New England. I enjoyed going and doing all the things, going on hikes with them and going overnight, and—

EARDLEY-PRYOR: **<T: 65 min>** Where were some of those trips? Do you remember? Around New England?

KARPLUS: Most of them were relatively local, in the area. It was a scout troop in Newton, and I don't really remember who was involved. None of the people that I interacted with became friends but there was something—I think it was partly belonging, doing something that was really [American], the Boy Scouts of America. And in those times, I didn't know about all their prejudices and everything. And there were no problems, as far as I know, with homosexual interactions, and certainly nothing that affected me, though when I was at Cornell one summer, I was working with Don [Donald] Griffin on bats and birds, and some people befriended me, said, "Well, why don't you come over to . . ." They were a bit older. I was in college, so I was seventeen.

And we had nice conversations, and then ended up in the bedroom where they had a big bed. I was very innocent, but then finally I realized that I didn't want to have anything to do with it, and just got out. Nothing at all happened.

And then when I was in [Harvard University's] Dudley House where [. . .] I had a roommate who was homosexual, but he had no interest in me. He just had some other people that would come over, and he'd say, "Well, it'd be nice if you weren't here this evening."

CARUSO: Did you—and this is a focus on the Boy Scouts—

KARPLUS: I mention this because there's been a lot of publicity recently—

CARUSO: Right.

KARPLUS: —about [homosexual approaches by the group leaders].

CARUSO: Yeah. I mean, I only made it to I think Life [Scout]. I never made it to Eagle [Scout].

KARPLUS: Life. That was the one just before [being an Eagle Scout].

CARUSO: Right. And I grew up, I was raised Catholic, but I wasn't exactly religious, though I do remember from my time at Boy Scout meetings and occasionally going to Boy Scout camp that religion, at least in the form of prayer, was present, before a meal, or doing this, doing that. Did the religious aspect of the organization exist at the time that you were going through it? And if it did, did that play any complication for you?

KARPLUS: It did. There were prayers before [meals]. But I just didn't participate in the prayers, and I didn't do anything ostentatious, to say, "get up," or something like that. But it certainly was there, and I did talk to my parents about it, and I said, "Look, this has nothing to do with me." And nobody said, "Well, you must say the prayers before you can eat," or anything like that. It was just fairly low level. And also, there is the pledge of allegiance, which, at a certain stage, "under God" was added to it.

CARUSO: Right.

KARPLUS: We often said this at the beginning of class. I guess nowadays it's probably not allowed to be said in most schools. But again, I just would not say it, and so I didn't make a big issue out of it, but I just personally was satisfied with the fact that I was not violating [and] it was not because of Judaism. It was just because I really **T: 70 min>** wasn't religious, and still am not religious. So sometimes it has come up. When people ask me do I believe in God I say, "No, but as a scientist I do have a faith. I have a faith that the earth, that the world can be understood. There's no proof for this, but that's certainly a faith just as much as being religious."

EARDLEY-PRYOR: The transition from the apartment in Boston, in Brighton, to Newton, where you began junior high, and I assume Bob was stepping into high school around then—

KARPLUS: Right. He was already in Boston Latin School, where he'd been I think for a year, and then when we moved to Newton, he went to Newton High School.

EARDLEY-PRYOR: What was the impetus for the move to Newton? Why leave?

KARPLUS: The school.

EARDLEY-PRYOR: It was for you and for Robert?

KARPLUS: It was the school for me. [. . .] Well, it was a junior high school, and—I'm just trying to think about when my brother started Boston Latin. He started very early, so maybe he went very quickly to Boston Latin, but it was when I was going to go to junior high school that my parents felt moving to Newton was a good thing to do. It was essentially for the schools [for me].

EARDLEY-PRYOR: What was your memory of that school, that transition for you, being at the new junior high?

CARUSO: Well, actually, if we can just back up slightly—

EARDLEY-PRYOR: Yeah.

CARUSO: —given that you did go to school in Austria for a few years, you spent a little bit of time at a school in Zürich, and then you came to the United States, did you have any or do you have any reflections on the nature of the different school systems? Based on my understanding, was Austria on the traditional gymnasium . . . ?

KARPLUS: Yeah, but I never—

CARUSO: Okay.

KARPLUS: —I mean, I wasn't there.

CARUSO: Right. Right.

KARPLUS: I was too young. I was just only the first and second grade.

CARUSO: Okay.

KARPLUS: [. . .] One thing when there was a difference, I believe, is that when I was in Austria, although I'm left handed, I was forced to write with my right hand. And when I came here, and noticed the contortions that kids went through writing with their left hand—here it was considered not a bad thing to do,—I was very happy that I had been forced to learn [to write with my right hand]. I was still—and when I throw a ball, I basically throw it with the left hand, and I'm somewhat ambidextrous. And when I hurt my wrist here, I wrote with my left hand, but [I was] never really very proficient with it. But that was one difference of the rigidity of the school system: just you had to write with your right hand. [Also, we went to school Monday through Saturday with homework starting in the first grade and no extracurricular activities].

[. . .] We had a very nice teacher, Herr Schraik. When we [. . .] visited the school [for the film], they were able to look up about how he had taught here, and there was some reason given why he left. He was forced to leave, but they still had some record of it. But I mention him because, you know, when I came here, as I wrote, I had this very wonderful teacher on whom I had a crush, and she kept me after school to help me learn English. Unfortunately, I learned too quickly. So she said, "Well, there's no point in you getting any [more] special lessons," and so, in a way, I had this warm feeling when I started school here, as I did with the teachers in Austria.

CARUSO: So you mentioned that your parents wanted to move to Newton because of the schools. Do you have a sense of what they thought was lacking in the school that you were at, that they wanted you to be out in a school in Newton?

KARPLUS: I would have to go to a **<T: 75 min>** new school, you know, [I] was in a grade school or grammar [school]—or whatever it's called—and then it was time for me to go to junior high school. [. . .]

CARUSO: Okay.

KARPLUS: Newton still has the reputation of having very good schools.

CARUSO: Okay.

[. . .]

EARDLEY-PRYOR: What was that new school like for you?

KARPLUS: It was——again, was a special experience. The teacher very quickly discovered that I could do a lot more than the regular curriculum, and so they let me and Martha Palmer—who I had a crush on for a while as well—

EARDLEY-PRYOR: It's a good motivating factor, isn't it? [laughter]

KARPLUS: —worked together on our own, and we just had to take the important exams. And they would help us so we could learn a lot more. It was really one of the great things about the school, that they actually did that.

The other thing was that we had to take some sort of manual training courses. What I did was printing, which I played with for a while afterwards, and the other was cooking. I've always been very interested in food, and used to watch Mitzi cooking for me in Vienna, and then [spent time] in the kitchen with my mother and grandmother when we were here. And what happened with my grandmother [when she came to America, was that] she would basically spend one-third of the year with us, one-third of the year in New York [with Aunt Lene's family], and one-third of the year with [Aunt] Claire—the three daughters who were in the US. She was somewhat of an invalid. She had had a fall, and it hadn't been corrected in any completely successful way, but she always was around the kitchen. She always wanted to help.

And so we'd be sitting in the kitchen peeling [vegetables] and helping my mother. So I'd always been interested in cooking, which has developed over the years, which is another whole story. But anyway, I took cooking class, and it is true that I was the only boy in the class. But it was really good. And at the end of the year, the exam was to prepare a dinner for a bunch of teachers and the other children in this class in the whole school of that grade. I don't know how much you want me to talk about my cooking experiences or not.

CARUSO: I mean, as much as you want to, but I'm also curious, when you say "printing", are you talking about printing press? Are you talking about—

KARPLUS: Yeah, we had the letters, and put them into lines, and then there was a printing press, and we would print out things. We could take something that we had to write for another class and actually print it. It was an old-fashioned printing press with letters that you [. . .] put together into some sort of—I don't know the word for this— holder that held them when you put them in the press.

CARUSO: Because I wasn't sure—I know later you developed an interest in photography, so I wasn't—

KARPLUS: Right.

CARUSO: —sure if it may have been like photographic printing, so I just wanted to check.

KARPLUS: No, no. It was real printing.

CARUSO: Okay.

EARDLEY-PRYOR: With the move to Newton, more of a suburb in Boston or even just being in the United States itself, I'm wondering—this is in the early 1940s—**<T: 80 min>**with the war going on across in Europe, what was the experience of what was processing in Europe at this time? Was that something that was kept in front of you, or was that something that was in the distance then? How did the war play into your experience and memories at this time?

KARPLUS: We did talk about it, and obviously my parents were very concerned about it. They didn't talk so much to me or my brother, but when we would get together with other families, and some of these families had not been as lucky as our family on terms of almost everybody getting out. It was clear that there was a concern of what was going on. And of course, the US had then gotten into the war. And—there was this one experience when—we're now at the stage where my microscope had been put aside, and I was very much interested in birds and birdwatching, which was, again, an observational thing, like looking through the microscope, which I think I've always had, and it's also played out in the photography that I did. I was interested in nature around me.

And then thanks to my friend [Alan] Al McAdams from high school, he had noticed—I don't know quite why—the Lowell Lectures.[4] There was [a series] on birds given by Ludlow Griscom, who was professor [of ornithology].

EARDLEY-PRYOR: Here at Harvard?

KARPLUS: Here at Harvard. He was a professor of ornithology here, and he was the leading field ornithologist in the area. There's Roger Tory Peterson, who wrote these field guides, which [led to] a complete transformation in going out and watching birds.[5] The idea being that rather than looking at pretty pictures of them, like [those of John James] Audubon, and you would try to know for each bird what's called the field marks, what you had to see to know that it was this bird rather than another bird. [. . .] And Griscom was one of the people, not that he had anything to do directly with Peterson, but who had personally developed this way of being able to identify the birds.

And one time when I was into birdwatching—which we can talk more or less about later on—there was a snowstorm, and so there was no school, and I took a train up to Gloucester, or Rockport, I don't remember which. I think it was Gloucester. I hadn't done this before, when going out on field hikes, but I just went by myself, because I knew with the storm, it was very likely—it was a nor'easter—that some of the seabirds, which are normally way out to sea, would come close to the shore. And so I went to a place where we usually went and sat there, with my binoculars, looking out to sea, and indeed I did see several birds.

But then after I'd been there for a while, a car drove up, and a couple of people came out, and I thought at first they were birders who had come like me, except by car rather than by train. But they didn't really look like birders, and they didn't have field glasses, which was the characteristic. And then all of a sudden I realized they're showing me their badges, that they were from the local police, and wondered what I was doing. And at that time I guess I did have somewhat of an accent, and they asked me where I was from, and everything, and it was at a

[4] The Lowell Lectures were sponsored through the Lowell Institute, an education foundation in Boston, Massachusetts, that provided free public lectures. The Institute was endowed by a bequest of John Lowell, Jr., who died in 1836.
[5] Roger Tory Peterson, *A Field Guide to the Birds of Eastern and Central North America*, Fifth Edition (Houghton Mifflin, 2002, c1934). See also Douglas Carson, *Roger Tory Peterson: A Biography* (University of Texas Press, 2012).

time when there was danger of submarines off the coast. And so they thought I was signaling or something. I was fourteen, and obviously was very scared.

And so they brought me down to the police station, and **<T: 85 min>** it took a couple of hours of their telephoning to the Audubon Society and [asking] various people that I had interactions with until they finally let me go.

EARDLEY-PRYOR: So at that point, you had already had these interactions with the Audubon Society, enough that they could vouch and say—

KARPLUS: That's right.

EARDLEY-PRYOR: —"Oh, Martin, of course, he's been on several of our trips." Tell us a little bit about how these Lowell lectures that Ludlow Griscom was delivering. Tell us about the path into birdwatching if you could.

KARPLUS: It was Alan who had said, "Why don't we go there?" It was at the Boston Public Library. They had them regularly and they still have them. [. . .] I was fascinated by Ludlow's lecture. Alan actually just came for the first one and then stopped going. And then—I think there were eight lectures— by the third or fourth one, Griscom had noticed me, that there was this boy listening, and he asked me about my interest in birds, and then basically invited me to go on some bird hikes with him.

EARDLEY-PRYOR: And how old were you around that time?

KARPLUS: Well, I must have been . . . I was in high school, so I must have been, what . . .

CARUSO: Fifteen?

KARPLUS: Fifteen, probably. [. . .] He introduced me to the Brookline Bird Club. I'm not sure whether he introduced me, or whether I actually found it myself, because I started going to the Mt. Auburn Cemetery, but I think he introduced me, and also to some of the people at the Audubon Society, that I got to be very close to. And I was always the youngest, which has sort of been a theme of my life—that I've been the youngest, as the Eagle Scout, and so on. And it's funny for me to realize now that I'm the oldest in all of these things.

But anyway, he invited me to go along with them, and then I met other people who went on bird hikes with him who were all very good birders. I had binoculars from my father that he had had. I think he had had them when he was in the army in the First World War, which he wasn't [in] very long. [. . .] He was actually in the cavalry on the Austrian side. But fortunately, he very early on, he dropped his pistol and hit his little finger. And some people thought, well, he must have done this on purpose, but I think it's pretty hard to drop a pistol—

CARUSO: And shoot yourself in the pinkie.

KARPLUS: Yeah. And so he was demobilized because he could no longer ride very well, and so he got out of the army.

EARDLEY-PRYOR: Wow.

KARPLUS: So anyway, he had these binoculars, which he then let me use. I still have them, though I have other binoculars now—although they're quite powerful, it would take a lot of work to readjust them because I dropped them once. So it was Griscom [who] introduced me to people at the Audubon Society.

EARDLEY-PRYOR: What was it about the birding and the lectures that drew you in?

KARPLUS: Well, it just seemed so exciting; the research aspect he presented of trying to understand why birds lived in different habitats, how the number goes up and down and **<T: 90 min>** such. And also, this observational part, which as I said has always been part of my life, was exciting to me. All the free time after that that I had when I was in high school, I spent either going on trips with groups, or like this business of going to the North Shore by myself, I would do that. Nowadays, I don't really go out on bird hikes anymore. [I'm] still aware of birds, and when we're in the countryside, I usually take my binoculars with me and watch. One of my former postdocs who was in Houston, [Texas], invited me to come down there. I said, sure, I would come, if—it's known that the wintering area of [whooping cranes is in marshes near Houston]. He would take me out [to see them] . . . they summer in Canada— in the winter, they come down there, and you can see them. [. . .] We went out in a boat that goes around the area, and it was a great trip. And he got interested in birds after that.

CARUSO: You mentioned earlier that at least in your mother's family, it seemed to be kind of a tradition that someone would become a physician. I know that you were doing well in school, you were excelling in school. How did your parents respond to your interest in birds and ornithology? I haven't heard you talking much about whether or not your family has been influencing you or pushing you in any directions in terms of the career that you would want to pursue, and so I was kind of curious what was going [on] at home with relation to your studies and things like that.

KARPLUS: Well, it was—both in my brother's case and my case—just supportive.

CARUSO: Okay.

KARPLUS: I think they were very happy that we were interested in science probably rather than in business or something like that, that it was an intellectual activity which was part of the family, as you've heard.

They were always supportive. I would tell them, talk to them about my field trips and such, and it was always supportive, and it was not [them] saying, "Well, you're supposed to be the doctor."

CARUSO: Okay.

KARPLUS: Actually, my two daughters are both doctors, so even though we skipped a generation . . . later one of my cousins, he became a doctor—this was my Aunt Lene, a sister of my mother—as I mentioned before—who was a doctor, had these two children, Gus, who was a year older than my brother, and George, who was younger than me, and George actually became a psychiatrist, so somebody in my generation [did become a doctor], even though I didn't.

But no, [they never said], "Well, you should be a doctor." I expected to be a doctor until I went to Harvard as an undergraduate, where I first realized that I was more interested in understanding how things worked than actually being a physician.

EARDLEY-PRYOR: Was your brother Robert also interested in the birding and the ornithology?

KARPLUS: Not at all. No, no.

EARDLEY-PRYOR: That was a track that you took on your own?

KARPLUS: Yeah.

EARDLEY-PRYOR: What was it like with your brother in school? Or did you attend the same high school together?

KARPLUS: We attended the same high school, and there's a whole story about [what happened to me there]. In junior high school, as I mentioned before, I was allowed to do what I wanted to do, if it meant that my studies were going along well. When I went to high **<T: 95 min>** school, it was very different. It was the first time that my brother had actually preceded me in the same school. And he was very bright, and so basically I was considered the little brother who was not as bright as my older brother. And so it—in many cases—really didn't come up in history or whatever, but it was in science in particular, in chemistry even more so, that the chemistry teacher [John Hall]—I did fine. It wasn't that I didn't do well, but he constantly reminded me, "Oh, your brother." And a specific thing that was most important was the Westinghouse Science Talent Search, where my brother actually encouraged me to apply. He hadn't—I don't know [why], I think it had existed already. But he [the chemistry teacher] said, "Well, your brother should have applied, and, you know, there's no point in your applying." He would have been the person who should have [encouraged me], since that was the science I was taking in that year. It was biology, chemistry, and physics, in the first, second, and—

CARUSO: [Right].

KARPLUS: —so with the encouragement of my brother, I talked to the principal, who said that if I wanted to apply he would help me to do so. And the main thing really was to get a proctor. I had to take a test, and get a proctor who would proctor me on the test, and fill in the forms, so everything did get done. I was one of the forty people who were selected to go down to Washington for the finals. Finally I actually was the co-winner. In those days, there was one boy and one girl who won. Nowadays, I don't think it's gender-related.

EARDLEY-PRYOR: What was your project?

KARPLUS: The project was on birds. [*looking through the "Spinach on the Ceiling" article*] Here's a picture of me showing this bird, which we "collected" on one of the field trips in Newburyport with Griscom. We spied a bird that he couldn't recognize what it was, and he had a license [to collect birds]. He had a pistol with a very long bore, so he could aim it like a rifle. He asked me to go out and "collect the bird," as one says. I didn't have a license, of course, and I had to go through the mud. [The bird] was sitting out there on the mud flats, which are uncovered when the tide goes out. I'd never shot a [gun]—maybe I did at some country fair, but I had no idea—but I did manage to hit it, and we collected it. He decided that it was a hybrid between two different gulls, one that lives in the US, the Bonaparte's gull—very common here, and one that's very common in Europe—the black-headed gull. So one of them must have come over and this was their offspring.

It was here in the Peabody Museum [of Archaeology and Ethnology] for a long time, and then it was given to the Peabody Essex Museum in Essex County, [Massachusetts], which has a large collection of local birds. We visited it one day, and found it. I brought back a couple of feathers because there was a project of involving gulls and other birds that get caught in **<T: 100 min>** the jet stream, and sometimes enter the jet engines. So they—and these birds of course are completely destroyed when they're in there— want to be able to identify the birds. There was essentially a barcode research project, so they could identify birds. There was a new professor [at Harvard] at the time when I wrote this who was interested in genetics, and then somebody else, to actually take these feathers and find out whether we had guessed from their field marks was actually correct, but they never did it.

CARUSO: That was Scott Edwards and—

KARPLUS: Right.

CARUSO: Yeah.

KARPLUS: Yeah.

EARDLEY-PRYOR: But they never sequenced the DNA?

KARPLUS: They never, no, I never could get them to do it. I don't know exactly why. But it just never—I mean, they had gotten the feathers from—the museum, [they] had permitted me to take a couple of them. You don't need very much. I tried until fairly recently. I still have some email exchanges with a woman who was doing some of this, but it never . . . so we'll never know, I guess.

EARDLEY-PRYOR: Yeah. Well, it earned you a trip to Washington, DC, in the mid-forties.

KARPLUS: Right. Actually it was more about the Massachusetts alcids—like the little auks—and describing their migration. I think it's the sixty-fifth anniversary of this Westinghouse [Science Talent Search]—though it's no longer Westinghouse. It's the Intel [Science Talent] now. So in the spring, they're inviting people down, all the Nobel Prize winners that have come through there [for the celebration].

EARDLEY-PRYOR: Oh, wow.

KARPLUS: And having a symposium about different things, I decided I would go, and I think the reason I want to go is, that it played a very important role in my life, as I mentioned, in terms of my comparison with my brother and everything—that I won this.

EARDLEY-PRYOR: Did you ever have any interactions with that chemistry professor after having the Westinghouse experience?

KARPLUS: No. I mean, I still have a clear picture of his face. He was partly bald around . . . But no, and he never said, "Oh, congratulations," or anything like that. [laughter]

EARDLEY-PRYOR: Had you been to Washington, DC, before?

KARPLUS: Had I been to Washington? I think the answer is no.

EARDLEY-PRYOR: So you had gone there just around the time that the war had ended.

KARPLUS: Right. It was when [Harry S.] Truman was president, and we met Truman.

EARDLEY-PRYOR: What was that experience like?

KARPLUS: It was a great experience. Somewhere I have the photograph of us, all of us standing with Truman. And when I won the Nobel Prize, [President Barack] Obama—I don't know whether other presidents, I presume so, invite all the American Nobel Prize winners down to Washington to meet him—we have a very nice picture of Marci and me with Obama. But before going down there, [. . .] I said to Marci, "You know, if it's just going to be a photo op, I don't think it's worth going." But I knew the science advisor [John Holdren], and sort of talked with him about it, and he said, "When the President invites you, you don't refuse unless either you're deathly sick or there's somebody in the family who has a funeral." And then I asked him, "What will happen?" He said, "It's really up to you. He's the President, and so he can do what he wants. [If he's interested, it will be longer]."

And so when we were down there, and when we were in the Oval Office, because of the way the [Nobel] Prizes [are ordered in] Chemistry, in Physiology and Medicine, **<T: 105 min>** and in Economics, in that order, and for the Chemistry prize, [I am] first in the alphabet, so it's Karplus, Levitt, and Warshel. [Marci and I] were the first ones in there. I had my photo catalogue with me, with a dedication to him [and to Michelle Obama].[6] First, I said to him, "You know that you're the second president that I've met." And he said, "Yes?" And I said, "Well, I met Harry Truman, and he was the first president to try to get universal health care, though he didn't succeed."

And so Obama stopped—I don't know what your politics are—and thought for a little bit, and he said, "No, that's not true. It was Theodore Roosevelt." And then he thought again and he said, "Theodore Roosevelt did propose it, but that was when he was campaigning for the office, and he wasn't elected." So he agreed that Truman was [the first]. And then I gave him the photo book, and he looked at it a little [and then gave it to an assistant]. When I met President [François] Hollande of France, when they celebrated me—he came actually to Strasbourg, [France], in part to see me, and partly to give a speech. [He used the visit to] give a speech about science and how well France was doing. Each country, once you get a Nobel Prize, the US, France, and Austria all—

EARDLEY-PRYOR: Want to claim you.

KARPLUS: —want a little piece. He came, and I chatted with him, and at a personal level he was really very engaging. So I also gave him a [copy of the] photo book, and I said to him, "I know you're going to see President Obama in two weeks or so, so ask him whether he's looked at my book." Anyway . . .

CARUSO: So another thing I'm curious about is, you know, given the time period we're talking about, this is also when the atomic bomb is first used. Do you recall any responses or reactions, either in your household in terms of politics and thoughts about the use of the bomb, or in school, in response to this new military weapon coming out, this scientific event? Was anyone talking about it at the time? [. . .] And were you interested in it?

KARPLUS: I was always very interested in politics. The big question was—and that was also with Truman,—whether dropping the second bomb was a valid thing to do. There were two questions which we discussed with friends and relatives. One, whether dropping the bomb in the middle of the ocean or something would have been enough, didn't have to kill all these people.

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[6] Martin Karplus, Sylvie Aubenas, Nathalie Boulouch, Jean-Pierre Changeux, *Martin Karplus: La Couleur des Annees 1950* (Paris: Editions de l'Oeil, 2013). See also Martin Karplus, *Images from the 50's: Kodachromes from Europe and America* (Parker, CO: BookCrafters, 2011).

And secondly, whether dropping the second bomb was necessary after the first. [. . .] We knew that something was going on. We didn't know exactly what it was, because a cousin, Robert Frisch, who had worked with Lise Meitner on first showing the possibility of chain reactions—she never got a Nobel Prize, which is another story, but anyway—Robert Frisch, who was a good friend of my parents, and also related, would come and visit us. That was the time when the atomic bomb was being made in Los Alamos [National Laboratory, New Mexico], and he would come [for a vist], and then said he [would say], "Well, I can't tell you what's going on, but . . . ," and then he would disappear, and then he would come back again. So there were things in the air about what was going on at the time, and **<T: 110 min>** he was involved in it.

CARUSO: Yeah, I was just curious if you recall anything specific about the use of the bomb, or discussions about—

KARPLUS: That most certainly was a real question, and the explanation that's given, why this was dropped, first of all, on some city where it had really an effect, and secondly, why two were dropped—originally, they weren't really sure that it would work at all. That's all they had, was two bombs, and so they didn't work, then they didn't have anything else to do it. I don't know whether the argument has [actually] been resolved. And I did meet Robert Oppenheimer—who had been sort of running the project, essentially, at Los Alamos—when he was the head of the Institute of Advanced Studies, where my brother went as a postdoctoral fellow after being here at Harvard.

EARDLEY-PRYOR: So you also went to Harvard after your brother had gone there?

KARPLUS: Right.

EARDLEY-PRYOR: And I'm wondering about that transition as well. But before we step into that, perhaps you could tell us a little bit, back to the birding, because I also understand there was a really unique opportunity to go to Alaska—

KARPLUS: That's right.

EARDLEY-PRYOR: —before it had become a state, but was part of the American territory, of course.

KARPLUS: Yeah.

EARDLEY-PRYOR: Can you tell us about how that happened, who was involved? How did that come across your experiences?

KARPLUS: Well, I had heard that Robert Galambos, who was working in the lab in the basement of Memorial Hall [at Harvard University], was interested in bats, and so I'd gone to see him.

EARDLEY-PRYOR: Memorial Hall, the giant cathedral—

KARPLUS: Yeah.

EARDLEY-PRYOR: —that we passed.

KARPLUS: I guess that doesn't mean anything. I just say Memorial Hall, everybody here would [know].

EARDLEY-PRYOR: Yeah. It's a striking building.

KARPLUS: It had a basement where there were some laboratories. I think they're now a cafeteria. But he had, with Donald Griffin, discovered the echolocation that bats used, when they're flying around, like radar. They bounce it off insects, and they can tell how far away by how long it takes [to come back], how far away they are. And they're pretty much blind, living in dark caves. That's how they find insects. Somebody long ago had had some ideas about that, [but Galambos] did really careful experiments on that with Donald Griffin, who was at Cornell.

I had read about this and was interested in it, and went to see [Galambos] and talked to him about my interest in birds. So he said that Don Griffin was actually a professor of ornithology at Cornell [University], and he wrote me an introduction. And then Griffin invited me to come to Cornell for a summer and work with him on experiments, and we worked on pigeons. That was my main project. But I also worked a little bit on bats, and one nice thing about bats was that since they're cold-blooded [heterothermic], you can just put them in the refrigerator, and they'll just hang there, the way bats do. And then when you want to do an experiment, you just take one out—

EARDLEY-PRYOR: Pluck one out.

KARPLUS: —and warm it up, but again, I did some experiments on pigeons, which were interesting, but they didn't really lead anywhere. I mean, nothing publishable. Actually, I haven't mentioned this, but my first paper or papers were on birds, and one has to do with Alaska, so I'll get to that.

And so then he invited me to go up to Alaska, where they were going to—

EARDLEY-PRYOR: Donald Griffin did?

KARPLUS: Griffin did. Right. Galambos had faded from the picture. And basically, the idea was to study bird migration and how birds find their way. And one of the experiments that we were interested in doing was to—there are two types of golden plovers, the Atlantic **<T: 115 min>** and Pacific one, but they nest together in Alaska. And then one of them, [the Atlantic] flies down, and in the fall, you can see them flying here, if you go out birding. And the Pacific ones go in the other direction.

And so we tried various experiments. [We would trap] the plovers and attach little magnets to them, and release them [away from their nesting ground] and see how they would fly around, [following them in a small airplane], and [see] whether they could find their way back [. . .].

EARDLEY-PRYOR: How did you attach a magnet to these little plovers?

KARPLUS: We attached [it] to the wings very close in. Not really on their heads. And I don't know how good the experiment was, but the results weren't really conclusive. The reason we were able to go to Alaska was because there was the Arctic Research laboratory, which was funded by the [United States] Navy, to study how people would live under conditions there, [as well as] all kinds of research. I mean, the Navy—I don't know whether you know this— after the war, was the first government agency to support fundamental science, and many people had their first grants from the ONR [Office of Naval Research], which was very important in science funding before there was a National Science Foundation or NIH [National Institutes of Health].

There was this laboratory [at Point Barrow, Alaska] where you could easily work and live [in some dormitories]. We also went to a small place called Umiat, [Alaska], where there was a hut where we . . . I think we were trying to study some of the plovers that were not nesting inland in the tundra. I had the idea of doing a study of robins, which are very common down here [in Massachusetts], but they also occur in Alaska, the same robins that are here. And the question I asked was, "What is the survival value of robins that come to Alaska and go through this horrendous flight to get there?"

And so the hypothesis was [that they] have continuous daylight [in the summer], and so the robins would be able to feed their young over a sixteen- or eighteen-hour period, rather than what happens around here [where the days are never that long]. They're most exposed to be caught by predators when they are in the nest. I don't know quite how I had all this idea. Anyway, I thought maybe they would grow up faster, because they were being fed more.

[I was in Umiat] with a couple of older people, and got them to work with me to take eight-hour shifts, and watch the nesting birds for a couple of weeks, and see what would happen. And we had enough nests around there, so we got the data, which suggested yes, they in fact did grow up faster. And so I published a paper on that.[7] I think [it was in 1953].

EARDLEY-PRYOR: Were you still in high school, or was this a while after you—

[Background noise]

KARPLUS: This was when I was in college. That's when I met Galambos and everything. This was all—

EARDLEY-PRYOR: Oh, it was after you were at Harvard that you then—

KARPLUS: Right.

EARDLEY-PRYOR: —got connected with Donald Griffin.

KARPLUS: I was at Harvard, so it was easy to go over [to see Galambos], and it was [1953] that it was published, "Bird Activity in the Continuous Daylight of Arctic Summer." The amusing thing is there's still a controversy [about] whether this result is actually correct or not, and it's still cited. **<T: 120 min>** If you look it up in CiFi—there's still articles, now maybe it's one or two a years [a go]—where they discuss that.

EARDLEY-PRYOR: That's wonderful. What was the experience of getting to Alaska like, either from Ithaca or Boston or wherever you want, all the way to the Arctic, across the continent?

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[7] Martin Karplus, "Bird Activity in the Continuous Daylight of Arctic Summer," *Ecology* 33 (1953): 129.

KARPLUS: Right. I first flew to Alberta, [Canada], and then from Alberta up to Fairbanks, [Alaska], and then from Fairbanks [in] a little plane up to Point Barrow,, which had an airfield—and I stopped off in Alberta to meet with someone named [William Rowan] who was the first person to realize why [birds] nest in spring or summer. What he did was to keep birds in the [constant] daylight or [increasing] daylight [. . .] and studied what happened to their gonads. He found that they developed only if the daylight increased [. . .].

EARDLEY-PRYOR: So they're photo-responsive?

KARPLUS: He kept them in cages and watched them. And I stopped off to visit him, because I'd seen [a reference to] that. And I also discovered in his basement he had this unbelievable model railroad, which he like to play with. I spent a few days there, and then flew up to Fairbanks, which was a pretty rough town in those days.

EARDLEY-PRYOR: Yeah.

KARPLUS: And what I remember is that it had a church which had a direct entrance to a saloon. [laughter]

EARDLEY-PRYOR: From the church?

KARPLUS: After going to church. And yeah, it was an exciting experience. From there I went to Barrow, and did [the things I already mentioned].

EARDLEY-PRYOR: And all this air travel was—

KARPLUS: It was all air travel. It was [with what is] now Alaska Airlines. [It was then] called Wien Airlines. [There was] Mr. Wien who owned two airplanes which he flew from Fairbanks [. . .] to Point Barrow. That's now Alaska Airlines, which now is all over the country, I guess.

EARDLEY-PRYOR: I'm wondering, what was this relationship you had like with all of these more senior researchers, as this very young man, eighteen or seventeen, perhaps?

KARPLUS: Yeah.

EARDLEY-PRYOR: My notes show that—did you finish high school in three years?

KARPLUS: I finished high school—I finished college in three years. High school I think I went [for four years].

EARDLEY-PRYOR: Yeah. It seems like you moved rapidly through any schooling you had.

KARPLUS: Yeah.

EARDLEY-PRYOR: So here's this young man coming to Alaska to do bird research at the tip north end of the continent. What was that experience like, and how were you treated, and what was the social environment?

KARPLUS: Well, I learned to drink coffee, which I had never liked before, but everybody drank coffee, and of course, when we were keeping weird hours. But I really only interacted very much with the people, with Griffin, and the other people that I was with. [. . .] There was a cafeteria, and so we would see the people, and—

EARDLEY-PRYOR: Even the people on Griffin's team, were they also older than you?

KARPLUS: As I said, I was always the youngest in almost everything that I did, and they treated me like an equal in many ways. My book, I have them here, some one of the other things I did with the Eskimos living there. And I took— [*showing Dr. Eardley-Pryor and Dr. Caruso color slides, or Kodachrome, of old photographs*.]

EARDLEY-PRYOR: These are Kodachromes.

KARPLUS: Yeah, these are old. Here are some of the polar bears.

CARUSO: Wow.

KARPLUS: And here's an **<T: 125 min>** Eskimo woman chopping up a polar bear.

EARDLEY-PRYOR: Wow.

CARUSO: It's gorgeous.

EARDLEY-PRYOR: Were these polar bears pets? It looks like they're wearing collars.

KARPLUS: Hmm?

EARDLEY-PRYOR: It looks like they're wearing collars. Oh, wow.

KARPLUS: Here's one of the boat going out, I guess to catch seals.

CARUSO: And so these are photographs you took?

KARPLUS: Yeah.

CARUSO: I thought that photography, for you, started after graduate school. Was this something that then you were doing earlier than . . .

KARPLUS: Well, I was trying to [record what I saw and someone at the lab lent me a camera. After my visit to Alaska, I did not do any photography until I was given the Leica].

CARUSO: Okay.

KARPLUS: But then here is the baby . . .

CARUSO: Oh, wow.

EARDLEY-PRYOR: That woman chopping the polar bear meat, looks like she and her baby are sitting on a—she's chopping the meat, and the child is sitting on a dog sled.

KARPLUS: Yeah, where it—

EARDLEY-PRYOR: In the summer.

KARPLUS: Yeah. And there's the—

EARDLEY-PRYOR: Out of wood.

KARPLUS: No, they're actually—

[Crosstalk]

EARDLEY-PRYOR: Oh, these are the—

CARUSO: These are gorgeous—

EARDLEY-PRYOR: These are the golden plovers that you went to see.

CARUSO: Yeah. The babies. Yeah.

EARDLEY-PRYOR: Captured in a hat.

KARPLUS: I haven't looked at them for a long time.

EARDLEY-PRYOR: Now these photographs of people that are living in places that seem so foreign to you, to your experience in the suburbs or in cities, is something you've continued. Is that right?

KARPLUS: Right. I hadn't really associated it with my later interest in photography.

EARDLEY-PRYOR: Beautiful.

CARUSO: These are beautifully framed shots.

EARDLEY-PRYOR: Yeah. Are any of these in your photo book?

KARPLUS: No. No. I've actually never done anything with them. Now that I look at them, they look pretty good.

EARDLEY-PRYOR: Yeah, you—

[laughter]

CARUSO: They look very good.

EARDLEY-PRYOR: —need to do an exhibition here.

KARPLUS: Yeah. Maybe. I'm actually working on an exhibition from the meeting in Morocco.

CARUSO: You know, along the same lines with Roger's questioning, I remember my experiences in high school in the science classes that we had, and I remember my experiences in college in the science classes that we had, and I don't think at any point did I learn how to be a colleague with someone who was practicing science for a living. How is it that you felt comfortable or became knowledgeable enough to interact with these scientists at what seems to be a more advanced level, when you were still learning how to become a scientist? I mean, were you going out and reading scientific journals on your own? Were you doing experiments outside of lab that were beyond what was required?

KARPLUS: Not really. Certainly in writing this article about the robins, I looked at the literature to see—of course, it was much harder to look at the literature then. You didn't just put [into an online search engine] "robins, Alaska. . . ," and there it is. I guess I haven't looked recently. No, I don't really know. I've always been very quick. [laughter]

EARDLEY-PRYOR: Okay.

KARPLUS: And I think people recognize this, and I think in all these things like the fact that I was able to get these two people to work with me to watch the robins. I can't really tell you, whether they just think, "Oh, it's nice that this kid is doing that," or what it was that made them accept to do this with me. It's true, there wasn't that much to do where we were. The other interesting thing that happened is that—and again, I realized this, and then told it to them, though they observed the same thing, that the question we had—basically, we had continuous daylight. **<T: 130 min>** When we were at Point Barrow our schedule was determined by when we had dinner at the cafeteria, or breakfast, but there we had nothing to determine our schedule. And it turned out that—we did our own cooking—we ended up having an eighteen-hour day, and a twelve-hour night cycle. I don't know, I've never looked this up, but I remember this [. . .] that's what we ended up doing, guess we slowly shifted, and . . .

EARDLEY-PRYOR: You're altering space and time by being there.

KARPLUS: Yeah. Whether people now have studied this in more detail. I thought I should look it up, but I never looked it up. [. . .] I mentioned this to them, and they said, "Oh, yeah, yeah," but I guess it's always been that I've had this sort of ability to find something [interesting in whatever] my father did.

CARUSO: We're going to stop for just a minute, and then I actually want to—I think something we skipped over was hearing about why you wanted to go to or how you wound up going to Harvard for your undergraduate degree. So let me just turn this off, and then—

KARPLUS: Okay.

[END OF AUDIO, FILE 1.1]

KARPLUS: Yeah. That's fine.

EARDLEY-PRYOR: About the photographs from Alaska?

KARPLUS: I took these pictures, [but] I'm wondering what camera I took them with, because my mother had a Kodak Retina, but I don't think it would have taken pictures like that, so I must have had some sort of a plate [camera]—I don't know exactly what it was. [. . .] I know I used her camera a bit when I was at Caltech [California Institute of Technology], before I got the Leica [camera], which started me on my photographic road. But people, when I've had exhibits, sometimes they've asked me, "How could you just go out and take pictures like this without having any education as a photographer?" And the one thing I've come up with, I don't know whether it's true, is that birding, you see something rustling somewhere, and then you somehow have to keep the exact point there in your mind when you lift your binoculars, so you actually find it again. That's not easy to do, and I find nowadays I'm not as good at it as I used to be, but I think maybe having this ability to get a picture in my mind of what I want to see had something to do with being able to do it in photography.

EARDLEY-PRYOR: Framing the bird with the binoculars—

KARPLUS: Yes, right.

EARDLEY-PRYOR: —and then framing the lens of the camera—

KARPLUS: In a lot of my pictures, [like] this one [*holding photograph*], you can look at it if you'd like to, a lot of them are of people like this, where often, the people are not aware that I'm taking pictures of them.

EARDLEY-PRYOR: This does bring something I'm interested in, and I hope we could follow up on it later, but to ask now, is this tradition you have of observing nature from afar, that begins with the microscope, moves through the birding, and then even in your career, as in molecular dynamics particularly, the simulation work, observing nature and seeing it in process, but not necessarily intervening in that process, is that something that you're conscious of through time? Or have you thought about your scientific work in that realm?

KARPLUS: Well, certainly seeing things, observing them, has been very important. Whether the question of interacting with people or not, I don't know. It's true, in many of these cases, the idea was to take photographs of people where they were acting normally and actually didn't know that I was taking photographs of them. I had a Hector lens for my Leica camera, which my uncle brought over, and I got as sort of a PhD present. It's a lens which has a little viewer on it [. . .] and you could look down at this viewer. Say if I wanted to take a picture of you, I would face like this, and hold the camera—

EARDLEY-PRYOR: Away from me.

KARPLUS: —looking at the camera—I would face away and take the picture. And many of the photographs, if you look at them, you will see the people know I'm doing something, and they often are looking to [see] what I'm taking the picture of, but they don't realize that I'm taking a picture of them. I don't [know] whether I can find it, but there's one very classic picture in the Southwest. [. . .] You know, this guy is looking at me. He's wondering what I'm doing. He's looking in my direction; he's not looking at me. He's has no idea that I'm taking a picture of him.

CARUSO: I did something similar when I was at Cornell. **<T: 05 min>** [. . .] I was using a Leica camera. It was manual, and a lot of people were expecting the whir and the buzz of film winding, and I just sat on a bus, rode around on a bus, and just had a camera in my hand, pretended like I was playing with it, and every so often I would snap a picture. And I actually have one of those pictures hanging in my office, because I thought it was just great. It was someone who was looking at the camera, but didn't know I was taking a picture.

KARPLUS: I've actually done that. There's somebody who's actually published a set of pictures taken on [the] subway in New York—not all of his pictures would come out—

CARUSO: Right.

KARPLUS: —because he would have the camera down here. But you learn after a while. I've done it a little bit. What kind of Leica did you have?

CARUSO: I don't even—I don't even remember which one it was. It was probably a 1960s, 1970s Leica.

KARPLUS: And it was film?

CARUSO: Film. Yeah. Completely manual.

KARPLUS: Right, so it was one of the little . . .

CARUSO: Yeah.

KARPLUS: That's what I had. I have it somewhere, but not here.

CARUSO: Yeah.

KARPLUS: It's a beautiful camera.

CARUSO: Yeah.

KARPLUS: I had a 3C, which was probably similar to that. It's very light. It makes no noise, because it has a cloth shutter. [. . .] I used Hector lenses a lot for doing this. Where I've gotten into trouble, once I wanted to submit some of the photographs, portrait photographs, and they asked me did I have permission. I said, "Well, they're all dead." Or very likely. But they wouldn't let me.

CARUSO: Yeah.

KARPLUS: I guess now they're very concerned, and now that I use a digital camera, if I take a picture, still with the same objective, that they don't know I'm taking the picture, but then I'll show it to them, and then often get them to sign something.

CARUSO: Oh, really? Can you tell us a little bit about why—I mean, we know that your older brother, Robert, went to Harvard. Why did you want to go to Harvard, or why did you go to Harvard?

KARPLUS: I did go to Harvard. There was just no doubt that I wanted to go to Harvard. It was a local school, that was certainly an important part of it, and I never considered anything else, never applied anywhere else, and I was somewhat concerned about getting in. There was Richard von Mises who was a professor [at Harvard] in applied mathematics, that my family knew [from Vienna]. I went to visit him, and [after interviewing me] he wrote me a recommendation, but I always did very well on tests and all these SATs [Standard Aptitude Test].

CARUSO: So you applied to one school, you went to that school?

KARPLUS: Right.

CARUSO: Okay.

KARPLUS: The first semester I lived at home, and then Harvard gave me a national scholarship with the specific [aim of making it possible for me to live in a house at Harvard]. I already had the Westinghouse scholarship. It cost two hundred dollars per semester to go to Harvard, which nowadays would be more money, but it's nowhere near what it actually costs nowadays. The Westinghouse scholarship paid for the tuition. Then they gave me a national scholarship. I don't remember how much it was, but the stipulation was that I would live actually in houses [at Harvard], which was a very important part because so much goes on outside [regular classes], and if you have to go home to Newton, every night—

CARUSO: Right.

KARPLUS: —and public transportation isn't so great anyway. It was much worse then than now. I moved into Adams **<T: 10 min>** House, which I moved into for two reasons. It was the most "intellectual" house, and secondly, it had the best food.

EARDLEY-PRYOR: Cooking again.

KARPLUS: I mean, food certainly has played a role in my life for a long time.

CARUSO: Did you have a sense of what you wanted to major in the moment that you arrived at Harvard, or were you—

EARDLEY-PRYOR: You were still involved in the birding experiences at this time, too, right?

KARPLUS: Relatively little [after] Alaska, and I was still thinking when I came to Harvard that I'd go to medical school. It was really in the first semester, and I had Leonard Nash, who was the first Jewish professor in chemistry, and was a great teacher, in the, whatever freshman course I took. And there was a group of us, Gary Felsenfeld, with whom I continued to interact for a long time, and DeWitt Goodman—Gary became a scientist and went to NIH, and Dewitt Goodman actually did go to medical school. There was a group of four or five of us. We had a similar interaction with Nash as I'd had in junior high school, that we worked together, and talked to him afterwards, and could explore things in more detail, and didn't have to worry so much about the exams and such. That had a very important effect on me.

At that time I decided, as I mentioned, that I was more interested in learning about the biological systems than actually being a doctor and applying it. That was one part. Then the other part was that I realized, and I think that was unusual, that I realized that really, to understand biology, you should know chemistry and physics, which nowadays is obvious to everybody. So I majored in chemistry and physics, [a program for undergraduates], which Harvard was one of the few schools to have. My brother had majored in the same area.

EARDLEY-PRYOR: He had done that before? Robert had done that before?

KARPLUS: There were always these good reasons, not really real [good] reasons, but mixed reasons. If you majored in chemistry and physics, you didn't have to take analytical chemistry, which was a good course, but it's not one I wanted to take. I think my brother had also gotten out of it. That was another benefit. There were lots of things that I did when I was at Harvard that were somewhat unusual. [. . .] It was also, in general, a much more open program. You had to take a certain number of courses and a certain number in chemistry and physics, and it was really almost up to you what you took.

I didn't take elementary organic chemistry, which was taught by Louis Fieser—I don't know whether you interviewed him or not. [He and his wife Mary] may have been too early. It was a famous course. They had some notes for the course that [they] had written before he finally wrote the textbook, which was a textbook widely used for many years.[8] I think I got them from my brother. I studied them, and never took elementary organic. There was an advanced course. In my view, [in] elementary organic in those days, you had to learn lots and lots of reactions, and there wasn't very much interest to it. Then there was an advanced course taught by Paul Bartlett, which was the principles of—I don't remember the exact name, but basically, it was much more concerned with understanding why reactions happen.

I took that course without having taken the **<T: 15 min>** elementary course. It was hard for me—not because the material was difficult—but he assumed, you know this reaction, and you know that reaction. Let's talk about what happens. I think it was probably a mistake. It would have been good for me to really have had this knowledge of organic chemistry, particularly [for] trying to understand molecules and biology. I survived the course, and I think I got an A in it. Again, nobody else had ever done this, as far as I know—I did that. I was interested in biology, so I took a course by George Wald, which was a very exciting course on molecules and biology or something.

[8] Louis F. Fieser and Mary Fieser, *Organic Chemistry*, Trade Edition (Boston, MA: D.C. Heath and Co., 1944).

EARDLEY-PRYOR: What was it like in class with George Wald?

KARPLUS: He was a very exciting lecturer, and I got to know him and his wife, Ruth Hubbard, [with whom I] did undergraduate research, mostly with her rather than with him. [. . .] The discovery that retinal to trans-isomerization is basic to vision, was made by them. I think she was in a way more instrumental, because she was a chemist, but until very late in her life, she never was a professor at Harvard. She finally did become one. [. . .] He was a wonderful lecturer. Not everything he said was correct in retrospect, but that's not really, for somebody learning, necessary. There are a number of books. In Bartlett's course, I was first introduced to *The Nature of the Chemical Bond*, [Linus] Pauling's book, which is a very famous book.[9] And that excited me about the idea that it presents chemistry as something you can understand, rather than just learning a lot of things by rote or whatever. Another book was by Albert Szent-Györgyi on—I guess that was called [*On Oxidation, Fermentation, Vitamins, Health, and Disease*].[10] He's the one who got the Nobel Prize for discovering [Vitamin C] in paprika—there was a lot of it—and that's how people got their vitamin C in Hungary, where they eat lots of paprika. And I think his book has not stood the test of time. And then there's [Erwin] Schrödinger's *What Is Life*, which, again, was a very exciting book, and—[11]

EARDLEY-PRYOR: Schrödinger's lectures on "What is Life" happened in the forties, around '43 or so.

KARPLUS: It was a new book at that time, and—

EARDLEY-PRYOR: Was that something that at Harvard was passed around as in discussion?

KARPLUS: I don't know. I discovered it and I read it. And I heard in an anniversary of Schrödinger's life, Max Perutz, who I also had interactions with, as you'll hear later when I was interested in hemoglobin, I was invited to give a lecture in a symposium, and Max Perutz gave a lecture. And what he said about *What Is Life* was either what was in there was known or it was wrong, which was not a very charming thing to say. Max Perutz was very didactic, and he

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[9] Linus Pauling, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry* (Ithaca, NY: Cornell University Press, 1939).

[10] Albert Szent-Györgyi, *On Oxidation, Fermentation, Vitamins, Health, and Disease*, The Abraham Flexner Lectures Series Number Six (Baltimore: Williams & Williams Co., published for Vanderbilt University, 1939). See also, Joseph S. Fruton, *Molecules and Life: Historical Essays on the Interplay of Chemistry and Biology* (New York: Wiley; 1972).

[11] Erwin Schrödinger, *What Is Life? The Physical Aspect of the Living Cell,* Lectures delivered at the Dublin Institute for Advanced Studies at Trinity College, Dublin (Cambridge, UK: Cambridge University Press, 1944).

would say things like that, though he was a very sweet person, and wonderful person to know. Well, we'll get to that later on, when we get to hemoglobin.

But what I'm trying to say is that a number of these books that—either at the time or later—have turned out not to be correct can present something, **<T: 20 min>** a picture of something. In this case biology was very important to me in terms of saying, "Gee, this is something that one can really do something with." And then I decided that chemistry and physics would be very important to know, and that was one [part] of my development in that area.

CARUSO: So what I'm curious to know is, again, going into college, you were thinking maybe being a physician, and then your thinking starts to change about what it is that you want to pursue and the courses that you want to take. Did you have a sense of what you would be doing with a degree in physics, in chemistry? Was there a career that you had in mind when going into that major, or did you have a sense of what it is that a scientist—maybe not necessarily an academic scientist—did for a career?

KARPLUS: [. . .] I felt I would want to be a professor; there was no doubt in my mind.

CARUSO: Okay.

KARPLUS: I suppose I was a little bit following [in] my brother's footsteps, I never thought about industry, though I had one experience, which will come up later with IBM. I don't know whether this is normal for people to—I just knew I wanted to go, would go, to Harvard. And I knew I wanted to do research in whatever would develop out of my background in biology. I was very much interested in vision as a result of Wald, and that was one experience. And [Kenneth V.] Thimann—one of the dreams I had was I had observed plant galls, these little things that plants make, where an insect lays an egg in the plant, and then the plant makes this beautiful egg-like [structure]—you can compare it to an egg, essentially—where there's enough nutrient, so by the time the grub has grown up and is ready to come out and become a butterfly or a moth, he's eaten its way out of this egg. [. . .] It was always curious. And it may have been that my father called my attention to that, and I thought this would be a great thing to study: how does having this grub there get the plant to make an egg-like structure? I never actually called it that before now, talking about it, but really [a real] egg has enough nutrients, so by the time the little bird has eaten its way out, it's ready to come out.

[The insect] gets the plant to do this special thing, which doesn't do it any good. I thought this would be really a nice project to look at, but I never did. I never became really an experimentalist, but—and it may have been now that I think back on it—I think my father showed them to me, and you can cut them in half and you can see how far along things are. Then I read about them. [. . .]

CARUSO: So you and your brother overlapped for one year at Harvard?

KARPLUS: Yeah, I—

CARUSO: And so he was applying to graduate school during that period of time, or had he been accepted already?

KARPLUS: He had already been accepted at Harvard.

CARUSO: Okay. Okay.

EARDLEY-PRYOR: Did he stay at Harvard for graduate school?

KARPLUS: And let me just make sure I'm saying the correct thing. No, he was already in graduate school at Harvard—

CARUSO: Okay.

KARPLUS: —when I came in '47.

CARUSO: So he finished Harvard—

EARDLEY-PRYOR: Undergrad.

CARUSO: —undergrad early?

KARPLUS: He took only two years.

CARUSO: Oh, okay.

KARPLUS: That's no better than my finishing in three years, because this was **<T: 25 min>** after the war, and [during the war, when my brother was an undergraduate], Harvard was teaching three terms a year.

CARUSO: Okay.

KARPLUS: So essentially taking two years was the equivalent of taking three years.

CARUSO: Right. So six semesters' worth of—

KARPLUS: Right. He did finish in a shorter time than normal, but it wasn't quite as [exceptional as it might appear].

CARUSO: Right.

EARDLEY-PRYOR: I noticed that you were drawn to these biology professors, like George Wald and Albert [Szent]-Györgyi—Nobel winning professors—who were becoming increasingly interested in the chemical dynamics of life.

KARPLUS: [Yes].

EARDLEY-PRYOR: Was that something that you think—

KARPLUS: The chemistry of life. I wouldn't say "the dynamics."

EARDLEY-PRYOR: The chemistry of life.

KARPLUS: Right.

EARDLEY-PRYOR: Was that something that was new to their careers at that point, or was—I guess I'm interested in the trajectory of biology becoming increasingly more molecular biology in part because of the work that Linus Pauling had been doing and how these Harvard professors across the other side of the continent were pursuing either similar—or maybe responding to some of those interests. So I'm wondering—because it spurred your career, certainly, your interests—if this was a new field for them, if this sort of chemical view of life happened to just be something that was new and shaping some of the work happening at Harvard, and you came in at that moment.

KARPLUS: Right. The answer is one has to look up what Thimann [did]. It was certainly unusual at Harvard—one of the great things about Harvard was that you could take any courses you want. There were these requirements, but they were pretty minimal, and the attitude was you take the course and if you didn't have prerequisites, that's your problem if you fail. [Most] of these courses I took had prerequisites which I never took. I took the courses because it seemed to be interesting, and from my point of view, they were trying to understand life chemically.

I think they were unusual at that time. Now whether in their history this was something new—my guess is it wasn't—Thimann had been working on auxin in plants, and how plants adopt different faces to sun, which people are just now really finding out how it really works. My guess is it'd been a long part of his career, and Wald's, too. They're the only courses that I took in biology. I took a course on the structure of government, taught by [Louis] Hartz. [He was] known to be an outstanding lecturer. And one in [abnormal] psychology of the mind [by Robert White]. I think there [already was] the Confi [Confidential] Guide to Courses, which [identified] these people [who were] great lecturers, and I looked around, and I took probably a [half dozen or so] courses that I had no—[12]

EARDLEY-PRYOR: Electives?

KARPLUS: —reason to take. One didn't have to [satisfy] general education requirements [at that time]. It's much more structured nowadays to force people to go out to fields [outside their majors]—and those courses start at an elementary level, so that anybody can take them without prerequisites. The courses [I took were ones you took] if you were in that department, you went through a sequence, and then ended up there. It was really an exciting experience for me to be able to do that. I think that was one of the important parts of being at Harvard [for me].

CARUSO: I think that might be a good stopping point, unless you have—all right. Well, thank you so much.

[12] The "Confidential Guide to Courses" is written annually by the staff of *The Harvard Crimson* for incoming freshmen, as a review of the available courses written by one or more upperclassmen who have taken the course before.

EARDLEY-PRYOR: Yeah.

KARPLUS: Thank you.

[END OF AUDIO, FILE 1.2]

[END OF INTERVIEW]

INTERVIEWEE: **Martin Karplus**

INTERVIEWERS: **David J. Caruso**
Roger Eardley-Pryor

LOCATION: **Harvard University**
Cambridge, Massachusetts

DATE: **4 March 2016**

CARUSO: So today is the fourth of March, 2016. We're here for another interview with Dr. Martin Karplus at Harvard University. I'm David Caruso. I'm here with Roger Eardley-Pryor. As we mentioned, we're going to pick up where we left off last time. We had been speaking about your time at Harvard. I'm not sure if we necessarily got into a lot of detail about why you chose the California Institute of Technology, but I think that might be a good place to start to—

EARDLEY-PRYOR: I'd actually like to step back—

CARUSO: Sure.

EARDLEY-PRYOR: —for the last class you had at Harvard was that Wood's Hole [Oceanographic Institution] seminar in the summer.

KARPLUS: Right.

EARDLEY-PRYOR: What are some of your memories of that experience?

KARPLUS: I was in the physiology course. It was a course mainly for graduate students and postdoctoral fellows, and I was the only youngster in the course, so that was rather special. And while I made a number of friendships there, with Alex Rich and Jack Strominger, that lasted for our lifetime. Strominger is still alive, and Alex died recently. For me, it was very special. The way I was able to go there was that I'd been working with George Wald. He recommended me, and if Wald recommended you, then you got it.

[. . .] There was a lot of free time. One of the traditions was to go to the beach, and all these famous people would be there on the beach: Szent-Györgyi was there, and Otto Loewi was there, and I got to know them. George Wald would introduce me. One of the things I discovered was that Otto Loewi—now I'll see whether I can really remember the details—he did studies of the heart, and how the heart responded to stimuli. He discovered by isolating it, that there were hormones that were affecting the heart.

I realized that actually what he did was exactly the same thing as my grandfather did in Vienna in the 1900s, when he discovered that function of the hypothalamus, [. . .] by taking cats, cutting all the nervous impulses that could come from the hypothalamus. One of the things it controlled all kinds of—I can't think of the word right at the moment, there was a word for it, where it's not something that you do consciously—involuntary actions—he isolated it and watched the cat's pupils opening when he stimulated it, and he reasoned that there was some sort of fluid which was actually transmitting the information. It is now realized that the hypothalamus is the only part of the brain that has endocrine cells, just like in other parts of the body, that release hormones. At the time that I met Loewi and talked with him, I wasn't aware of the details of what my grandfather had done—my paternal grandfather—there were lots of things like that.

Also, the social life was very active there. It was a lot of fun. **<T: 05 min>** People in the course did various experiments, and I did experiments on photoreactivation in bacteria that were sensitive to light. Nothing really very exciting came out of it, but it was one of the times I decided I wasn't really an experimentalist.

The other thing also was that I was already very much involved in cooking, and there were squids and lobsters and all these other wonderful things, that were hardly used. They took the giant axon out of the squid, and then the squid was left over, so every evening I would go around and collect all these things, and then make a stew for my friends. Being away from my parents, really, because when I went to Harvard, I lived at Harvard, but it wasn't the same thing. I think it was very much a formative experience.

When I went to Caltech, I roomed with Alex [Alexander] Rich for the first year, which we should get into later on.

EARDLEY-PRYOR: At Wood's Hole, this is late forties, early fifties, around 1950, and this is as—

KARPLUS: Forty-seven.

EARDLEY-PRYOR: Forty-seven, even?

KARPLUS: Yeah.

EARDLEY-PRYOR: That early? So the United States is—

KARPLUS: No, sorry. It was 1950.

EARDLEY-PRYOR: The United States is moving closer and closer to this Cold War confrontation with the Soviet Union. Was politics an issue of discussion on these beaches at the summertime between scientists?

KARPLUS: Not that I remember. It was much more on the science and new ideas and exchanging ideas.

CARUSO: Do you recall any responses to the development and use of atomic weapons, the potential for—I mean, the government had such a major role in the development of atomic weapons. It took in a lot of scientists, a lot of scientists participated in it. After the war, you start seeing scientists reject the use of such weaponry. So even if there wasn't discussion of the politics of the Cold War, were the people that you were talking with, speaking with, thinking about the potential of their research being used in governmental ways or anything along those lines? And—

KARPLUS: I think George Wald was involved in some activities, wondering about the atomic weapons and what to do. Yeah.

CARUSO: Okay.

EARDLEY-PRYOR: With the decision to go to Caltech, you knew you wanted to be on the West Coast. Why?

KARPLUS: I thought it would be good for me to—I couldn't imagine being in the middle of the country, and so there was the choice of being on the East Coast, and following in my brother's footsteps, or being on the West Coast. And the two institutions that attracted me were Caltech and Berkeley. I had to decide which one. I applied to both of them, and got into both of them, and then had to decide where I wanted to go. It's the story which I presume is in there—the *Spinach* article—that my brother was at the Institute of Advanced Studies [at Princeton University], and I visited him there one day, and he was working for Oppenheimer, who was at that time a professor at both Caltech and Berkeley.

I asked him about what would be the best place to go, and we talked about—that Berkeley was a huge institution. Caltech was a much more intimate institution. He didn't know that much about the chemistry. He didn't know Linus Pauling, personally. And he made this remark, which was that Caltech was a shining light in a sea of darkness. And so talking with him and then also with my brother, I decided **<T: 10 min>** I would to go to Caltech. And—

CARUSO: What did that mean, a shining light in the sea of darkness? Just—

KARPLUS: Well, the Pasadena area, in contrast to Berkeley—

CARUSO: Okay.

KARPLUS: —was a very reactionary area. There was nothing to do there, while Caltech was really an outstanding institution.

CARUSO: Okay.

EARDLEY-PRYOR: How did you get across to California?

KARPLUS: My parents had given me a car, and I drove out there. I made a number of trips back and forth, and started with going through Canada [to California], and I would come back in the summer, usually, for visiting my parents. The last one was through the south of the US, with various experiences that happened there.

CARUSO: Well, we'd like to hear about some of the experience—you had come to this country at a relatively young age, but you had been situated principally in Boston. And so I'm curious to know why you were trying different routes, and what it is that you experienced on those routes that kind of stood out, either about—you mentioned you were in Canada, so the differences between American culture and Canadian culture at the time, or were you sightseeing along the way? Did you wind up going on Route 66 at some point? I'm just curious to know a bit more about some of the adventures you had on the road going back and forth between the East and West Coast.

KARPLUS: Going through Canada, [. . .] I went across, and stopped in the national parks, and rode around on horses. It was mainly to admire nature. I don't remember whether we talked about when I went to the Gaspé Peninsula earlier. I was very much interested in birds, and I persuaded my parents to go out to the Gaspé Peninsula, where there was a big rock. You couldn't go to it—it was protected—but where there were various alcids that nested there. I bring it up now because I remember they were driving through the countryside in Canada to get there, and seeing that there were these towns, relatively small towns, with local agriculture and small inns. And the one big building was the Catholic church. I still have this memory of driving through, and the first thing you saw was this huge church. I had the feeling the people were relatively poor, but somehow they managed to have a big church.

But in this trip through Canada, I would sleep in the car or [in a tent]—that trip I was all by myself. Some of the other trips I had people with me. And I was mainly enjoying nature, and birdwatching. Those were the two main things along that northern route. The other route that I mainly remember is the one that went through the deep South. Route 66 appears later [. . .]**<T: 15 min>** When we drove through the deep South—

EARDLEY-PRYOR: Who was we?

KARPLUS: —with a friend, Irwin Oppenheim. And we [were driving through Texas] and it was very hot. We decided we'd take a swim to cool off. We passed an area where there lots of people, and we went further along, along the river, and saw there was a completely empty area, but it still had sort of a dock, and nobody was swimming there, so we went swimming there. After we'd been there a relatively short time, all of a sudden a truck came up, and several people jump out of it. They're all carrying guns, and we had no idea what was going on. But they said, "This is the area reserved for niggers," which was the word they used, and, "What are you doing here? You northern agitators or something?"

It took us a long time to persuade them that what we were doing was [just to swim where we would not bother anyone because we wanted to wash ourselves]. They finally let us go, and we, of course, were deathly frightened. We didn't know what would happen. We had read about lynchings and all that sort of thing. That is one experience I [will never forget].

CARUSO: What was the reason that you wanted to go through the deep South? Was it just to see a different part of the US?

KARPLUS: Yes, these drives were an opportunity to see different areas of the US, and—

CARUSO: Were there any landmarks that you wanted to visit along the way, or any specific routes, or was it just "let's go through the South" and then—

KARPLUS: In South, there wasn't that much. We went through Las Vegas [Nevada] and spent a little bit of time there. We decided that we could lose, say ten dollars, which in those days was not negligible. You could play for half a day, if you were conservative. Landmarks that I visited were in the middle of the US. Outstanding were Bryce [Canyon] and Zion National Park.

EARDLEY-PRYOR: What did you do at these parks? You mentioned going to Banff [National Park] and Jasper [National Park] and Bryce and Zion down in Utah. What were—so when you go to a park, what's your typical experience there?

KARPLUS: They're variable, depending what it was. We would camp for several days, and walk around, ride horses around, and they are so beautiful and spectacular. Birding was always in the background, and I knew what birds we might be able to see that were very rare on the East Coast, so I was looking for some of the birds. Don't ask me the names. It was that type of experience. When I graduated [with a PhD from Caltech], my parents gave me a Leica that my uncle had brought over from Germany. Then I went on Route 66 [. . .] and I took [a large number of Kodachromes]. For example, I ended up at a Navajo festival just by accident. I was driving there, and visited some of the Hopi pueblos, and Navajo country, as I just said. It was their annual festival, which was just a festival for them. They had a Ferris wheel, and a shooting gallery, and other things. And there were only Navajos. And I have some beautiful photographs of them. And I was the only **<T: 20 min>** non-Navajo there. I took lots of pictures. I actually spoke very much with the people, but they saw me taking photographs. They didn't know that I was photographing them, but [thought I was photographing] something else. It was a great experience.

Nowadays, this annual Navajo festival has ten thousand tourists who come there, and the Navajos are really performing, rather than having their own experiences, where they also were trading and such.

EARDLEY-PRYOR: What are your memories when you came to California that first time, coming into the Valley, the LA [Los Angeles] basin?

KARPLUS: I remember when I came to the LA basin. I drove from Canada, south along the coast, which was very spectacular.

EARDLEY-PRYOR: Oh, down from Big Sur.

KARPLUS: Route 101, which is the coastal route. I remember on the way finding a place that had abalones, which was a great introduction to them. But when I ended up in the [LA] basin, what I remember is the smog. It was really terrible in those days. I had a very bad headache for several days. I just couldn't do any anything. Then you sort of adapt to it. I still remember that, from Pasadena, from Caltech, the mountain range there, and every afternoon it would disappear, the fog was so thick. Nowadays, it's obviously much, much better. It's all the control, emission control and such. But that was my first impression of the area.

EARDLEY-PRYOR: Did you regret not going to Berkeley? [laughter]

KARPLUS: I'm not sure. I'm not a person to regret things. I'm always moving forward, which my wife describes [it is because] I don't have enough feeling about what's happened.

EARDLEY-PRYOR: So at Caltech, your interest initially was biology, in the biology department.

KARPLUS: Right.

EARDLEY-PRYOR: And you were going to work with Max Delbrück.

KARPLUS: Right.

EARDLEY-PRYOR: Tell us about that experience.

KARPLUS: At Harvard I had majored in chemistry and physics, and I'd majored in that because I had decided that if you wanted to understand—I may have said this before—understand biology, you had to know chemistry and physics, so I was already directed towards this. So I decided it was about time to start doing some biology. And Max Delbrück was a physicist who had become a biologist. He was one of the people that put phage genetics on the map, with [Salvador] Luria at MIT [Massachusetts Institute of Technology], and other people. There is the story, I don't know whether it's true, that when he was a young physicist and working for Niels Bohr, Bohr told him, "You really should go into another field. Biology might be an interesting one to work on." I don't know whether that's apocryphal, but it certainly [appears reasonable].

I decided to work for Max, as everybody called him, within the biology department at Caltech. And one of the things that Delbrück did—at the time, I didn't know that he did it to everybody, that it was sort of a rite of passage—was that he had you give a seminar. I decided to give a seminar about vision, about the work I had done on that.

EARDLEY-PRYOR: With George Wald?

KARPLUS: With George Wald, right. Delbrück did not know very much chemistry, but I don't think that was really the problem. I started my lecture. Of course, I was nervous. And Delbrück , after a couple of minutes, said, "I don't **T: 25 min>** understand," by which he meant not that he really didn't understand, but that I wasn't being very clear in my explanation.

This went on for fifteen, twenty minutes or so and I was getting more and more upset. I had hardly gotten beyond my introduction because of all the questions from Delbrück. Nobody else asked any questions. He was sitting in the back of the room. I had gotten to know Richard Feynman. I had taken his course, and then he used to come up to our house and play the bongo drums when we had parties. I'd invited him, because he was interested in everything, as was clear from his lecture book, *The Feynman Lectures*.[13] He was also in the room.

At a certain [point] he, Delbrück, who was in one seat in the back, [again asked his question]. Feynman was maybe three seats away. It was a relatively small room. And Feynman all of a sudden whispered, but so everybody could hear, "I can understand what he said, Max." At this point, Delbrück got very red in the face, and rushed out of the room. That was the end of my seminar. Then I think he said, "Come to my office," where he told me, "There's no way we can work together. You'll have to find somebody else."

I went to George Beadle, who was the head of the department, and talked with him. We talked about various things, but I finally decided I would go back to chemistry, maybe because I felt safer there. I decided to work for [John ("Jack") G.] Kirkwood, who was doing some biologically—that was not his main interest—related research about electrolytes and proteins, and I started to work on that.

CARUSO: So at Caltech, I mean, nowadays when I think about the way the graduate school works, you apply to a department, you're accepted into that department, and that's where you're going to work. Was it as simple as just going and asking to work with someone else who wasn't in the—or was Kirkwood also situated in the biology department?

KARPLUS: He was in chemistry. He was somebody, one of the outstanding people in statistical mechanics in chemistry. There was Onsager at Yale, and then Kirkwood, who was probably next in the hierarchy. I just went to see Kirkwood and asked him. He looked at my record and he said, "Okay." There wasn't any sort of formality of changing from one department to another.

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[13] Richard Feynman, Robert B. Leighton, and Matthew Sands, *The Feynman Lectures in Physics* (online edition), The Feynman Lectures Website, http://www.feynman lectures.caltech.edu/.

CARUSO: Okay.

KARPLUS: Here at Harvard, there is a graduate student who's very bright, and wants to do some work with me. I don't really want to take on a graduate student, because of my travels and everything else, officially. He's been trying to find other mentors in theory. One thing I said is, "You should look also at applied physics, and physics as well as chemistry." He looked into it, and they said there's no problem. He would still get his degree probably in chemistry, but he would work with somebody in these other areas, which is a little bit different from my case, that I actually switched to biology. But basically, Kirkwood said okay, and that was it.

EARDLEY-PRYOR: That original worst seminar for Max where he left red in the face, what was the topic that you were trying to explore?

KARPLUS: I was talking about vision. I had invented a mechanism for vision, which wasn't known in detail, but partly based on the experiments of **<T: 30 min>** Wald and his wife Ruth Hubbard, who was the more chemically educated person. That's another [case] where he was a professor, and for many, many years she was just the senior research associate, which permits you to stay at Harvard. There are not very many at Harvard. Harvard doesn't have [permanent] people—more now than then—who are not part of the teaching faculty. [There were] a few research associates and senior research associates, which were tenure positions, [except that their positions depended on outside funding.] It was only much later, I don't remember the exact year, that she finally was promoted to being a professor.

But anyway, that's what the seminar was, a mechanism for vision based on what was known and what wasn't known. Some of my ideas were correct, and others were wrong. But that had nothing to do with this being the worst seminar that he had ever heard. But then it turned out I learned it partly from some of his other students, and partly from something that the other students wrote, that he basically did the same thing to everybody. Everybody gave the worst seminar he'd ever heard. As I said at the beginning, it was a rite of passage that—I don't know exactly why— if you could survive that, then he would accept you as a graduate student. So I don't know what he actually thought of me, but it was just this incident with Feynman. Otherwise he had a very social relationship, Delbrück, with his students. He would give parties. He had Shakespeare readings. It was called the Shakespeare and Spaghetti Club and took place at his house. With his wife, he would invite the group of students, and they would do Shakespeare readings and have dinner. The other thing is that the story of what happened with me and Feynman was remembered by many people, but in the retelling of it, they didn't know who the person was, that it was actually me.

One time I met Delbrück when I was at Cold Spring Harbor for a summer, and he was there giving lectures, and he seemed to have forgotten that we had this incident. We had a very pleasant relationship. Other people [there] told the story about what happened [with] Feynman.

EARDLEY-PRYOR: Who were you living with at Caltech?

KARPLUS: Initially, I was living with Alex Rich. He had had a roommate, Bob Shulman, who went to work at Hughes Aircraft for a while. I don't remember what research he did. Alex, when I met him at Wood's Hole, said, "Would you like to live with me?" [. . .] I was going out there and didn't know anything about the place, so I lived with him for a year. And what living with Alex meant was sort of unusual, because Alex kept a schedule where he would get up sometime in the afternoon, and go to work, and work all night. I had a much more normal schedule, so we really only met for dinner. I would be cooking dinner, obviously, and we'd chat for a while. But otherwise, we never saw each other. And so it was nice.

The next year, Gary Felsenfeld, who was officially the same year at Harvard, but I finished a year early with taking the physiology course, also came out to Caltech. We rented an apartment, and then we rented a house, actually, finally, in Altadena, [California], where we had the parties **<T: 35 min>** [I already mentioned].

EARDLEY-PRYOR: What were the parties like?

KARPLUS: They were great fun, with dancing and drinking and Feynman playing the bongo drums. One of the things we did was that we would buy very cheap wine. We had a number of bottles of good wine that we had drunk, and I would just pour the cheap wine into these bottles. Then people were [thinking they were sampling] different great wines, and people would say, "Oh, this is really much better than this." It's amazing how little most people who are wine connoisseurs really know about this. I also made whiskey taking some alcohol from the lab, very pure ethyl alcohol, and putting in some burned sugar and a few other items. Those were the experiments that I did. We would also have that at these parties.

And one time the Paulings came. We had a backyard and there were lots of snails. I remember that he collected the snails to eat them, but I just wonder whether that's really true. Certainly he collected the snails, but I later discovered when I was collecting snails that it's really a very complex procedure [to prepare them for eating]. You have to let the snails diet so they eat up all their slime before you try to take them out [of their shells] and cook them. So I don't know, I never asked—I didn't at the time know the complication, [whether the Paulings actually ate the snails.]

Caltech really had a wonderful atmosphere. One time with Delbrück, and sometimes with just friends, we went to the Mojave Desert, which is not that far away. In the spring, there are rains, and then there are plants that come up. They're called belly plants, because you have to get down on your belly to see them because they're so small. They last for a little while, enough to form seeds. There were a lot of good experiences there. One time—this has nothing to do with the science— we had decided that we would go, I think it was New Year's Day, that we would go up into the mountains and go skiing in the morning, and then come down to the beach and go swimming in the afternoon. That was just sort of an experience that you could have. In that sense Caltech was really a very friendly environment. All the professors treated you essentially as equals.

EARDLEY-PRYOR: Was Feynman any good at the bongos?

KARPLUS: Yeah.

EARDLEY-PRYOR: Was he?!

KARPLUS: He was good enough. He was good for dancing and jumping around. Yeah.

EARDLEY-PRYOR: That's funny.

KARPLUS: There's a picture of him on a website [playing the drums], actually, which I have in one of my lectures.

EARDLEY-PRYOR: You began work with John Kirkwood in the chemistry department, and then Kirkwood got an offer to leave—

KARPLUS: From Yale.

EARDLEY-PRYOR: From Yale.

KARPLUS: So the question came up, what would I do? While Kirkwood was there, Alex Rich and Irwin Oppenheim, both whom I've mentioned, and I asked Kirkwood whether we could—he gave an advanced course, very rigorous course in thermodynamics—[prepare] lecture notes. Each one of us would take one of the lectures in cycles, and write them up, and then work on them together. That was a very good experience. Irwin Oppenheim—who had been working for Kirkwood for quite a while, **<T: 40 min>** and knew more about the subject than either Alex or

I did, but we worked together on this and put out the set of notes, which is still in the Harvard chemistry library. A year or two later, after Irwin had graduated, he wrote them up and published them with Kirkwood as a book.

I had done something, but I had not completed anything with Kirkwood by the time he left. I hadn't worked with him very long. Pauling asked all of Kirkwood's students whether or not they would like to work with him. At the time, Pauling wasn't taking any graduate students. He had only postdoctoral fellows working with him, but he said, "If you stay here, you can work with me."

All of the other people, [Robert] Zwanzig and Irwin Oppenheim and others, had worked with Kirkwood for a longer time, and went with him to Yale. I was the only one who stayed, and so I had a chance to be a graduate student with Pauling.

EARDLEY-PRYOR: Was that the drive for why you stayed, to work with Pauling?

KARPLUS: I had to decide, would I go along with Kirkwood? But I really liked Caltech and its atmosphere.

EARDLEY-PRYOR: What was working with Pauling like?

KARPLUS: He was very open, and he had many good aspects. You had to learn what it was like to work with Pauling, and there were a number of items. One was that at Caltech each graduate student had a little open mailbox. Nowadays, the mailboxes aren't open anymore. Every morning when I came in, I'd see a little yellow note in my mailbox, which was a note from Pauling, signed Linus, where he would say, "Wouldn't it be interesting to . . ." I can't remember all the subjects, but I would see that, and I'd say, "Oh, Pauling wants me to look at that," and so I would start working on it. Then I would receive another note the next day saying, "Wouldn't it be interesting?" Fortunately, I knew some of the postdocs—like Alex Rich, Massimo Simonetta, who was a friend for a long time, Jack Dunitz, who was there at the time—and they all said, "We all get these notes from Pauling, and we just either throw them away or file them away. Maybe sometime later we will work on this subject, but he doesn't expect you to do anything on that." So that was one thing.

I did want to do something biologically related, and decided—Pauling was interested in hydrogen bonds, and he had some suggestions—to take the simplest hydrogen bonding system, which is the bifluoride ion, which is $(F\text{-}H\text{-}F)^-$, and try to do a quantum-mechanical study of the hydrogen bonding and the origin of it. Pauling said okay, and I would talk to him about questions related to it, and hydrogen bonding in general. One time I asked him a question, what he thought would happen in this particular hydrogen bonding environment, and he said, "Well . . ." This was his custom. He would look at the ceiling for a while, and give me an answer. And I asked him, "Why do you think this is what's going to happen?" And he gave me an explanation. I said, "Yes, yes," and walked out of his office, and thought about it, talked with my friends about it. Clearly, the explanation was wrong, and so I presumed the answer that he came up with was wrong. **<T: 45 min>**

I went in again the next day and told him, "Well, you know, this really doesn't make any sense." I probably said in a somewhat more polite way, and Pauling said, "You're right. You're right." And he thought again, and gave me another explanation, but the answer was the same one. And this happened again, it was wrong, his explanation. The third time that I went in, he came up with a new explanation. The answer was just always the same, and this time it really made sense.

This was very important, that somehow he intuited the answer. He was a man who had an astronomical knowledge of chemistry and everything else. And somehow he was able to find the right answer without having thought through the problem. If he wrote a paper, then he would work out why it was true. But this was very important in my life, I think, in believing in intuition, that you can actually work things out very crudely and come up with an answer that you think is meaningful. And often with my students nowadays, I'm at the same stage, that I have an idea, "I think it would give such and such," and then I would give them this idea, and they would work through it to really find a good explanation. If they asked me, I would give them my rationale for this. But this [idea], that you should believe in intuition—not always, you might be wrong in some cases. But that was very important in being able to do things.

So Feynman once remarked that he worked in a similar way. He would have an idea. He would very crudely try to see whether it made sense. And if it did seem to make sense, then he would go back and work very carefully to make a description—a derivation I guess is a better word—which was acceptable to the general public for a journal. [. . .] It was very important to have new ideas, but you shouldn't work your way to a result if you don't know or don't have the feeling that it's really something very interesting.

EARDLEY-PRYOR: How did that manifest for some of your later work, later in your career?

KARPLUS: I believed in my ideas, and even if other people said they made no sense in some cases.

EARDLEY-PRYOR: What was an experience where you got pushback and you continued to pursue?

KARPLUS: That has to do with molecular dynamics and what the Nobel Prize is for, in my thought—though not in the thought of the committee, but that's another [matter]. I'd been working on very simple systems, and realized that for even light atoms, which you would expect to be—like hydrogen atoms— as quantum mechanical as possible [Richard N.] Porter and I, [. . .] we calculated with classical mechanics the reaction of a hydrogen atom with a hydrogen molecule, to give a new hydrogen molecule, and have one of the atoms kicked out [. . .].

I felt that if classical mechanics could be used for these light atoms, it should be applicable to studying proteins, and so that's what started the—**<T: 50 min>** molecular dynamics [simulation] of the BPTI [bovine pancreatic trypsin inhibitor] molecule. And many people in chemistry—some of them still here now—said, "We can't really understand the collision and reactions of three or four atoms at a time. Why do you think you're going to [be able to] study the behavior of a molecule that has five hundred atoms or more?" And the other was the biologists, who I talked to them about doing this. I had some friends who said, "You know, it's not really very interesting, even if you can do it, so what?"

And so in the initial stages when we did this, it was an area where people said it couldn't be done. If you could do it, it wouldn't be very interesting. I felt they were wrong, and certainly that turned out to be true.

EARDLEY-PRYOR: Yeah. Follow your intuition there.

KARPLUS: Yeah.

EARDLEY-PRYOR: So you're at Caltech from 1950 to '53. You're around twenty years old when you start there.

KARPLUS: Right.

EARDLEY-PRYOR: And you finish your PhD with Pauling at '53. What was the process of finishing your dissertation like?

KARPLUS: Let me mention something earlier. One of the things you did in the middle, you had some sort of a candidacy exam, and this was an oral one. Harvard and other universities have tried to decide what's the best way of doing this. They have mainly good students, so it's not really to try to get rid of people. And so [the department] goes from having oral exams, or written exams on special subjects, or having qualifying exams, where they don't know what it's going to be on. At Caltech at that time they had the system of an oral exam. Pauling and a number of other people asked me various questions. It was going along fine. And then Pauling asked me about his theory of metals, which I knew about, so I said, "Let me talk about copper." And I said, "Let's see, what's the atomic number of copper?"

And Pauling said, “Start at hydrogen and go through the periodic table until you get to copper.” And I couldn’t do that. I’m not sure how many other people could do it either. Finally he said, “Okay, well, this atomic number, copper,” and then everything went fine, and we had a big celebration with Feynman and other people at the house.

But afterwards, Pauling said, “You should really learn the periodic table. Every chemist should know the periodic table,” which I don’t think is true. It was in a gentle way he took me aside. It wasn’t a question about my being able to do things. I [began my] work on the bifluoride ion, and realized very quickly that if you just did a quantum mechanical calculation, which—you could do at that time—with IBM card machines and tables for integrals. There are a lot of things that now you just press a button and you can do. At that time it was difficult to do. I realized that at the level that one could study this very simple molecule quantum mechanically, you couldn’t get [a meaningful] answer without putting in some sort of empirical information. And it’s particularly true [in a problem where] there are both ionic and covalent contributions. The bifluoride ion has one negative charge. And the extra electron can be on one fluorine atom or the other fluorine atom, or you can have **<T: 55 min>** a structure which has a negative charge on the fluorine, and hydrogen, and a positive charge on the other fluorine, so the net charge is always minus one.

To get the correct spacing of the different energy levels which you include in—in my case, it was a multivalence bond description—it would require much higher-level calculations than you could do. My idea was to put in experimental energies for putting an extra electron on these various atoms, or removing one electron, so that the atomic description would be done from data that are known. There was a table of atomic energies where you could look them up.

I developed a method for introducing the [data] into the problem. That was [an important part of my thesis]. There are two things [that happened]. One is that about the time I was writing up my thesis, [William E.] Bill Moffitt—my predecessor [at Harvard], who was a really outstanding theoretician—came up with a method that was very similar to my method. His method was better in some ways, and mine was better in other ways. So I asked Verner Schomaker, who was one of the professors [that I trusted]. He had the function, amongst other—he did electron diffraction—of being the person that Pauling bounced his ideas off. He was the only person there who could tell Pauling, “Well, this doesn’t make any sense, Linus.” I can still remember some of these meetings.

I talked with him about it, and he said, “Don’t worry. You did this originally, and [there will be no problem about you getting your degree],” but I was both so upset and disgusted that I never published my thesis. But then in actually writing the thesis, which you asked about what happened there. [The research] was essentially done, but I was procrastinating [about writing it up]. Pauling came into [the office] one day and said to me, “I’m going away for three months in about a week or so. [. . .] It would be nice if you finished before I went away.”

So I worked very hard, and I wrote my thesis in long hand, and various friends, like Alex Rich and others, typed it all up. We finished it in time, and I had the exam. It went fine. [. . .] Not the work of doing the thesis, but the writing, was done in a very short time, and I suppose

I'm lucky, since I was able to do it. It was great that Pauling said that he [was leaving]. I guess he was aware what the situation was, that I was done, and just somehow wasn't writing it up.

EARDLEY-PRYOR: How did you hear about the Moffitt publication?[14] Did somebody come to you with it?

KARPLUS: No, people didn't know. It was [included in] a compendium [of a meeting, I believe], that appeared at that time, which included Moffitt's method and others. And I don't remember exactly how I found it, but I found it.

EARDLEY-PRYOR: What was the initial reaction? Was it you need to go camp in the wilderness for a while, or just get away from work for a little bit?

KARPLUS: I was very unhappy about it, and I worried that having this—I'm sure it was not actually published. [. . .] But maybe that I wouldn't be able to **<T: 60 min>** get my degree with what I had done, even though—it was significantly different and more specialized than what Moffitt had done. I was very unhappy for a while, and didn't talk to anybody for a little bit. Then finally, I talked to Verner Schomaker, and he said, "Don't worry about it," [as I already mentioned].

EARDLEY-PRYOR: How has your writing process changed from that frantic three weeks of hammering out the dissertation and getting it done? Do you have a similar process now, where you kind of lock yourself away and hammer something out, or how has that evolved, the way you write and publish now?

KARPLUS: The first paper I published in chemistry was when I was a postdoc with Charles Coulson in Oxford.[15] At the time, I had a similar problem [to my Delbrück saga]. I was going to work with [Sir John] Lennard-Jones, who was at [University of] Cambridge and was one of the outstanding theoretical chemists. He went to be the head of another university, so I had to look for other people to work with. I decided finally sort of last minute [on Charles] Coulson in Oxford, and went to work for him as a postdoctoral fellow. I had already begun to think about what I would like to do [for my future research. If I was going to do theory in chemistry, that I would do something that was of utility in chemistry, not just of interest to theoretical chemists, who [formed] an "in group" that talked to each other, but they didn't do that much at the time that was very useful [in chemistry as a whole].

[14] William E. Moffitt, "Atomic Valence States and Chemical Binding," *Rep. Prog. Phys.* 17 (1954): 173-200.
[15] Martin Karplus, "Charge Distribution in the Hydrogen Molecule," *J. Chem. Phys.* 25 (1956): 605-606.

I had the idea that one should calculate certain experimentally measurable properties: to predict them and try to understand where they came from. I took, again, a very [simple system]—the hydrogen molecule—and calculated its quadrupole moment. When you asked did I just sort of write papers easily? I really suffered over that paper, thinking about [whether it] could it be wrong, and . . . this and that. It took me a long time to finally submit it for publication in *J Chem Phys*. Nowadays, things have changed a lot, and I tell my students this, that when you start out, it may be very hard to be willing to expose yourself to the public, [. . .] and that it was very hard for me to write papers. Nowadays, mainly what happens is that—if I write a paper, whatever I write—it still takes me forever to be sure that I want to publish it, and not do I want to publish it, but how to make sure that everything is correct [and, if almost equally important, that it be clear and easy to understand]. I go over and over a paper, over and over again. If I'm working with students who may be writing the first draft, they suffer through—they give it to me, and it's still true that I mark all over it by hand and give it back to them, until I'm convinced that we have a paper that's clear and correct.

Various students have told me that they were very unhappy with me, that I kept them for such a long time from actually finishing the paper, but now that they are professors, that they do the same thing. When they [are] working with their students, and [they realize] you should be careful about what **<T: 65 min>** you write, and that the more interesting your result is, the newer it is, the more you should really try to check that it is correct.

Since a lot of the work is done on computers, it's hard to check. [It often involves] a very complicated program, [written by the students. An important aspect is an institution, sort of like Pauling's], that something that doesn't make sense, and they should go back and check it. Sometimes it was okay, and other times I'd picked out something that was wrong, even though you can't—unless you go through the program, line by line, which is impossible to do—check every detail. That's part of the process of writing papers and doing science nowadays.

I don't know whether that's okay. I mean, we're sort of wandering all around. I don't know what you—

CARUSO: No, no. That's fine. I mean, sometimes we like to—when there's a relevant question that we could ask later, sometimes we like to ask it now, just so that way we don't lose it for later. But I think hearing a bit about your time at Caltech and finishing up your dissertation, there are two questions that I think are important to get to. One of them is, Pauling gives you a relatively short time frame in which to finish your thesis, and of course, once you finish your thesis, your time at the university traditionally ends. Did you have plans in place when Pauling asked you to finish things up, about what the next step would be? I know that you wound up at Oxford [University], but I wasn't sure if you had been planning to go to Oxford anyway, and it just happened to coincide with finishing your thesis, or were you scrambling to find something that you were going to do once your thesis was finished? I think that might be a good place to start.

I also do want to ask a little bit about the Rosenbergs [Julius and Ethel Rosenberg], who were executed in June of ’53. Because I know that you were involved in some protests about that, but I’d like to know a little bit more about what your plans were for after Caltech, and when those came to fruition.

KARPLUS: I had gotten an NSF [National Science Foundation] postdoctoral fellowship, and it was to [. . .] start—I was actually I suppose a little bit late, as it happened—early in the fall of ’53, but I actually finished my thesis somewhat later than it should have been.

I had the NSF fellowship for three thousand dollars, which was a lot of money in those days. [As I already mentioned], I shifted it from Lennard-Jones to Coulson. It was one of the very first years of NSF postdoctoral fellowships. Most people didn’t use them to go overseas, but there was [no] rule about it. When I said I had to change it, there was no problem about that. So I was all set in terms of going to Oxford.

CARUSO: Why is that you wanted to go to Oxford in the first place? I mean, why did you apply for this—

KARPLUS: I first applied to Cambridge, actually.

CARUSO: Okay.

KARPLUS: Yeah. I was born in Europe, and I just wanted to go back to Europe.

CARUSO: Okay.

KARPLUS: I decided I wanted to do [some] traveling. Basically I wanted to go back to Europe. I decided to go to England because for theoretical chemistry—I could have gone to Sweden, where Per-Olov Löwdin was,—the best centers were in Cambridge, London, and Oxford. I decided I didn’t want to go to London, exactly. I suppose I had been living in a relatively small—Cambridge is sort of a small town, and Caltech and Pasadena is a small town. So I decided that I wanted **<T: 70 min>** to have a similar environment, though it obviously would be very different. And so that was all set.

CARUSO: I understand wanting to go back to Europe, getting to travel a little bit, but, since these postdoctoral fellowships were new, was it common for individuals to do postdocs at the end of their graduate career at this time, or was it pretty common for individuals to go straight into positions? I mean, I don't know what the norm was at that period of time.

KARPLUS: Much more so than nowadays, the norm was to go into positions, and particularly organic chemists would go to work [and] would try to get an assistant professorship or instructorship. Nowadays, almost everybody goes on and has a postdoctoral position, either paid by a fellowship or paid by whoever he's working for. A relatively small fraction of the PhDs went on to a postdoctoral fellowship at the time, but I don't know the statistics.

CARUSO: Did you have any concerns about taking on a postdoctoral position instead of going to find a professorship, or something like that?

KARPLUS: No. I don't think I worried about it, and nobody said to me, "Look, you should really be trying to get . . ." and they thought it was a good idea [for me] to get a postdoctoral fellowship, particularly since I had not really been in a place working with Pauling where theoretical chemistry in the computational sense was being [. . .].So I thought, and people I talked to thought that it would be good for me to be in a group where everybody else was a theoretical chemist, and that talking with people would be useful. [. . .]

EARDLEY-PRYOR: I'm interested about that computational aspect. When was your first interaction with computers? Did Caltech have a computer you could run computations on?

KARPLUS: No, it had all IBM punch card machines. [Many of the calculations were] done on these electric calculators, the equivalent of electric typewriters. And a lot of what I did [used] tables of integrals and all of these things that you could look up and interpolate. It was really at the limits of what you could do.

EARDLEY-PRYOR: Is that part of the reason why the *ab initio* efforts with the bifluoride ion, there was a need to have the empirical data as part of it?

KARPLUS: That was part of it. It was the same thing with Moffitt [work], that you couldn't take care of all of the excitations by just putting them in. [. . .] Nowadays, it would take you maybe seconds to do the same calculation with a program like Gaussian and a reasonable computer.

CARUSO: Sorry. Go ahead.

KARPLUS: I was just thinking, it wasn't really true of the bifluoride ion, but one thing that can happen, is that you can have an idea, and execute it, but it's before its time, before anybody else will use that idea and carry on. I mention these things because they come up [in my mind], and wouldn't necessarily come up [later, but we have nothing to do it with] the bifluoride ion. It was just the hydrogen fluoride molecule. We were doing an *ab initio* [molecular orbital] calculation, with a minimal basis set. I had the idea that we would get a better description of the wave function if we **<T: 75 min>** constrained the calculation so that the dipole moment of the molecule came out to agree with the experimental value. [. . .] We could have tried using the Moffitt type method, which actually—I went back to a student, Gabriel Balint-Kurti, and wrote a number of papers about improving it and putting it in the framework of better calculations. So I did publish something [based on my thesis idea], though the [thesis itself was never published].

The idea of constraining the wave function with experimental molecular data [was before its time]. However, recently, maybe in the last five years or so, people have rediscovered this idea, and it's become very popular. And some of the people actually are aware of [my original] paper, but I don't think it had any real effect. And there's somebody at MIT worked on this, and I told him, "Look, the idea is the same as what you're doing now," and he was very interested in it. The point is that it was a good idea, but it had no effect on scientific progress. I don't know what that says about ideas like that. It has happened a number of times, where we did something [. . .], and it didn't contribute in any way. I don't know how you decide that you're ahead of your time, but you discover it afterwards.

CARUSO: [Right]. When you're looking back.

KARPLUS: Yeah.

EARDLEY-PRYOR: Before we move into the political realm, do you mind if we take a break?

KARPLUS: Oh, right, the Rosenbergs.

CARUSO: Oh, sure. Do you want to—

EARDLEY-PRYOR: Yeah.

CARUSO: Okay. [Break in audio] So you did mention that you switched from Cambridge to Oxford. You're going to go to the Coulson group. I don't know if you specifically mentioned why it was that you wanted to switch from Cambridge to Oxford. Was it the city that you wanted to be in, or was there something about the Coulson group that attracted you?

KARPLUS: No, it was that the person I wanted to work with in Cambridge left Cambridge. [. . .] This seems to be part of my life.

CARUSO: Yeah. Yeah.

KARPLUS: I had to choose, and I think we recorded that, I had to choose someplace, and—I didn't mention—Coulson had actually just come to Oxford from London, and was working at what was called the Mathematical Institute, which was mainly almost entirely devoted to his group, and he was just establishing his group there. And there were some people there that I was aware of, but I didn't know personally. So in terms of the possible choices in England, that seemed to be the best place to go.

CARUSO: Okay. And you mentioned that you deferred this a little bit because of finishing—originally, it was supposed to be the fall that you were going to be taking the fellowship, but you pushed it. When did you wind up starting there?

KARPLUS: I started a little bit before Christmas.

CARUSO: Okay. So closer to the end of the calendar year.

KARPLUS: The calendar year.

CARUSO: In '54.

KARPLUS: [No, the end of '53.] There was no problem about that. And what happened is that, well, I came there, and it was just before Christmas. One of the friends that I had made, Sidney Bernard at Caltech—had lived in the same house that I had—was in Cambridge, and he had been to Paris a couple of times. He suggested that we go to Paris together [over Christmas]. I basically went in to see Coulson, said, "Would you please sign my fellowship [stating] that I have arrived [so I can start my fellowship]? But I'm going to go to Paris for a couple of weeks."

CARUSO: So you finished up your degree in ’53. You went abroad in ’54. What were you doing in the interim?

KARPLUS: No, no. That was—

EARDLEY-PRYOR: That was in the fall of ’53, the writing and getting there just before Christmas.

[. . .]

CARUSO: Okay. Before we touch on that and your trip abroad, you had earlier mentioned receiving the Leica camera, so I’m sure that we’ll talk a little bit about the photography that went on. But I also did want to know a little bit more about how you became involved in the protests over the deaths of the Rosenbergs. We may touch on it more later on, but were there any ramifications for you in becoming involved in protesting their deaths?

KARPLUS: I don’t remember exactly how I was involved. There was a Unitarian church in LA—we used to go to LA to go to movies—which had various speakers that were interesting, and I and various other students sometimes would go there. I had a car. Some of the others had cars. There was no other way to get around in the LA area [in those days]. It’s still pretty difficult. The Rosenbergs, they were accused of being spies [for Russia], but it wasn’t really clear. It turned out that in fact they really had been, [at least Julius was]. There were protests about what the government was doing to them—[that if we were going to execute them, which had never before happened in peacetime]—and so I participated in one of these meetings.

[At the door] they asked for your names, and it was my impression that there was an FBI agent there who was taking down these names. We didn’t really do anything—certainly it was nothing illegal—but somehow, it appeared in my record. Actually, thanks to the Nobel Prize, I was able to get in touch with the lawyer of [President] Obama, and say, “Look, for years I’ve been trying to get my FBI file, because I know there are some things in there.” I had applied, and with the help of my son Mischa, who is a lawyer—though he’s [now] going in other directions—and always gotten answers that said, “Well, we’re working on it,” something or other. But as soon as this happened one of the legal people told them that they should give me my file, and then it then took about a month. They said, “Well, we have to go through all the papers and make sure that anything that should be redacted should be pulled out. Within about a month I got the file of almost four hundred pages.

EARDLEY-PRYOR: Your FBI file?

KARPLUS: Mainly junk. The amazing thing that comes out of it is how much effort the government, the FBI, wastes on this, where there's really nothing that's particularly incriminating. There were a few things—[. . .] there were two things that happened, three things that happened, actually. You mentioned what were the after-effects, and I think with the Rosenbergs, it was that we felt that the government was doing something wrong, and also, it was part of a social activity, that people, like-minded people, [could work together]. This is really an aside, but between Illinois and Columbia [University], when I walked **<T: 85 min>** down the street in Urbana, Illinois, I had the feeling that almost everybody there—who wasn't necessarily connected with the university—had different political views from mine, while walking down the street in New York, I felt that almost everybody had the same political views. [The feeling] of being more comfortable in an environment.

But—after-effects. There were several things. One was that I was invited to participate in the National Academy [of Sciences] meeting in Wood's Hole—where they have a building—on [nuclear] disarmament. [. . .] People had to have the clearance to participate in this meeting. I never got a clearance. I went to the first meeting, [which was open], and after that you had to have a clearance [to attend]. The feeling was that the clearance was required at the behest of the National Academy, because they said if people didn't have a clearance, then the people they were trying to influence would say, "Well, you don't know what you're talking about, because a lot of this is secret."

So I didn't get a clearance, and had a nice summer in Wood's Hole [with my wife and] young children. So I knew there was something in my file. I never found out [what at the time]. Then my brother was invited to spend some of his time at [Lawrence] Livermore [National Laboratory]—Edward Teller wanted him to work there—[and he] was doing some theoretical work that had nothing to do with the hydrogen bomb, but at that time, to work there, you had to have a clearance. His clearance, when he applied, was denied. Then Teller or whoever said, "Look, we want this guy," and then he did get a clearance.

I didn't know what [my] brother had [in his file]—there was no reason. The only thing I could think of was that I was the person in his past that was suspicious. But it turns out, in the FBI report that I got, not to be entirely true. When he had young children, he started to teach elementary [school] science. He got very interested in elementary education. One of the schools where his children were going—the head of that school had some leftist leanings and [that was] held against him. That was in the report, that I was the brother of this person who had—it wasn't only I that was guilty, but he was also guilty. But it's, again, one of these crazy things that happened.

The third thing that happened is that when I was on the faculty of the University of Illinois [Urbana-Champaign], I kept getting visits from the FBI. What usually happened is that there was one person from Chicago who came down, and he came with somebody else. They asked me questions. When I was taking trips—one was actually with Gary Felsenfeld—we drove through Yugoslavia to Greece, and [I had done] a lot of photography. And they asked me, "Did you associate with any communists in Yugoslavia?" And I said, "Most people are communists." One time they came down and brought somebody along, and he started speaking to me in Serbo-Croatian, expecting that I would show that I really secretly knew this. Of course, I didn't. This kept on going for a while, and then finally it stopped. [. . .] I was never told, "Well, you're all right." And this appears in my file. There was some reference of my being inducted into the Army. [. . .] Actually I had deferments during the Vietnam War, and my local board wanted me [to join up]—they kept saying, "Why don't you get it over with?" And I said, "I'm happy to wait as long as I can get a deferment and not serve." It may have had something to do with that. But I never found out what was going on. There's only so far that you can go [. . .].

Overall, the effect on my life was very small. I would say my one take-home lesson is that the government wastes a lot of money trying to follow up on these things for no reason. There's in fact an earlier experience when I was going to junior high school. We moved to Newton from Brighton, where we had lived. We bought a small house [in Newton]. One day an FBI man came to our house, and he was very polite and very apologetic. He said, "Your neighbor," whom we had never had really good relations with—I think we were one of the very first Jewish families in Newton [at the time]. Now it's probably 50 percent Jewish. Maybe that was it. I don't know. But he said that, "Your neighbor says that every time when your father goes off to work, he faces the porch and raises his hand and says, 'Heil Hitler.'" And the FBI agent said, "I know this must be crazy." He knew our history, that we had escaped from the Nazis. But he said he was sorry, he had to come and check on it. And he said, "You won't hear anything more about it," and we didn't. That's not in my record, but I know from remembering what happened at the time.

EARDLEY-PRYOR: Pauling went on to have a lot of political engagements with the government, getting his travel visa revoked at certain times from the State Department. Did you and he ever talk politics? Did he ever talk about his political views with you?

KARPLUS: Yes. We talked quite a bit about atomic energy and [atmospheric testing]. One thing that happened is that he was sued—no, the *Daily Mirror* called him a communist, and so he sued the *Daily Mirror*, and there was a trial in New York.[16] Since I was at Columbia, he asked whether I could be a witness for him. He had various other people as witnesses [as well]. I came down there, and said that he was against the atomic [testing], and he was—at that time—already trying to stop testing of nuclear weapons in the air, for which he [had received] the Nobel [Peace] Prize [1962].

I testified for him. Finally he lost the case, and the reason he lost the case was that he would have had to show that it did him harm to have this published, and [the judge] said, "If you can get all these great people to vouch for you, obviously there isn't any harm."

[16] Linus Pauling, Plaintiff-appellant, v. News Syndicate Company, Inc., Defendant-appellee, 335 F. 2d 659 (2d Cir. 1964), Argued March 18, 1964. Decided July 7, 1964.

EARDLEY-PRYOR: Legal rationale there.

KARPLUS: That's the way things go. This May [2016], I've [been invited to] **<T: 95 min>** give a talk for the Organization for the Prohibition of Chemical Weapons [OPCW, The Hague, Netherlands]. They're having a certain anniversary. Of course, it's been very much in the news recently because of [chemical weapon use in] Syria. [OPCW] got the Nobel Peace Prize the same year that I got the Chemistry Prize [2013], so they invited me to give a keynote lecture. I [wondered about] what would I say. One [item] I found, by looking back about when Pauling got his Nobel Peace Prize. He said that [Alfred] Nobel had hoped that his weapon, dynamite, was sufficiently destructive— it was used in war, [though he invented for use in] mining and [road building]. [Nobel hoped that] it would be strong enough to make people realize that you couldn't have war, that if you could annihilate battalions in a few seconds, war would just be impossible. Of course, he was wrong about that, and the world had to wait until the atomic bomb [for that]. It appears to have been so horrible that there haven't been any world wars [since then]. Of course, local conflicts [do occur], but its existence may well have had the effect of making world wars impossible. This balance of destruction [appears to have] helped. What will happen with North Korea, I don't know, but my guess is that it's just like India and Pakistan. They both have half a dozen [or so atomic] bombs. They're not going to use them, and maybe it's even helping them to try to make peace, that there is this destructive power.

So anyway, that's the sort of thing I will talk about a little bit, and then other things about actual chemical warfare.

CARUSO: It's actually interesting. I mean, you can look throughout much of modern history, and many of the inventors of destructive weapons have discussed the fact that they thought that that destructive weapon would stop warfare. Like Hiram Maxim when he was talking about his machine gun, it was this machine is so destructive, no one would be fool enough to engage in warfare, so war will stop because—

KARPLUS: That was who?

CARUSO: Hiram Maxim, the inventor of the Maxim machine gun. So like one of the first automatic machine guns.

KARPLUS: I see. Can you send me a reference to that?

CARUSO: Sure. Sure.

KARPLUS: Because I might add it [to my lecture].

CARUSO: Sure. Definitely. So in December you go over. You take your trip to Europe. It's been fifteen years since you were there last. You get Coulson to sign your form that you showed up, and then you wanted to take a trip, right? Were there specific places that you wanted to visit? You mentioned going down to Greece, I believe.

KARPLUS: This first trip was just to go to Paris.

CARUSO: Okay.

KARPLUS: Paris [was in part] for food. My French was limited, but we went there to wander around where everybody goes, on the Left Bank. [I met my friend] Sidney Bernard [there.] He had been there earlier and had found the Hotel du Continent [to stay]. For a long time we used to go there. It was an inexpensive hotel. [. . .] [Sidney and I also went] to the Lapérouse, which was a very famous three-star restaurant in Paris. **<T: 100 min>** [. . .] I had gotten a card from the [*Harvard*] *Crimson* that I was reporter for them, which was true. I was planning to write an article about how an American that doesn't know very much French would thrive in one of these very fancy restaurants. And so we went to Lapérouse, Sidney and I. The owner, Monsieur Topolinski, thought that [this] was really a great idea. His maître d' was less favorable, but since the owner thought it was a good idea, he said, "Fine." They gave us a very nice [fancy] dinner and asked us to comment on it. I had my Leica with me, and Sidney was officially my photographer, though he really didn't know much about photography. He took some reasonable pictures, though most of them were pretty bad. I had to say, "Oh, you know, it looks as if he doesn't know what he's doing, but he really takes great pictures."

The high point was that they took us down into the wine cellar, where they had these great wines. In particular, they had one area where there were wines that are without labels, because the Seine flooded, and so they don't know [which wines they are]. We went down there, and they would open the bottle and say, "Ah, yes, this is Chateau Margaux from 1934," it could be "great vintage." [. . .] The maître d' would discuss the wines, and ask us about the course, we had no idea about it, but whether they really could tell or not, I don't know. It was a wonderful, unbelievable experience. I did write an article, and actually I wrote it for *The New Yorker* but they never published it.

CARUSO: I wonder if they were filling old bottles with the cheaper wines, as you were doing? [laughter]

KARPLUS: I think this was for real. The wine was good, but to say that it was from . . . I could tell whether it was a Bordeaux or Burgundy, but to tell which vineyard and which year, I mean that was just [beyond me]. These were all very good wines, and it was interesting to hear these people [discussing the wines]. I think they probably did know. From what I've seen later on, when I worked in some of the three-star restaurants, [it became clear that] the sommeliers really know what they're doing.

EARDLEY-PRYOR: Where else did you visit in Europe? I know you took multiple trips. Where else were places that you really stood out for you?

KARPLUS: I took a trip that I mentioned that went through what used to be Yugoslavia all the way to Greece. It was a great experience. There essentially weren't any tourists there. [. . .] The roads were in terrible shape, except for this one highway. This was still under the communists, as I mentioned earlier, under [Josip Broz] Tito, when it was one country. **<T: 105 min>** Everybody was very friendly. One thing was that it was just after the war [World War II], and so many of the people spoke German, so I could easily communicate with them, which was very good. It was seeing this culture, which I realized, ten years later probably wouldn't be there anymore, the way it was then. We had a number of experiences. One was that the roads were very rough, and the axle of the Volkswagen broke. We were near enough to a town, and went to a garage, and the person said, "We can order you one, but that'll probably take a month to get here." And he made me a new one [for the next day]. He didn't charge us anything for it. [It was so special to have a foreigner there.] We had dinner together.

Another time—I have a photograph—we were at one of the inland lakes, and there were a couple of fishermen, and a fish buyer. [Pause. *Finding an image in his photobook, Martin Karplus: La Couleur des Annees 1950.*] This is the picture. The fishermen had come in, and this man was probably some government official that was buying fish. When they finished with that they said, "It's lunchtime." They made a fish stew and invited me to have the fish stew with them. I also found out what the ladder [in the picture] was for. Somebody climbs up on this ladder and throws down rocks, [to drive] the fish into their nets.

There were a lot of experiences like that, because they had very few people, and particularly people that could speak German to them. There was no real trouble getting into [Yugoslavia]. We did have a visa, but my name was misspelled so at the border when we first went there [we were held up]. One time we got lost, and we drove toward Albania, and there we were met by armed guards [at the border]. I was finally able to communicate with them and say, "Look, we're just lost. We're not some sort of [provocateurs]."

CARUSO: We're not invading your country.

KARPLUS: Provocateurs. So we left.

EARDLEY-PRYOR: Did you make it back to Vienna during this stint?

KARPLUS: Yes. Yeah.

EARDLEY-PRYOR: What was that like, being back there?

KARPLUS: At that time, Vienna was still under the four-power agreement [and] divided into zones, just the way Berlin was. My uncle had come, who had been in New Zealand during the war, [had come back to Vienna]. **<T: 110 min>** [. . .] He was actually a chemist, and was interested in food chemistry. He passed the war in New Zealand, and then came back after the war, and the family got the Fango Heilanstalt back, and he was running it, and so we visited him there, and stayed there.

What was it like? I was just interested in looking around and seeing what was going on. I didn't really have strong feelings about belonging. Now that I had the Nobel Prize, I was really feted by Vienna. A year ago in April we were there, and were inducted into their National Academy, and many other things. People ask me what do I feel. Each time I was given something like the Legion d'Honneur, I always had to make a little speech. And various times I said, "I left Vienna seventy-five years ago, and I heard nothing. All of a sudden to be remembered, it seems to be a little bit late."

People [generally] took it very well. I was made honorary citizen of Vienna, which is nice, because in part of the city hall they have a stone plaque where they carve your name [. . .]. There are not that many people whose names are there. The mayor said in his speech, "We can't undo what we did, but we can try to make sure that it will never happen again, and that the young people are aware of what was done."

[Before I went, the president of the Austrian National Academy, Anton Zeilinger,] asked me, would I accept these honors if Vienna offered them to me? [He said] they would understand if I said no. [However,] I did say yes. In one of my speeches I said, "It's very important for me to be back [in Austria] and bear witness for young people, somebody who still exists, is alive, and to strengthen the idea of what a horrible thing it was that was done, and that it [must not] happen again." There's a lot of anti-Semitism still [in Austria now], as was then. [. . .]

CARUSO: So, you know, we heard a little bit about some of the trips that you were taking. When did you—so you came, you saw Coulson. You went on the trip to Paris. When did you actually wind up settling in Coulson's lab? Was it around January of '54?

KARPLUS: It was just after New Year, because in France, New Year is more important than the Christmas holidays. I basically started working then.

CARUSO: So what was it like coming into his lab? I mean, how many people were there? What was it [like]?

KARPLUS: There were a couple of senior people. Simon [L.] Altman, who I became very good friends with—him and his wife—and he was very well versed in group theory. It was a subject that I had had at a group seminar that we held at Caltech that I had organized, because there aren't courses in group theory. So we taught each other group theory. There were other people who were theoretical chemists, and then there were visitors, like [Donald F.] Don Hornig was there for part of the time, and [William N.] Bill **<T: 115 min>** Lipscomb [Jr.] visited.

There were two things about my stay with Coulson. One was that I wasn't at all interested in the problem that he gave me, and, as I mentioned, I worked on trying to understand the quadrupole moment [of the H_2 molecule]. I wanted to do things that were of chemical interest. I spent quite a bit of the time thinking about what area could I work in so that I would [. . .] have utility in chemistry as a whole. There was the course taught by Professor [Maurice Henry Lecorney] Pryce in physics [on] electron spin resonance—mainly in solids—and I talked with Don Hornig and other people. I did nothing for Coulson. I did the small project [on H_2] which he wasn't interested in. Magnetic resonance was an area which was just beginning [to have] chemistry applications— nuclear magnetic resonance—[I decided] that would be an important area to work in.

I also decided since I didn't want to do the problem that Coulson gave me, I would follow the instructions of my fellowship, [literally]. It says that you should obey the customs of the country, of the university where you're at. In England, they have terms that are six weeks long, and then in between the terms, they have eight weeks of [free time]. What normally happens is that the students have a good time during the six weeks in term. There are plays and all kinds of other activities, and then between terms, they actually do their work. But what I did was I'd be there during the term, and then in between terms, I would go off on one of the trips that we took. I wrote the NSF and said that that's what I was doing, and they said, "Fine." I was twenty-three years old. I worked very hard all through school to get a PhD. I felt this was a good time to see a little bit of the world. Gary Felsenfeld, who I mentioned, came over the year after, and we bought a Volkswagen [together], and [we used that to] travel in to various places, [as I already described].

Interestingly, years later I was in Paris with my daughters [Tammy and Reba Karplus] and my son [Mischa Karplus] because there was an exhibition of the photographs, of which this is the catalogue, at the Bibliothèque Nationale [de France].[17] They couldn't come for the

[17] Martin Karplus, et al, *Martin Karplus: La Couleur des Annees* 1950.

opening because it was in the middle of school, so they came at the beginning of the summer. It turned out that the hotel where we had stayed [many years before but] had stopped staying there—we're now staying in a better hotel—was having some sort of an anniversary, and they were again [offering] very inexpensive rooms [to former customers]. So we stayed there.

One time we were in the lobby—[to have breakfast—I was very surprised to see] Gary Felsenfeld there with his wife Naomi. It turned out that they had continued, every time they came to Paris, to stay in this hotel. [I also learned] that he'd taken the Volkswagen back to the US and used it for another ten or twelve years. Although I knew he was [now] at NIH, I'd not been aware of all this. I told him about the exhibition. [They went to see it and particularly enjoyed some of the pictures from trips that we had taken together]. The serendipitous [meeting was a really nice occasion].

[. . .] I was reading a lot, [talking with people and] as I said, finally decided [. . .] that chemical applications of nuclear **<T: 120 min>** magnetic resonance would be an area where there would be new information, and that it would be a good area to work in.

CARUSO: In terms of nuclear magnetic resonance, was this theoretical, or were—I'm trying to think of the best way to phrase the question. I'm also curious about the instrumentation that winds up getting used and developed over time. Did Coulson's lab have an NMR? Were those devices really available?

KARPLUS: [Coulson's institute did not have an NMR machine]. At that time they were mainly homemade. Harvard had one [built by Robert Pound working with Edward Purcell in physics]. There was Felix Bloch's [group]. He was at Stanford [University]. [Bloch and Purcell received the Nobel Prize in Physics for their discovery of NMR].

[. . .] Both Herb [Herbert Sander] Gutowsky, when he was a graduate student at Harvard, [with Professor George Kistiakowsky], and Charlie [Charles Pence] Slichter [who, with Purcell, learned about NMR]. They both went to the University of Illinois. Charlie Slitchter was a physicist, and Herb Gutowsky was a chemist. Both built instruments there, and [Gutowsky] started doing measurements on organic molecules and Charlie Slichter on solids. Also, Charlie did some theoretical work on chemical shift, and was a very important force in these early days [. . .]. [Illinois] was the place where chemical applications [of NMR] were going on. I think at Stanford, they mainly were doing physics, solids and such. It was pure luck that Pauling gave a lecture, I guess, in chemistry, at the University of Illinois, and that they asked him did he have any students to recommend, and so he recommended me. I had not published any paper in chemistry. The H_2 molecule [study] hadn't come out yet.

I had published papers on birds. They just offered me the job. They didn't know anything about me, other than that Pauling said they should hire me. They didn't interview me. They didn't really offer me much of anything, compared to what happens nowadays, where there are long courtships, and students visit. There was none of that. As it turned out, they offered me the job before they got the recommendation letter from Coulson, which said, "He's a very bright guy, but he really didn't do anything," so I don't know what the effect would have been.

[. . .] It was sort of a laughing matter that this had happened. I asked Gutowsky—they had divisions there, and he was in charge of the physical chemistry division—what they would have done [if they had received Coulson's letter], and he never said **<T: 125 min>** whether they would have offered me the job anyway or not.

The other thing that was important at Illinois was that for a long time, Roger Adams had been head of the chemistry department, and he was anti-Semitic, so there were no Jewish members of the chemistry department. When he retired, Herb Carter, who was an organic chemist, [became head and] he hired four Jewish [instructors]—three physical chemists, with Herb Gutowsky's advice, and one inorganic chemist. [There were the four of us]—plus a couple of other young instructors—a whole group of young people. It was a very friendly [atmosphere]. These were all junior faculty members. There were lots of friendly interactions.

CARUSO: So just one quick question. How did you find out about the position at Illinois? I mean, obviously, there's no internet. People knew that you were at Coulson's lab. Did you receive something in the mail? Was it a phone call to the lab offering you the position? How did you actually find out about that?

KARPLUS: I heard from Pauling, by letter, that he had recommended me, and then I received a letter from Herb Carter offering me the position.

EARDLEY-PRYOR: What was that transition like from being at Oxford to Champaign-Urbana?

KARPLUS: For me, it was a place that was boring in terms of living compared to being in Europe. I had not accomplished very much while I was in Oxford, scientifically; in a real sense, deciding that NMR was an area to work in was very important in my life, but in terms of producing things, [I had done almost nothing], so when I came to Illinois, I felt ready to try to work hard and do something in NMR, where I thought I could do things that could be really important. I think it was good for me to be in this nowhere place. It turned out that Aron Kuppermann was my office mate. He was an experimentalist, but also theoretician. He had arrived a bit earlier. There was an apartment for rent right next door to where he lived. [I rented that, which led to] a lot of interactions, which were very positive, [with Aron and his wife, Roza].

CARUSO: If you had had the choice, would you have—so I think this might be a long, complicated question, and I'll see if I can pare it down. Obviously, if someone offers you a job, it's very nice just to jump on that offer, right? But had you had any plans prior to that job offer to go on the job market, and if so, were there certain universities that you were thinking of applying to?

KARPLUS: I think it happened early enough that I hadn't started to worry about what my future would be like.

CARUSO: Okay.

[. . .]

KARPLUS: If you asked me would I have picked Illinois if I had gotten other offers—

CARUSO: Or, you know, were there other universities that you were thinking of yourself as wanting to be at going forward? Obviously, you have a network of individuals that you've worked with or spoken with over long periods of time. You've seen those individuals go to universities. You have a sense of what the departments are like at those various universities. I was just wondering if there was someplace that you thought you would want to be, even if it was going to be something down the line, but did you have visions of where you wanted to situate yourself in terms of the science that you wanted to look into?

KARPLUS: I always thought about Harvard, but I also thought that I didn't want to go to Harvard unless I had tenure, because just like with Delbrück , I mean, my psyche wasn't such that I wanted to sort of suffer, not **<T: 130 min>** knowing what would happen. And of course, in those years, junior people were very rarely promoted [at Harvard], and they almost always hired people from the outside. Nowadays, the situation really has changed, I would say for two reasons. One, I think there's too much competition for Harvard, and people wouldn't come here as junior faculty if their chance of staying was very, very low. They'd just go to somewhere else, maybe to Stanford—I mean, there are many schools that compete with Harvard.

And the other thing is the realization that if Harvard said, "Okay, you have a chance for tenure," it could get much better junior people to come here. All of the junior people who have been in the last few years have been promoted. They're all outstanding. They've been promoted very, very quickly, and so the policy really has changed. But in my day, "Come here," and then to be told, "Well, nice having had you here"—the idea was that if you were at Harvard and did good work, you'd have a very good chance of getting a job elsewhere. To a certain extent that was true, but I just didn't like the idea of it.

[. . .] At various times, Harvard asked me about the possibility [of going there as a Junior Fellow], and I said I wasn't interested [to go there without a tenure appointment].

EARDLEY-PRYOR: The position at Illinois was an instructorship.

KARPLUS: Right.

EARDLEY-PRYOR: Right? So was your hope to move towards a tenure track? [. . .]

KARPLUS: An instructorship was tenure track in those days.

EARDLEY-PRYOR: Oh, it was?

KARPLUS: It was just they paid you less. My salary was five thousand instead of the three thousand dollars I had as a fellow. No, no, it was just the first position on the tenure track.

EARDLEY-PRYOR: Okay. The work with nuclear magnetic resonance at Illinois, how did that proceed?

KARPLUS: [. . .] I talked with Herb Gutowsky about what they were doing, and that was one thing. [. . .] Ethyl alcohol was one of the classic systems where they were able to identify all the nuclei and look at their spin-spin coupling. I realized that measurements of that type, where you have two hydrogen atoms that are not directly bonded to each other, but say, as in ethyl alcohol, you have a hydrogen, a carbon, a carbon, and another hydrogen. [. . .] From the simplest point of view, you have two hydrogens that in a simple description [a hydrogen could have] a bond to their carbon, and they would make carbon-carbon bond, and then there would be another CH bond. I realized that if there was actually an interaction between the two—

EARDLEY-PRYOR: The two hydrogens?

KARPLUS: [The Gutowsky group] measured by spin-spin coupling constants [the interaction between the two hydrogens]. It would tell you that there was necessarily not only the simplest valence bond structure, but there were also structures where the hydrogen atoms were bonded together. [. . .] My idea was that you would be able to measure the deviation from the simplest possible model, that there had to be some structures where these two [hydrogens] bonded together. It would make a very small contribution. It would be, say, I don't remember, 90 percent this, and maybe three or 4 percent this, and then there were other structures. So my idea was that if one could interpret that, one would actually have a measure of what the wave function was like, just like measuring the quadrupole moment of the hydrogen molecule [in my first paper]. **<T: 135 min>** This theme appears over and over again, that if you had a model, you would be able to get information about the wave function from experiment.

That's why I started looking at this particular problem. I worked out the formulation, and [estimated] the molecular integrals that you have to put in, and set up the calculation. And then Illinois had a computer called the ILLIAC, which had one thousand words of memory, which is unbelievable nowadays.[18] I programmed the problem for the ILLIAC. If I did it once, the calculation once, it would have been just faster to do it [with a desk calculator], than writing the program, which was pretty complicated. But if you had done it once, and then you wanted to look at the same interaction, but you changed the angle between the hydrogens, let's say as the methyl group rotated, then once you had a program that worked and gave the correct answer, redoing the calculation would be much, much faster. [. . .]

I wrote the program, and it was a program on paper tape in those days, and you punched holes in the tape to do the program. If you made a mistake, you filled in the holes with nail polish. It all worked out. It just turned out that a fellow from a university in Canada, [Raymond U.] Lemieux [then at the University of Ottawa] gave a lecture about organic chemistry, and I went to this lecture. And I don't remember why I went to this lecture, because I usually didn't go to organic [lectures].

He actually had measured coupling constants in some molecules, and seen there appeared to be some sort of angle of dependence, but he didn't [know exactly what it was because you would have needed] to be able to fix the different angle, and that you can't do experimentally. He mentioned this and I realized that he had data that showed that my model was correct.

I wrote up a paper and published it in *J Chem Phys*. My idea, as I mentioned, was just to use the measurement to understand the wave function,[19] but measuring these coupling constants has turned out to be very important for finding the confirmations of organic molecules, and it is now being used in protein structure determinations by nuclear magnetic resonance.

I mentioned that we're a number of young people who weren't married at the time, and we used to go out to dinner at a Chinese restaurant in Urbana [once a week] and chat about new things that we had discovered that might be of interest. And E.J. [Elias James] Corey was [one of the people who usually came along].

[18] The ILLIAC (Illinois Automatic Computer) was a series of supercomputers built at different locations, including the University of Illinois at Urbana-Champaign. Five computers were built in the series between 1951 and 1974.
[19] Martin Karplus, "Contact Electron-spin Interactions of Nuclear Magnetic Moments," *J. Chem. Phys.* 30 (1959): 11-15.

EARDLEY-PRYOR: In Urbana?

KARPLUS: Yes. In Urbana.

EARDLEY-PRYOR: Oh, okay.

KARPLUS: He was on the faculty in Urbana. I told him about the calculation, and he was very excited about it, and very shortly after published a paper, where he used the measured coupling constants to determine what certain angles were in some rigid [organic] molecules. That was the beginning of the Karplus equation, which now is very famous.[20] I would say that more people know my name because of that, because it's taught in all the organic courses, than about molecular dynamics. **<T: 140 min>** Maybe now more people begin to know about the other, but that really was—it's one of the most cited papers. There's other stories that go along with that. Organic chemists started using it and testing it, and then they found there were small deviations where they could measure the angle in some other way.

There were three communications that said the equation wasn't all that good. I then published a paper saying they should have really read the original paper and seen that it's mentioned that there are many perturbations that can happen, e.g. if you put in a highly electronegative atoms, the simple model wouldn't be accurate.[21]

I ended the paper with a statement something like that "anybody who tries to determine the angle to a few degrees the dihedral angle does so at their own peril." Fortunately, people didn't take [my comment] too seriously, and kept on using it. People have refined it, done lots of things with it. It's really turned out to be very, very important.

And there, in contrast to what I did for HF [hydrogen fluoride] that I mentioned earlier, where I had no effect in chemistry, this was just at the right time, when more and more people were using magnetic resonance, and having this relationship turned out to be very important. But it's a [serendipitous] accident. I wasn't doing it to do conformational analysis, but Corey published something about it.[22] He was already a well-known organic chemist. It certainly helped to spread it around.

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[20] The Karplus equation describes the correlation between ^{3}J-coupling constants and dihedral torsion angles in nuclear magnetic resonance spectroscopy. See Martin Karplus, "Contact Electron-spin Interactions of Nuclear Magnetic Moments," *J. Chem. Phys.* 30 (1959): 11-15.
[21] H. Conroy, "Nuclear Magnetic Resonance in Organic Structural Elucidation," *Adv. Org. Chem.* Vol. II (1960): 265; Martin Karplus, "Vicinal Proton Coupling in Nuclear Magnetic Resonance," *J. Am. Chem. Soc.* 85 (1963): 2870.
[22] W.H. Bradshaw, H.E. Conrad, E.J. Corey, I C. Gunsalus, D. Lednicer , "Microbiological Degradation of (+)-camphor," *J. Am. Chem. Soc.* 81 (1959): 5507.

CARUSO: How did the publishing process go for you with this paper? You hadn't published much previously. I'm assuming by this time the quadrupole moment paper had come out.

KARPLUS: [Yes].

CARUSO: What was it like submitting this for publication, and how did the editorial team respond to it?

KARPLUS: I think it was very easy to publish it. I don't think it took me quite as much time as for the H_2 paper to be willing to let it out.[23] I had Corey and Aron Kuppermann, other people read the paper. I don't really remember how long I took, but it certainly was nothing like for the H_2 paper. It certainly happens now that things go more quickly, even though I wanted to be very sure that it's correct.

EARDLEY-PRYOR: You and Aron Kuppermann taught each other as officemates different things that you each had expertise in.

KARPLUS: Right.

EARDLEY-PRYOR: How did those interactions help play out in your later career?

KARPLUS: Aron was mainly an experimentalist, as I mentioned, but he was also a good theorist. He got me very interested in chemical reactions, understanding them. It was basically one of the next directions that, after—I won't say I left magnetic resonance—I went to Columbia, I started working on trying to look at chemical reactions. That's when I did the H plus H_2 problem with Dick Porter.[24] I couldn't have done it at Illinois because the computing machinery, the ILLIAC wasn't good enough compared to an IBM 650, which they had at the Columbia Watson Lab, where one could do the calculations.

[23] Martin Karplus, "Charge Distribution in the Hydrogen Molecule," *J. Chem. Phys.* 25 (1956): 605-606.
[24] Richard N. Porter and Martin Karplus, "Potential Energy Surface for H3," *J. Chem. Phys.* 40 (1964): 1105-1115.

EARDLEY-PRYOR: So when you left Illinois and went to Columbia in 1960, **<T: 145 min>** was the computing power a big drive for you? Were you searching for access to a more powerful computer?

KARPLUS: It was certainly one part of it. It was also that I had decided five years in one place was enough, and that I should go to another place to get exposed to other problems. One of the things is that in terms of trying to do theory that's useful, it's good to be with other people who do different things. [. . .] But having access to the 650 [IBM 650 Magnetic Drum Data-Processing Machine] at the IBM Watson Lab was important, though, again, it was an accident that I got the offer. I was with Ben Dailey serving on a summer NSF program for teachers. [. . .] We were standing in the washroom, and he asked me would I be interested in coming to Columbia. And I said, "It sounds an interesting possibility." At that time, I wasn't aware of the Watson Lab. The offer I got was actually a position at the Watson Laboratory, and some adjunct professorship at Columbia.

At first I said I wouldn't accept that. I already had tenure—I was an associate professor with tenure at Illinois—and I said I wouldn't go anywhere where I didn't have tenure. I said I was willing to work at the Watson Lab for a while—because it had all these facilities, and had some very good people there, that were interested both in magnetic resonance, and some in reactions—but I wanted to have a permanent position reserved for me at Columbia. I also was paid more going to the Watson Lab. They finally arranged that, and I stayed at the Watson Lab for a number of years.

It was a very productive, but at a certain stage, IBM started saying, "You're doing all these interesting things, but what good is it to us?" They wanted me to go up to the IBM Watson Laboratories—outside of New York—and start consulting. At that time, I told Columbia, "I want to give up my Watson Lab position and just be a regular professor at Columbia." I also had to do less teaching when I was at the Watson Lab. Fortunately, it all worked out fine.

Often I tell my students that working in industry when you start, it's great. You don't have to worry about getting grants or anything, and they may have laboratories where you appear to be completely free to do what you want. But you never know, so you should really go with your eyes open, that this nice environment, high salary, and everything else, might not last. Certainly true in my case.

CARUSO: How was the Watson Lab structured? Did you go in and have a laboratory and, you know, you get to hire staff? Were you put in someone else's laboratory, and you had to report to a specific manager? I mean, how did it function for you?

KARPLUS: It functioned like being an assistant professor at a university. I had space and was given machine time and did what I wanted. I reported to the head of the Watson Lab [Wallace Eckart], who was a very open-minded person.

CARUSO: All right. So, I mean, it sounds like the Watson Lab in some ways wasn't **<T: 150 min>** what we might think of a traditional corporate lab.

KARPLUS: Absolutely.

CARUSO: It was more of a hybridized version of an academic and corporate space.

KARPLUS: Right. Some of the people there, like Dick Garwin, did a lot of consulting for IBM. He was partially the head, and he was one of the people who started urging me to consult the way he did, where he also did things on his own. Most of the people there—like Seymour Koenig and Thomas—just did their own research. Also, Al Redfield, who was in magnetic resonance. At a certain point, all of them left, except Garwin, who was so much involved in the corporate structure. [. . .] Why IBM did this, I think partly it was for the reputation of having a laboratory with all these famous people, and partly, I think it hoped to get some sort of consulting. It was a very unusual lab [for a company. Also it was within walking distance of Columbia, which helped in fostering collaborations].

EARDLEY-PRYOR: Why not do some more of the consulting? What was your reason for not—

KARPLUS: I thought that's not what I was there for. My interest was not the business, but to do research. Partly it was out of principle. I think that when you do something, or when you apply to an agency for support, you should be careful that what you're interested in is really what they're interest is. For example, the DOE [Department of Energy], or it was actually the Atomic Energy Commission at the time, said they were very interested in some work I was doing on reaction kinetics, and said, "Look, you have NSF grants, but we will take them over. You have to do less write-ups and [this will] make it very simple for you." I said okay, and for several years this was a great relationship. Then they decided they weren't interested [in my work] anymore; it wasn't playing any role in the use of atomic energy, so they said they weren't interested in supporting me [anymore].

Fortunately, they were very helpful [in my getting] back my NSF grant, but it was really another lesson that I hadn't learned, though it worked out okay for me. [. . .] At a university, well, it's also slightly odd. If you want to be a salaried member of the [Harvard Chemistry] Department, you get actually paid for teaching, although you'd never get a job, never be promoted here, if you didn't do outstanding research. Teaching graduate students and postdoctoral fellows doesn't count. It is a slightly odd system. You would think that if you were just doing research and educating graduate students and postdoctoral fellows, which actually takes much more of your time than giving your courses, somehow would be figured in, in terms of whether or not you get paid by Harvard. When I said, “I’m going to spend part time in Europe,” I taught half time for a while. I could still take the rest of my salary from grants, but as far as Harvard is concerned, all the rest I was doing, publishing many papers, doesn’t count. It’s a slightly odd, inconsistent system, but one lives with it.

CARUSO: The individuals at the **<T: 155 min>** Watson Lab, did they also have joint appointments at Columbia?

KARPLUS: Some of them had adjunct appointments.

CARUSO: Okay.

KARPLUS: But none of them had [an appointment like mine].

CARUSO: Okay. So during the period of time that you were at the Watson Lab, how much of your time was spent at that lab, and how much of your time was spent at Columbia?

KARPLUS: They’re within ten minute’s walking distance. Initially, all the postdoctoral fellows were at the Watson Lab, and all the graduate students were at Columbia. I would go back and forth. Each day I would probably go back and forth half a dozen times.

CARUSO: I mean, that’s part of what I was curious about, how you would be managing your time at two different institutions that had different needs and different wants. I know you had some freedom initially at the Watson Lab, but I’m assuming you had lab space at Columbia as well.

KARPLUS: Yeah. Well, lab space—

CARUSO: You were running that.

KARPLUS: It was lab space like here. It was a room where I had [students] and I had an office at Columbia, next to Rich Bersohn.

CARUSO: You have colleagues at the Watson Lab. You have colleagues at Columbia. So I'm just curious to know I guess a bit more about how you were able to manage those two different lifestyles simultaneously, and I think you mentioned a little bit that you were going back and forth twelve times a day. But—

KARPLUS: Six times.

CARUSO: —six times a day.

KARPLUS: Which probably is an exaggeration, too. Depending on the day, if I was teaching.

CARUSO: Right.

KARPLUS: I taught half time while I was at the Watson Lab.

CARUSO: Right. But it seems like a complicated situation to try to manage two different labs at the same time.

KARPLUS: It really wasn't. The Watson Lab, as long as it was there, required nothing of me, I would just be using their computing machinery, talk with people once in a while, maybe give a seminar or attend seminars if I were interested. It was almost—like here at Harvard. We have chemistry professors that are also at the medical school, and they have labs at both places. Some have labs at one or the other. Or people are in chemistry and physics. In general, they have more one than the other. I don't think what you're thinking, managing something, was [difficult]. It was just like if somebody has lab space in chemistry, they may have a few labs here and a few labs there, and it probably takes them ten minutes to go from one to the other.

CARUSO: Okay.

KARPLUS: [. . .] Then things began to change, and it was in the wind that IBM wasn't doing quite as well, and was not interested in some ways in keeping the Watson Lab, and finally it closed.

The other thing that happened is that Columbia got a reasonable computer, so that I could do the computations there, rather than depending on the Watson Lab. When I first came to Harvard, Harvard had a terrible system that you had to pay a huge amount for computer time.

Columbia for a while let me use their computer, which was essentially free. It had been a gift from [Thomas J.] Watson. Watson had a close connection with Columbia, [though he had not been a student there]. That also had played a role in the Watson Lab. [Columbia received] an IBM—[an IBM 7090]—computer, so we used that. When I came here, they very kindly allowed me to use it for a while, because Harvard's system was terrible.

EARDLEY-PRYOR: Were you still writing your own programs?

KARPLUS: I wrote the programs. As time went on, the students essentially wrote the programs, and I looked at them and **<T: 160 min>** tried to find—as I mentioned earlier—out whether they are right or not. I would say that 90 percent of the programs nowadays are written by the students.

EARDLEY-PRYOR: Yeah.

KARPLUS: And they're much better at it than I am. There's no question.

EARDLEY-PRYOR: Yeah. The social life in New York City, coming from Champaign-Urbana, in the middle of farmland, Illinois, to the East Coast metropolis, what was that experience like?

KARPLUS: It was wonderful to be able to go down to Greenwich Village. There are lots of things in New York that are very inexpensive. There are also things in New York that are very expensive.

EARDLEY-PRYOR: What were the things that you liked to do? Early sixties New York, just a lot of exciting cultural and social experimentation going on there.

KARPLUS: Go to theater. Nowadays, theater can be very expensive. The *Hamilton* musical?

EARDLEY-PRYOR: Yeah.

KARPLUS: If you want to get a ticket there—we actually have tickets, because we were going down [to New York]. My son is in New York, and his birthday is February 28, and mine is

March 15, so we're going down this weekend. We managed to get tickets for *Hamilton*, not cheaply, but not out of this world.

EARDLEY-PRYOR: That's a feat.

KARPLUS: I have always been very fond of the theater. That's one of the great attractions of London, which has probably the best theater in the world. We went to theater a lot, go to music in the Village, go to restaurants, and I mean we didn't have children at first. I was married, and so it's a great place to be. When you have children, I think what schools you send them becomes much more complicated.

EARDLEY-PRYOR: When did you meet Susan?

KARPLUS: When did I meet Susan? I met Susan here at Harvard one summer. It's horrible. I don't remember the date.

EARDLEY-PRYOR: When did you get married?

KARPLUS: Get married? That was in '61. It was after I was at Columbia. I was back at Harvard, and she was an undergraduate at Harvard, and I met her in the library, and helped her with some problem or other.

EARDLEY-PRYOR: That's great. So you moved in together in New York City?

KARPLUS: Right.

EARDLEY-PRYOR: Where in New York did you live?

KARPLUS: We were very lucky. I was looking around for an apartment within walking distance. That's another thing that I've always required, that I can walk to work. We can walk here, in Strasbourg, Illinois, and Columbia. I was visiting apartment buildings, looking for a place to live, and on 110th, near Riverside Drive, is an apartment building. It turned out they had a thirteenth floor, and people didn't like to live on the thirteenth floor. Normally, these apartments—this one had a beautiful view over Riverside Drive, the George Washington Bridge—they had a hard time renting it. So I went there, and I rented it, and it was great. I mean, it was a nice apartment. We had two bedrooms. After I left, I passed it on to someone and it stayed in the hands of young Columbia faculty for quite a few years. It was just that it was the thirteenth floor.

EARDLEY-PRYOR: That's great.

CARUSO: So I'm trying to be—well, let me pause this.

[END OF AUDIO, FILE 2.1]

EARDLEY-PRYOR: I'm interested in the time at Columbia, your beginning work with Richard Porter. How did you hear about Richard Porter's work to have him come join you as a postdoc at Columbia?

KARPLUS: He was actually a graduate student at the University of Illinois, and worked with Fred Wall, and did some trajectory calculations of H + H_2 for the linear collision, and used a potential surface that was not very good. I met him there and we talked a lot, and so I invited him to come to Columbia—when he finished his degree—as a postdoc.

EARDLEY-PRYOR: How did the work become semiempirical and the quantum calculated for the 3D H_2 trajectories come into play? How did you come up with that work together?

KARPLUS: The H plus H_2 exchange reaction—$H+H_2 \rightarrow H_2 +H$—is the simplest possible chemical reaction. Why was this a good time to do it? There were a number of reasons. One was that there were good experiments on the reaction as a function of temperature, so if one knew something about the activation barrier [one could try to compare with experiments]. Second, there was the beginning of the molecular beam work of [Ellison] Taylor and [Sheldon] Datz, who actually worked on H plus H_2—rather than measuring the overall reaction, you could measure the reaction as a function of the system energy in a single collision. So rather than having the averaging over many reactions, which would hide a lot, you could actually find how the reaction varied with the collision energy that was put in. Then there was the possibility of getting much more detailed information, which if you did a detailed calculation, they would complement each other. They could measure what happened in a single collision, and we could calculate what would happen in a single collision. That was the idea.

The important point was that we realized, or believed, that just using classical mechanics even for these very light atoms [. . .] it would work. There was no very good evidence that classical mechanics was good enough for just doing the trajectories, looking at the motions.

There were some arguments, but they were crude arguments. It was basically just going ahead and trying to see whether they would work. To do the calculation, you needed the surface on which the atoms moved. If you know the energy, know how the energy varies with distance, you can get the forces on the atoms. That had previously been done, but they'd used a very inaccurate surface. So the first thing that we did was to develop this, what became to be called the Porter-Karplus surface.[25] It was a little bit of various things that we talked about, putting in some empirical information, and sort of combining it with quantum mechanical rules, essentially, to be able to get a surface. And one knew the barrier height pretty well from some of the experiments. And so we could adjust the surface to **<T: 05 min>** be what we thought was a good representation of what actually happened. It was only some years later that people could do a full quantum mechanical calculation that was accurate enough so that the trajectories would be meaningful. There were two parts, and Porter worked on both of them, so he was very important. On the trajectories, it was also Ramesh Sharma, who mainly played a role in doing a lot of the calculations, once things were set up.[26] It wouldn't have been possible if we didn't have the 650 at the Watson Lab.

EARDLEY-PRYOR: To calculate.

KARPLUS: It was very exciting to do this. It must have been almost ten years later that the full quantum mechanical calculation was done, one of them by Aron Kuppermann, which showed that our results with the classical method, which took probably a thousandth of the time, was very accurate. And there was only one thing that we did that was special. If the system were quantized, then a molecule would have a number of vibrational energy levels, and the hydrogen molecule, since it has a very strong bond, has very largely spaced energy levels. One knows it's in the [. . .] lowest energy level. We put in that energy, which as the system reacts, the bond strength varies, and it becomes available for the reaction. That's what we call the quasi-classical method, and that was a very important part of making things work; the reasons why it worked exactly is more complex. George Schatz wrote an article [in 2000 connecting the] most important papers of 3D. The method that we used, the quasi-classical method, he wrote that it's still very useful, because it makes the calculations much, much faster, but does give accurate results.

EARDLEY-PRYOR: And you and Richard Porter later wrote a textbook together.

KARPLUS: Right. Right.

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[25] Richard N. Porter and Martin Karplus, "Potential Energy Surface for H3," *J. Chem. Phys.* 40 (1964): 1105-1115.
[26] Martin Karplus, Richard N. Porter, Ramesh D. Sharma, "Exchange Reactions with Activation Energy. I. Simple Barrier Potential for (H, H2)," *J. Chem. Phys.* 43 (1965): 3259-3287.

EARDLEY-PRYOR: *Atoms and Molecules*.[27]

KARPLUS: Actually, what happened is that we taught a course together. He came up to Harvard as a visiting lecturer and taught part of a physical chemistry course. Then we wrote the book over a long period of time.

EARDLEY-PRYOR: After you had transferred to Harvard?

KARPLUS: Right.

EARDLEY-PRYOR: So take us from that transition. You were at Columbia. You had your five-year plan. You were approaching your five years in 1965. What were your thoughts about the next step?

KARPLUS: I was up for a sabbatical, and I was trying to think where to go. I let people know that I was thinking of leaving Columbia, and I got twenty or so offers, including Caltech, Berkeley, Chicago, and various other places. I tried to narrow things down. Finally, I spent six months in Berkeley, and six months at Harvard. I've forgotten why I decided I wasn't interested in Caltech; [I think their offer was not very good and did not think I would like living in Pasadena]. Then decided to come to Harvard. Now why did I decide to come to Harvard? One, **<T: 10 min>** probably that I'd been at Harvard. That was an attraction. It's a very good place, and particularly it has very good students. So does Berkeley, but to me, at that time, Berkeley, well, it had a long tradition, going back to G.N. Lewis, that in chemistry you didn't need theoreticians, that experimental chemists could do their own theory.

Things there were changing. My friend Robert Harris, who was my first undergraduate student at Illinois, was on the faculty there. I had the feeling that it was a relatively sleepy [place], that people were more interested in their ranches than in doing science, even though they were very bright people. So I decided that Harvard was the better place to be. I think it was a good decision, though Berkeley now is much better than it used to be, and has some really outstanding people, like David Chandler and Bill [William] Miller. [. . .]

EARDLEY-PRYOR: When you went out to spend part of that sabbatical at Berkeley, in California, this was '65, '66. It's a pretty socially active time.

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[27] Karplus, Martin, and Richard Needham Porter. *Atoms and Molecules: An Introduction for Students of Physical Chemistry*, University of Michigan: Benjamin-Cummings Pub Co, USA. 1970.

KARPLUS: Right.

EARDLEY-PRYOR: Especially in Oakland, with anti-war protests.

KARPLUS: Yes.

EARDLEY-PRYOR: What are some of your memories of that, that time in the area?

KARPLUS: I was very much involved in some of the protests in some of the cases where students were marching peacefully against the Vietnam War, and the police came in, and [were] knocking them down. I took a lot of pictures of this, and I gave them to a newspaper. [They were not published] and I didn't have copies of them, unfortunately. I never personally got hurt or anything, but it was a lively time. Bob Harris was also a very liberal person, more so than I, and was very much involved. There were rallies on campus, and the student non-violent movement, which wanted to be non-violent. I was not a member of the faculty. I didn't have a direct connection with trying to persuade the university not to collaborate with the police, and let the students gather on [campus in protest]. At a certain point they were chased off [by the police], and again, it was a fairly violent interaction.

EARDLEY-PRYOR: When you chose Harvard, what was the political atmosphere here? This is still a pretty active anti-war movement in Boston.

KARPLUS: That's right. There also was that. There were a couple of sit-ins in chemistry, trying to [keep the faculty from being] involved in the war activities. An interesting thing was that Bob Woodward, who was pretty conservative, [supported the sit-ins]. It turned out that his daughter was one of the people in the sit-ins. He worked hard to persuade the administration to let the students sit here for a certain amount of time, and then let them get out. [Nathan M.] Pusey was president at the time, and there was a big meeting to discuss whether the police should be allowed to come in to remove the students from University Hall. I remember at that meeting I was part of the negotiators with Pusey to just take it easy and not call in the police, and give the students **<T: 15 min>** twenty-four hours to leave, to have a peaceful protest march, and then disperse. This did work out.

It was really very uncertain what exactly [would happen]. It was very unclear whether this would work or not, whether Pusey would really go along with it. His feeling was probably [that he] should call in the outside police, and not just have the campus police patrolling and making sure it was peaceful. It was an exciting time. And there, [in contrast to Berkeley,] as a faculty member, I played much more of a role.

EARDLEY-PRYOR: Who were some of the other faculty involved in this work? I mean, both here or at MIT or—

KARPLUS: At MIT, I don't know. [Howard] Zinn at BU [Boston University] was very actively involved, and—

EARDLEY-PRYOR: But people that you had—

KARPLUS: —[Everett I.] Mendelsohn —

EARDLEY-PRYOR: —contact with?

KARPLUS: Mendelsohn, who's a history professor, [was very active]. A number of them that were—it was an exciting time. Not a very good time for doing research.

EARDLEY-PRYOR: In terms of the research, you eventually found a shift to move your traditional work in chemistry over these past years and return to your original love in biology. How did you go about that transition?

KARPLUS: At various times in my life I've thought of doing something that was very different. Having a sizeable research group and being able to stay on top of everything that was going on, and having things going on, continuing to publish papers, gives you the luxury of spending a significant part of your own time on looking into something new. What happened is that a book was published in honor of Linus Pauling. I had an article in it, which was a little bit tongue in cheek.[28] It was about chemical reactions. I pointed out it was very important to know the structure and the energy. Pauling wasn't that much interested in dynamics. He was much more a structural person. I had an article in this volume.[29]

While I was looking at it when it first came out, I noticed that George Wald and Ruth Hubbard had an article about vision and retinal. I realized that the understanding of retinal and

[28] A. Rich and H. Davidson, eds. *Structural Chemistry and Molecular Biology: A Volume Dedicated to Linus Pauling by His Students, Colleagues, and Friends*. (San Francisco: Freeman, 1968).
[29] Martin Karplus, "Structural Implications of Reaction Kinetics," in *Structural Chemistry and Molecular Biology: A Volume Dedicated to Linus Pauling by His Students, Colleagues, and Friends*, edited by A. Rich, N. Davidson (San Francisco: Freeman, 1968), 837-847.

its isomerization hadn't much advanced since the time I was an undergraduate. Because it is a conjugated molecule, it's an ideal molecule to use a type of methods that Coulson and Pariser-Parr [Rudolph Pariser and Robert G. Parr] and [John] Pople had used, simplified methods for studying molecules of this type.[30] I had learned that much when I was with Coulson, though I hadn't done anything. I realized that one could really look at the problem of the initial event in vision, which is the isomerization of 11-cis-retinal to all-trans. Barry Honig came [to Harvard], and he had a good theoretical background, and we applied the Pariser-Parr-Pople method for calculating the isomerization barrier, and [used a mixture] **<T: 20 min>** of quantum mechanics and classical mechanics. This mixture is one of the things that supposedly the [2013] Nobel Prize [in chemistry] was given for, though from my point of view, it wouldn't have happened if molecular dynamics hadn't been developed to [make this an area of interest]. But anyway, that may come later.

We did the calculation, and thought it was very interesting, because it gave considerable insight into the mechanism of vision. We submitted it to *Nature*. In those days, it wasn't quite as it is nowadays, that you must publish in *Nature*, *Science*, or *PNAS*, or otherwise nobody will look at your paper, it doesn't count for you. Now it's really pretty terrible. But we did submit it to *Nature*, and immediately got a letter back saying, "There are no experimental data that prove that your calculation is correct," [so they would not publish it]. I was furious is the only thing to say. [. . .] If the experimental data exists, then we're not making a prediction, so what's the point? Even though many theoreticians call it predictions when they're in fact just getting agreement with experiment, and perhaps then they can get more insight [into the phenomenon].

I called up John Maddox, who was the editor, and talked with him for about three quarters of an hour or more, and finally convinced him that he ought to publish it, which he did.[31] Fortunately, about three or four months later, I don't remember, the crystal structure came out which confirmed what we had predicted. That was the beginning of using mixed classical/quantum mechanical calculations.

EARDLEY-PRYOR: Where did Barry Honig come from?

KARPLUS: He came from Israel. He had worked with Joshua Jortner, who was a very outstanding theoretician there. I think Barry was born in New York.

EARDLEY-PRYOR: You also went to Israel in 1968 or so. Is that about right?

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[30] Rudolph Pariser and Robert G. Parr, "A Semi-Empirical Theory of the Electronic Spectra and Electronic Structure of Complex Unsaturated Molecules," *J. Chem. Phys.* 21 (1953): 466-471; John A. Pople, "Electron Interaction in Unsaturated Hydrocarbons," *Trans. Faraday Soc.* 49 (1953): 1375-1385.
[31] Barry Honig and Martin Karplus, "Implications of Torsional Potential of Retinal Isomers for Visual Excitation," *Nature* 229 (1971): 558-560.

KARPLUS: Yeah.

EARDLEY-PRYOR: What was that experience?

KARPLUS: This was somewhat later. [One reason was] to have some time free to think about things, biological problems, and the other was to finish *Atoms and Molecules*, which was in the proof stage. Like journal articles, you're supposed to just correct little things in the proof, but my habit is to partly rewrite the proof, and then we often have to get a second proof. I did spend a lot of time rewriting *Atoms and Molecules*. I also was part of the group of Shneior Lifson, who was one of the pioneers who had come from a European background to Israel, and he was at the Weizmann Institute [of Science], and had a group which included, at the time I was there, Arieh Warshel, Michael Levitt, the other Nobel Prize winner, was not there [at the time]. What was important for me was that when Chris [Christian B.] Anfinsen, who regularly visited, came to the Weizmann Institute, he gave a lecture about protein folding. He showed a movie which was a cartoon of myoglobin, which starts unfolded and then forms helices, and those helices come together to form the [native] protein. I asked him **<T: 25 min>** what the basis was for this cartoon, and he said, "Well, it's just a cartoon." When I came back from Israel, even when I was talking to him, and I said, "We can take this model and put in some empirical parameters and use it actually as a model to calculate the rate of folding, if it follows a mechanism like that." David Weaver, who was a physics professor at Tufts [University], took a sabbatical, and wanted to learn about biology, and came over to work with me.

EARDLEY-PRYOR: In Israel? Back at Harvard?

KARPLUS: Back at Harvard. And I said [to him], "We have this mechanism. We have to just calculate how the helices, they fuse with each other, and what their binding energy is, and with a few parameters, we can actually estimate the rate of folding." This was—although people had talked about models like this—the first time that there was a model of protein folding where you made predictions as to what the rate of folding would be. It was only a few years later that the experiments were done to actually be able to check that our model was correct.

EARDLEY-PRYOR: And this all started from a cartoon that you saw?

KARPLUS: Yes, it all started [from that].

EARDLEY-PRYOR: That's wild. So this film, this is something we hadn't talked about before, but you also had had an earlier interest in film while you were in Caltech, searching through old silent movies and hosting kind of showings.

KARPLUS: Right. I and a couple of other people together with me formed a film society where we showed movies for a relatively low price. Two things that were nice were that for these silent movies, one of the other graduate students named [Walter] Hamilton, was a good pianist, and so he would make up the musical score for them. He'd just watch them and make up the score. It's sort of amazing that somehow your mind takes this score and makes it work very well for the film. Some of the things he did were great.

The other thing was that I went around to different movie studios, and to whether they were willing to let us have some films [for free]. One of the studios I went to was the [Charlie] Chaplin studio. I came in and talked with the secretary and told her I was a student at Caltech.[32] She was not very interested, and was just about ready to make me leave when Charlie Chaplin walked in. My first vision of him is how little he was. He asked what's going on, and so she told him, and then he talked with me, and he thought that it was really great that young scientists should be interested in seeing some of his films. I said, "Could we have *Monsieur Verdoux*," which was not being shown in the US, and he said, "I can't let you do that because it's not approved to be shown.[33] He did give us a number of cartoons, some of the classic cartoons, so that was a great experience. I still remember [and treasure it].

EARDLEY-PRYOR: And I thought it fascinating, the role of seeing and visualizing, and that it's played both in your scientific career and your outside pursuits, with photography, with this film work, with seeing the protein-folding film, and then that folding back into the model building you've done. So I'm wondering if that's something that—that role of visualizing, the role of seeing the model in action, if there's any relationship between your film work, your birdwatching, and the molecular dynamic work you end up doing.

KARPLUS: People have asked me how I could take pictures that are outstanding photographs, without any education and without any experience. **<T: 30 min>** One aspect of many of the [photographs] is that they capture—[Henri] Cartier-Bresson would call it the "decisive moment"—something which is really very striking and preserves it. I think it's probably true, that birdwatching actually was very important in being able to do that. When you are out watching birds, and [there are] leafy trees, you see something over there moving, but you don't know what it is, and you won't know what it is until you take your binoculars and focus on

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[32] Charlie Chaplin built his movie studio in 1917, at the corner of La Brea Avenue and Sunset Boulevard in Hollywood, California. After being sold several times and becoming different studios, The Jim Henson Company bought the studio in 2000. It was designated a Los Angeles Historic Cultural Monument in 1969.

[33] *Monsier Verdoux*, directed and written by Charlie Chaplin, adapted from a story by Orson Welles, United Artists, Beverly Hills, California, 1947.

them. You have to be able to do that intuitively, that you know where to look, because you can't see the bird when you're actually doing it. This ability to focus very quickly I think played a role in my photography.

There's of course another thing which we haven't [discussed]— maybe we talked about it last time very early—in the microscope, and looking through the microscope, and seeing the rotifers moving around. I've always been very visually conscious and very visually interested. I think there's some unity in it. How much I'd have to have a psychiatrist go into detail, but it does make some sense.

EARDLEY-PRYOR: Yeah. So that experience of the work that you did in Israel or were exposed to there, and then brought back to really continue the work here at Harvard, one of the things that came out of that as well is a continued work with Arieh—

KARPLUS: Warshel.

EARDLEY-PRYOR: —Warshel. You invited him to come have a postdoc with you.

KARPLUS: Right.

EARDLEY-PRYOR: What came out of that work together here at Harvard? Or what did it spur?

KARPLUS: I had done this work with Barry Honig, and—

EARDLEY-PRYOR: On the retinal?

KARPLUS: On retinal. And actually, with Arieh Warshel, we developed a much more detailed program which could take account of the vibrational motion. The idea is that the framework part of the system can be represented by using classical or standard vibrational analysis from experiment, and then the quantum mechanical part, which involves the pi electron system, you treat by one or another quantum mechanical model. [. . .] Arieh introduced this more detailed description of the classical part using experimental data such and so that you could calculate transition probabilities, and in fact, the vibrational spectrum, which played a role also in developing the potentials, the classical potentials, used for the molecular dynamics calculation. Some of this he had learned when he was working with Shneior Lifson, who was one of the early people to develop what's called a consistent force field approach, which [. . .] should make this force field more universal. That's what's special about what they developed, and [what Arieh] continued to develop here. Bruce Gelin, who wrote our program, which finally became the CHARMM [Chemistry at Harvard Macromolecular Mechanics] program, was really responsible for doing that.

EARDLEY-PRYOR: What was **<T: 35 min>** Bruce's role, Bruce Gelin's role in that? Where did he come from, and how did he join your group and then start doing this work?

KARPLUS: I don't remember where he was an undergraduate, but he came as a graduate student to Harvard, and when he first came, he worked on the quantum mechanics of very simple systems, the helium atom. Then he was drafted into the Army and worked a lab, because he was a chemist, [working] on LSD. LSD has two conformations, sort of like retinal, and one is active, and one is inactive. He got very interested in the biological effects of LSD. When he came back, he said, "I don't want to work on helium anymore. I was working with Neal Ostlund. I want to do something related to biology."

He's the person who developed our version of the force field, which forms the basis of the CHARMM program.[34] That was really a very essential contribution.

EARDLEY-PRYOR: To run the calculation on that pre-CHARMM program, was that still being done all the way down in Columbia?

KARPLUS: The calculations were done here by then. Things had improved here.

EARDLEY-PRYOR: The computer in Harvard?

KARPLUS: The big next step was to introduce the dynamics, which was done by Andy [James Andrew] McCammon, and now we're in the mid-seventies. I'd spent a sabbatical in France, and a number of people—Bruce Gelin, David Case, and others. Andy McCammon was a graduate student here when I went, but because his wife had a job—she's an MD—went to work with John Deutch at MIT, and then came back to Harvard [as a postdoc]. He got his degree from Harvard, though he'd worked with Deutch, and then came back as a postdoc when I came back from Europe. We had the idea of taking the program that Bruce Gelin had written to find the forces on the atom, which he had applied to hemoglobin, but there was no kinetic energy [in the system]. That's what began molecular dynamics.

[34] Bernard R. Brooks, Robert E. Bruccoleri, Barry D. Olafson, David J. States, S. Swaminathan, Martin Karplus, "CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations," *J. Comp. Chem.* 4:2 (1983): 187–217. Additional information and availability here: https://www.charmm.org/charmm/

EARDLEY-PRYOR: So Bruce's initial work on that was actually focused on hemoglobin?

KARPLUS: That was the system we were interested [in]. We had worked on hemoglobin for a while, and had developed a model of it, which goes goes back to 1971, when [Max F.] Perutz came to MIT and gave a talk on hemoglobin, and the mechanism of hemoglobin. Hemoglobin has one structure when it [binds] oxygen, and another one when it doesn't [bind] oxygen. For the first time, Perutz had been able to determine [both structures]. The oxygenated—actually oxidized—structure had been easy to determine, but the structure where there wasn't any oxygen [bound] is less stable. He finally had determined the structure of that. Looking at the two of them, he made some suggestions how [hemoglobin] works, [how it goes] from one to the other, and what was important for [the transition].

I heard the lecture—I think Alex Rich organized the lecture and had told me, "Martin, you should come. It'll be interesting." After the lecture, Perutz was sitting in Alex's office, and Alex invited me to talk with him. Perutz was sitting there eating a banana. He had a lot of stomach problems, and he could almost hardly eat anything. [He also had] a back problem. He was really an amazing individual in spite of that. He would stand for hours listening to other people's lectures.

Very similar to [what happened with] Anfinsen, **<T: 40 min>** I asked Perutz whether he had tried to actually translate his ideas into a quantitative [mechanism]. He said no and, "That sounds very interesting," but I'm not sure he understood what I was talking about. Anyway, he was very positive about it. When I came back from MIT to Harvard, Attila Szabo had just started working with me as a graduate student, and I said [to him], "We have a mechanism here. All we have to put in is a few parameters, and we can apply it." Attila was very bright—he's at NIH, and has been there for quite a while—and he developed a model very quickly. We published the model about hemoglobin, which has a number of results that went against the doctrine about hemoglobin. We were able to publish the article.[35] There is one story that's interesting. We tried to estimate various parameters that go into the model, and we got some results which looked sort of like the experimental results, but were not really right on top of them. I talked with John [Tileston] Edsall, whom you might have interviewed—

CARUSO: I can't recall him.

KARPLUS: —and Guido Guidotti, who were both in the biology department here, and both had worked on hemoglobin for a long time. I talked to them about hemoglobin [and asked them

[35] Atilla Szabo and Martin Karplus, "A Mathematical Model for Structure-Function Relations in Hemoglobin," *J. Mol. Biol.* 72 (1972): 163-197.

questions like], "There are these two experiments which disagree, which one should I believe?" [Also Guido told me], "Look, your [model and its] results are nice, but if you publish them and they don't really agree exactly with the experiment, biologists won't be interested in them." So we decided to fit the parameters to experiment, and explain why the values that we chose are physically reasonable. The paper had mixed reception, because it violated the [accepted] doctrine about hemoglobin that the cooperativity parameter is independent of oxygenation. [We showed that] it can't be and finally, experiments were done which showed that it isn't. But the hemoglobin crowd was a very closed group of people. After Attila made the model, it became clear that there were some questions that arose about the detailed atomic motions, structural changes, and going from one structure to another. And that's when Bruce Gelin applied the potential he had developed to hemoglobin, but it was without dynamics. It used just minimization. When I came back from France and Andy McCammon came back from MIT as a postdoc, [we extended the CHARMM program and] did the first molecular dynamics calculation on BPTI.

EARDLEY-PRYOR: Why not continue the work with the hemoglobin?

KARPLUS: It's too big. BPTI has five hundred atoms. Hemoglobin has four subunits, each of which have fifteen hundred atoms. Then to really do things right, you have to surround it by a box of water. At this very moment, somebody who was a postdoc with me in Strasbourg is [collaborating with me and] doing simulations of the whole hemoglobin tetramer; [earlier myoglobin, which is like one chain of hemoglobin, had been studied by molecular dynamics]. We are working together on this because there are some questions about how the molecule works. Now you can really do this, rather than simplifying, making a model. **<T: 45 min>** There are some results that are very exciting [and surprising]. We'll see. I'm not sure whether it will work out or not.[36]

EARDLEY-PRYOR: Who is that you're working with?

KARPLUS: It's Markus Meuwly. We published a number of papers together when he was [a postdoc] in Strasbourg. Now he's in Basel [University of Basel]. He's going to be coming here next week to discuss the work. So it goes on.

EARDLEY-PRYOR: Yeah.

[36] As of July 17, 2017, the paper was submitted to *Science*.

KARPLUS: Hemoglobin every five years or so reappears in my life. We also did another study—[the work was done by Guishan Zheng, a postdoc]— on the Bohr effect in hemoglobin. It interestingly goes back to one of the suggestions that Perutz made, which many people said weren't correct. We were able to do a calculation which shows that the salt bridge strengths do play the role that he suggested.[37] It's interesting, the way one goes back and can do things a little bit better. So how are we doing?

CARUSO: We can go for a little bit longer. I'm not sure if you had mentioned this already. What years were your daughters born?

KARPLUS: Sixty-three and '65.

CARUSO: Sixty-three and '65. Okay. Sorry. I just wasn't sure if we—

KARPLUS: No, I don't think I mentioned it.

CARUSO: Okay.

KARPLUS: No.

EARDLEY-PRYOR: So at Columbia, in New York.

KARPLUS: Right.

EARDLEY-PRYOR: So the work that turned into molecular dynamics seems to have begun in that late sixties period before your sabbatical and time in Paris, time in France, and then gets picked up again and becomes really dynamic after you've returned from Paris.

KARPLUS: There are two parts. There is the dynamics of small systems [reactions], like the H plus H_2 that I mentioned was done in the sixties, '64. We continued to do calculations on [small molecule reactions like H_2 +H_2 and K + CH_3CL]. As I said those calculations were stimulated

[37]Guishan Zheng, Michael Schaefer, and Martin Karplus. "Hemoglobin Bohr effects: Atomic origin of the histidine residue contributions." *Biochemistry* 52, no. 47 (2013): 8539-8555.

[in part] by the fact that you could treat individual molecule collisions—it's easy to do it on the computer, harder to do experimentally, [but as I mentioned it was being done].

We continued these calculations by averaging over the [initial] conditions, the kinetic energy, and [the collision impact parameter, and so an] averaging over a lot of molecules to find the macroscopic results that you reference by measuring the rate as a function of [the reaction] temperature. And Keiji Morokuma was one of the people, and Lee Pedersen, who worked on that.[38] [. . .] All this before actually saying, okay, let's try to this for something like a protein.

EARDLEY-PRYOR: Big.

KARPLUS: About ten years after the H plus H_2 calculation, the BPTI calculation was done. It couldn't be done on the computers—we had a VAX [Virtual Address eXtension computer] then [at Harvard]. It just wasn't big enough. In France at the time there were workshops on different topics related to using computers in chemistry, because they had [access to] what was then a very big computer, a CDC 1600, which was much [faster] than anything that was accessible here.

Carl Moser organized these workshops and invited people from all over. There was one workshop in 1976 that had to do with—the topic was protein dynamics but nobody actually had any idea what to do. It was just the name of the workshop. We knew that there we would have access to this big computer, so we worked very hard before [the time of the workshop], Bruce Gelin and Andy McCammon and I, to have a **<T: 50 min>** program that could do the BPTI calculation, so, as one says, we could hit the ground running. In fact as soon as we arrived in Saclay, [France], outside of Paris, we started our calculation. It was the only reason, because we had access to this computer, that we were able to do it. The calculation was done in France, and it [was only 9.2 ps (picoseconds) of dynamics;] it's only much later that the NSF started their computing centers in the US. Unless you had some sort of government relations, so that you could [use computers] at Livermore, for example, it was very hard to get near the [equivalent amount of] computer time [in the US].

EARDLEY-PRYOR: Did you build physical models after running the calculations and having these theoretical models?

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[38] Morokuma K, Eu BC, Karplus M., "Collision dynamics and the statistical theories of chemical reactions. I. Average cross section from transition-state theory." *J. Chem. Phys.* 1969; 51:5193–203;
Morokuma K, Karplus M. "Collision dynamics and the statistical theories of chemical reactions. II. Comparison of reaction probabilities." *J. Chem. Phys.* 1971, 55:63–75;
Morokuma K, Pedersen L. Molecular, "Molecular orbital studies of hydrogen bonds. An ab initio calculation for dimeric H2O," *J Chem Phys.* 1968; 48:3275–3282.
Pedersen L, Morokuma K. "Ab Initio Calculations of the Barriers to Internal Rotation of CH3CH3, CH3NH2, CH3OH, N2H4, H2O2, and NH2OH," *J Chem Phys.* 1967; 46:3941–3947.

KARPLUS: No. At that time, we made drawings, but the paper that shows the dynamics really just has one figure, which shows the structure, and not all the atoms, but just the amino acids. There are fifty-four amino acids, so it shows the initial structure and after, I don't know, 3.7 picoseconds, and the whole simulations was 9.2 picoseconds, which if you wanted to publish a paper nowadays and said you had done only 10 picoseconds, you would be laughed out of the hall.

On the other hand, it turns out that many of the things that we concluded from doing this very short simulation, including some sort of lucky accidents that did happen, gave insights into the type of motions that are still true today as they were then. And nowadays, David Shaw—does that mean something to you?

EARDLEY-PRYOR: Yeah. The Anton computer and the Desmond program?

KARPLUS: Right. He has an institute where—well, it's officially a company [D.E. Shaw & Co.]—they do very long calculations, and they have now done a calculation of BPTI that's, I think, one millisecond [in length].

EARDLEY-PRYOR: A millisecond long?

KARPLUS: It took them a long time. The fluctuations over the time are a little bit larger [than what we found], but qualitatively, the insights that you get from that are really not that important. [. . .] It's the bovine pancreatic trypsin inhibitor, it's called that because it's known that it binds to trypsin and inhibits trypsin. But it's not known whether that's a biological function or not. [However, the fact that with essentially the same potential as we used in the 9.2 ps, BPTI turned out to be stable—not unfold or anything—was an important verification of the simulation methodology.] Enzymes that undergo large conformational changes between active and inactive forms, then the simulations are much more important and being able to do these longer simulations plays a real role. In the basic [BPTI] dynamics—we didn't have any water [environment]. Now proteins are [simulated] in solvent. [That is also important.]

EARDLEY-PRYOR: So let's take back the transition to Paris. What was the impetus to get back to Europe?

KARPLUS: It was partly my more or less five-year plan. I thought I would go there permanently, and I liked the idea of living in Europe. I thought the lifestyle in Europe was more humane than here, where people were—I did like to work hard, but I also liked to take real time off, and I liked the culture there. As I mentioned, the theater, though it's good in New York, but nothing like it's in London, and also in Paris, with the Comedie-Francaise, and so it was the lifestyle [that interested me].

CARUSO: Had you improved your French since going to that restaurant?

KARPLUS: By the time I decided to go there possibly permanently, the answer is yes, because every sabbatical **<T: 55 min>** I had spent in France, mainly in Paris. And when I was at various institutes that I worked in, I told people if they wanted to talk to me, they had to speak in French.

Initially they spoke better English than I spoke French, but in those days, the French didn't speak—even the scientists—good English. So after a relatively short while, it was easier to speak in French. Probably 90 percent of my education [in French], was just orally learning though. I also went to the Alliance Française. The difference between Marci and me was that she didn't have the outside possibility to talk French, so it was much harder for her. She'd go to the market and things like that, but she didn't join any groups where people spoke French for a few hours. Anyway, that's how I learned. My oral French is much better than my written French.

CARUSO: When you were on these sabbaticals, leading up to the time in France, did your daughters join you when you were over there, or did they stay in the States?

KARPLUS: [As long as they were still in school, up through high school, they came with us].

[. . .]

CARUSO: I wasn't sure. We haven't spent a whole lot of time talking about your family. Your daughters became physicians. Did they come to lab with Dad and do things? Were you introducing them to science at the level that you were doing it? Did you try to look at their science homework when they were bringing it home and work on it? I'm curious if there was any involvement.

KARPLUS: I think they almost never came to the lab. And it wasn't clear whether both would actually become physicians. One [daughter, Tammy,] went to Brown [University] as an undergraduate. She was much more interested in writing, and somehow when she graduated, she thought of going to [University of] Iowa to the Writers' Workshop there, but she said, "Well, maybe I should also apply for something that could give me a career where I could earn some money." She applied to medical school to Tufts and Harvard, and she said, "Well, if I get in, I'll do that. Otherwise, I'll maybe go off to Iowa."

And my other daughter, Reba, the older one, actually, was very much interested in history, studied history when she was at Cornell. She lived in a Jewish house—we are Jewish—and she became interested in visiting Israel, and she decided she'd like to do her PhD in history there but history in Israel is a very narrow subject. You can study Masada or something like that, [but] it really is so focused. So she started working, and she took a job working with autistic children. She's very lively, much more so than her sister, and very outgoing. She was very good at working with the autistic children but it was a terrific drain [on her]. They become very dependent on you. She decided she couldn't do that as a career [and] decided to go to medical school to be able to work with them, but more on the medical part, rather than on the caretaker part. That's how she [decided to go to] medical school [in Jerusalem]. Now Tammy is a rheumatologist, and Reba works on infectious diseases. **<T: 60 min>** It's good to have a rheumatologist in the family. [laughter]

A couple of times when we were in Paris, they were with us, and then they had graduated and gone to college, but then Reba actually was in Paris. That was the year that [our son] Mischa was born. He was born in Paris.

CARUSO: What year was that?

KARPLUS: Eighty-one.

CARUSO: Eighty-one.

KARPLUS: Reba had finished high school, so she was just listening to some courses at one of the schools, and Tammy actually took her last year. She had great trouble with her English course, because the English teacher knew only English-English. The French education has some good elements. Mischa got his baccalaureate in France, and it's very rigorous and very strict, and there's the right answer and the wrong answer, in contrast to America. I think the combination of spending a year there and spending a year here, or whatever, is a good way of doing things. So maybe that's a good place to stop?

CARUSO: Sure. Yeah.

EARDLEY-PRYOR: I was wondering if you could talk just a little bit about the summers in the Alps.

KARPLUS: Ah.

EARDLEY-PRYOR: What that time meant for you, for your scientific work, and for your family**?** What the role that the—nature seems to come up again.

KARPLUS: When I was in Europe in the 1950s traveling around [and photographing], I visited this area, [on the Lac D'Annecy], partly because there was a famous restaurant there called Auberge de Pére Bise, which is a three-star restaurant, where later on I worked in for a while. I fell in love with this area. It has a beautiful lake, and then it has the foothills of the Alps which are striking. In the seventies, we spent some summers there, and rented [a chalet]. Then we finally decided we should try to buy some land and build a chalet there, which we still have.

When I am here [at Harvard University], and Marci would confirm that, I work all the time when I'm working, unless we going to go to New York like this weekend. Getting away—we used to go there, [to the hamlet of Chaumont], for a couple of months. We'd get on the plane. I would have a trunk with me with a bunch of papers. But once you get on the plane, what you've forgotten, you've forgotten. Then the different life starts, where in the morning you walk down to the bakery, or you speak to the neighboring farmer about how his cows are doing. It's sort of a different atmosphere.

I think that was very good for me [and also] it was fun for the children and Marci. We did a lot of hiking and [swimming as a family]. I found that being under less pressure, I would work out some of my ideas and solve problems that I hadn't been able to solve while I was here. I asked my program director at NSF—[at Harvard] you can take a summer salary. My colleagues thought it was weird that I would go off like that, because although they travel as much as I do, or more, they do it for two or three days. I think they are afraid that their research group wouldn't survive.

Anyway, [I told] my program director, "Look, this is what I do there, and I can show you the problems I've solved." He said, "Fine, you can take your summer salary. That's okay with me." Also, I said there was a picture I wanted to buy and put in my office, and could I pay for it out of NSF funds? And he said, "Well, does it help you?" I said, "Yes." And it was true, again, that I liked to sit there and every so often look up **<T: 65 min>** and look at the picture, and relax and clear my mind. I [doubt that] nowadays such things would [be allowed].

We were able to do it, and it was a wonderful experience. We'd go hiking. We'd swim in the lake [Lac d'Annecy], which is a beautiful lake and also has an interesting story. It was very polluted because all the surrounding tourist towns had all of their garbage and everything go into the lake, the sewers, essentially. Then they decided as a group that they would build some sort of canalization so no sewage went into the lake. It had been polluted, and was full of various weeds. In about a year and a half, it was the cleanest lake in the Alps. It just recovered on its own. It's special in that it has underground springs, so that made it all the more [easy to purify itself]. It has very little flow from rivers. It's a lovely place to swim. Those were really great summers. Once we lived in France most of the time, we actually went there less, because we'd say, "Well, we can go there any time." We still went there [for a few weeks] in the summer, and in the winter, but much less so.

CARUSO: All right. Well, thank you very much.

KARPLUS: Okay.

[END OF AUDIO, FILE 2.2]

[END OF INTERVIEW]

INTERVIEWEE: **Martin Karplus**

INTERVIEWER: **Roger Eardley-Pryor**

LOCATION: **Harvard University**
Cambridge, Massachusetts

DATE: **25 May 2016**

EARDLEY-PRYOR: All right. Hello. This is Roger Eardley-Pryor. I am here for an oral history with Dr. Martin Karplus. We are at Harvard University at his office. Today is May 25. It is a little after 1:00 PM. Dr. Karplus, thank you again for making time to chat with us today. During our last discussion, we had moved through some aspects of your work, beginning into the protein folding era, and moving towards the simulation of biomolecular dynamics. Were there some things that you wanted to cover about that time period?

KARPLUS: It's a somewhat later time period, but I thought I would go back. We really didn't discuss protein folding, other than the very early work that David Weaver and I did together, where he came over from Tufts, where he was a physics professor.[39] We discussed what he might do. I was very interested, partly having seen this film—

EARDLEY-PRYOR: The Anfinsen film?

KARPLUS: —the Anfinsen film. This picture of helices coming together, and all of this may already be [in the recording]. My having asked him did he actually make a model based on this. He looked at me, and the answer was no. So after that, I had this idea in mind. When David Weaver came along, who knew more about fluid mechanics than I did, we developed the diffusion collision model. It was a very coarse-grained model, but the first model which permitted one to actually calculate folding rates with reasonable parameters.

I'd continued to be in contact with David. When he retired—it must be now about ten years ago because some of his children and grandchildren were at [University of California] Davis, in California, he and his wife decided that they would retire there. He would continue to do research in protein folding, but leave the East Coast. Unfortunately, before David could actually move there, he had had a stroke. He somewhat recovered from the stroke, but then he fell down again, and he passed away before he actually could ever go to Davis. But his wife,

[39] David L. Weaver and Martin Karplus, "Protein-Folding Dynamics," *Nature* 260 (1976): 404-406. See also David L. Weaver and Martin Karplus, "Folding Dynamics: The Diffusion-Collision Model and Experimental Data," *Protein Sci*. 3 (1994): 650-668.

Elena, and Bruker [Optics] Company with whom he had collaborated for many years, set up a foundation funding for an annual David Weaver lecture [The David L. Weaver Endowed Lecture] in biophysics, I think it's called. The first lecture was actually ten years ago, in 2007, and they invited me, because I was very close to David, to give the first lecture. This year was the tenth anniversary. There was again a David Weaver lecture by [Sir Thomas Leon] Tom Blundell, who is an outstanding British biophysicist. He gave a lecture talking about his recent work on drug design.

I was invited to also give a lecture, but this was by the chancellor of the university. They have public lectures, about half a dozen a year, and so I had the opportunity to go out there and give a complementary lecture, which was my Marsupial lecture, which may have appeared before in our discussions.

EARDLEY-PRYOR: I don't believe so. What's the Marsupial lecture?

KARPLUS: In 2007, I was invited to give the [John] Stauffer lectures at Stanford. When you are invited to do that, you're supposed to give a scientific lecture—it's in chemistry, or chemistry and biophysics—and also a public lecture. So I prepared a public lecture which is called "Motion: The Hallmark of Life from Marsupials to Molecules." I didn't realize that **<T: 05 min>** when I prepared this lecture, that it would be very useful for me in the future. I continued to give versions of it. The latest version I gave was actually at Davis, just before I gave one in Milan, [Italy], as part of a Nobel lectureship at the University of Milan, where they were also showing my photographs. It's been updated, both in terms of content and new things being discovered. I must have now given it fifteen times. I never realized that the original investment of time, which was a huge investment, trying to put things together that would be scientifically correct, but interest to a broad public.

The most exciting part of it is where I'm talking about the importance of myoglobin and oxygen for getting energy. Myoglobin was first crystallized from whales. There was also a problem with—dolphins, actually, not whales—diving. Somebody calculated how much oxygen they had to make the ATP which they need to make the muscles move, and how long they were able to stay underwater and dive, and they came up that there was a shortage of about 20 percent. Then they did underwater photography of dolphins, and they noticed that when they swam, they would—they mainly are propelled by their tail fins— make a stroke, and then they glide, and make another stroke, and then they glide again. As a result they save enough energy, about 30 percent, of what it would require, so they're actually able to do it with the amount of oxygen that they have to make the ATP. This gives me an excuse to show some beautiful pictures with lots of splash noise of dolphins. In particular, there are the spinning dolphins, which are dolphins [. . .] that go up in the air and they keep spinning, and then fall into the water, and they keep on doing that. I show that and the sound effects. You hear this loud splashing of the water.

EARDLEY-PRYOR: That was something you gave at the inaugural—during the time when—David Weaver lectureship?

KARPLUS: No, I had not actually prepared it when the David Weaver lectureship started in ten years ago, in 2006. I gave a more general lecture on how proteins work. I hadn't actually prepared the public lecture. When I was invited to give [the Chancellor Lecture], it was supposed to be a popular talk. I wondered, did I actually give the marsupial lecture when I was first there? But then I looked up things, and it was clear that I couldn't have, because I only prepared it in 2007, [the year] after. I was able to give it there, and it's always well-received. The whole festivities around the Weaver lectures make it a very warm activity. Most of the people who have lectured have been people that I chose, like Chris [Christopher Martin] Dobson, Greg Petsko, and Arup Chakraborty [. . .]. They've all been outstanding . . . it's a lectureship that's done very, very well. It was very nice to be able to be there on the tenth anniversary. All the family is there. The Weavers [have] three boys, the youngest of which is the age of my son, whom you've just—

EARDLEY-PRYOR: Mischa.

KARPLUS: Mischa, who you saw **<T: 10 min>** here. They were very good friends when the Weavers lived in Medford, and we used to go over often to their house, and they'd play in the basement. It's a very warm occasion.

EARDLEY-PRYOR: How did you and David Weaver first meet, if he was at Tufts and then came over for his sabbatical to work together with you?

KARPLUS: He just asked me. He said, "Well, I'm tired of doing high-energy physics, and I want to do something else. I want to get in biology." He'd noted my name and asked me if he could come over. As I mentioned at the beginning, we discussed what might be a problem that was of interest, and that his background in physics was well suited for.

EARDLEY-PRYOR: When you chose your problem to work on, was the Levinthal paradox, Cy Levinthal's paradox, something that was on your radar for both of you, or was that something that came up later?[40]

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[40] Cyrus Levinthal, "How to Fold Graciously," in *Mossbauer Spectroscopy in Biological Systems: Proceedings of a Meeting Held at Allerton House, Monticello, Illinois* (1969): 22–24. See also R. Zwanzig, A. Szabo, B. Bagchi, "Levinthal's Paradox," *Proc. Natl. Acad. Sci. USA*. 89:1 (1992): 20–22.

KARPLUS: I'm not sure he had a radar in this area, to be honest, but of course it was on my radar. I don't think we discussed it, though we might have. One way of solving the Levinthal paradox—it probably is mentioned there—is that you simplify the system. [If you have] one long polypeptide chain where every amino acid can have three or four different orientations, [. . .] to search through them step by step would not work. That was basically Levinthal's assumption - they're all equally probable.

One way to reduce this search [problem is] that you form helices, which are relatively stable. They may not be completely stable, they may fold and unfold, but still, the search problem, say for myoglobin, which has one hundred fifty residues, and eight helices, [so the search problem is reduced to searching through the conformational space of only eight helices]. It is a way of solving the Levinthal paradox for helical proteins. We also did some work later on β-sheet proteins with the same sort of model as is mentioned in some of the later papers with David.[41] At the time that the model was made, there weren't enough data to actually test the model. It was only at least ten years later that the data were around which showed that indeed the model was consistent with the folding of helical proteins.

However, we wanted to have a more general approach to protein folding. Although you could do a molecular dynamics simulation of a protein in its native conformation, looking from one conformation to another to do protein folding, assuming even that everything was correct, your potential function was correct, just going to the computer, pressing a button, and doing molecular dynamics to fold a protein, that was just out of the question [at the time]. One still had to use a simplified model, and that was where the idea of lattice models [arose]. Basically the protein has twenty-seven [particles] in the particular lattice model that we used.

EARDLEY-PRYOR: This is in the publication from '94, in *Nature*?

KARPLUS: In *Nature*. Right.

EARDLEY-PRYOR: "How Does Protein Fold?"[42]

KARPLUS: We used a cubic lattice and a model protein, which had twenty-seven residues on the cubic lattice. Each residue, if it were completely free, would have one lattice side, and it could go to three others if it's on the edge, otherwise, it could go to five others. For that case,

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[41] For instance, see S. A. Islam, M. Karplus, D. L. Weaver, "The Application of the Diffusion-Collision Model to the Folding of Three-Helix Bundle Proteins," *J. Mol. Biol.* 318 (2002): 199-215; S. A. Islam, M. Karplus, D. L. Weaver, "The Role of Sequence and Structure in Protein Folding Kinetics: The Diffusion-Collision Model Applied to Proteins L and G," *Structure* 12 (2004): 1833-1845.

[42] Šali, Andrej, Eugene Shakhnovich, and Martin Karplus, "How does a protein fold?" *Nature* 369 (19 May 1994), 248-251

<T: 15 min> you can't solve for all conformations either, just like a protein. However, what you can do is to do simulations where the native state, which is a configuration of the twenty-seven beads in the cube, is of lowest energy. Also there is an energy gradient as the protein folds from an extended configuration to the native one. But there are many, many pathways of doing this. Although it's a simplified model, it still has the Levinthal paradox that if it had to do a search of all the conformations to find the right one, it would never [be able] to do it. These are actually Monte Carlo rather than molecular dynamics simulations, but it would take forever in terms of the computer time that was available.

Nevertheless, what we found was that if the native state was a relatively stable minimum, and we studied two hundred possible sequences by Monte Carlo simulations for a reasonable number of steps, we found that out of these two hundred, thirty or so actually folded to the native state. They clearly couldn't have done it by doing a complete search of the space, an infinite space in terms of the number of Monte Carlo simulation moves that were possible. We analyzed what happened, and we saw that the folding process was sort of step-wise. If we take an extended chain, first of all, it would collapse, into a random globule, as it's called. These collapsed states with no real structure are called random globules. Then within this collapsed globule, the available states are much, much smaller, and so it only had to search through those. This permitted it—it was doing a random search within that slight space. The energy bias permitted it to find the native state.

The paper with the title "How Protein Folds?" was published in *Nature*. Probably would have been—there were quite a few papers on protein folding, none from this point of view, but much more describing phenomenological models that people made, which weren't any good for doing calculations. They were conceptual models that had been in the literature for quite a few years. My guess is that, except for serendipity, a historical accident, this paper would have been just one more in the series of papers. However, Baldwin, who was one of the people working in protein folding, a professor at Stanford—Buzz [Robert L.] Baldwin—wrote a News and Views article in *Nature* saying that this was really something terrific, and that finally we had sort of solved the Levinthal paradox.[43] And as I write somewhere, it's my impression is that many people don't read the papers in *Nature*. They just read the News and Views. Thus the paper became widely known and widely talked about.

There was also a problem. Peter Wolynes, who has been working on protein folding for years—the Bryngelson-Wolynes paper, which is a famous paper on protein folding.[44] [There are several citations to him in our paper.] Unfortunately, Baldwin didn't cite him at all.

EARDLEY-PRYOR: Didn't cite who?

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[43] Robert L. Baldwin, "Matching Speed and Stability," *Nature* 369 (1994): 183-184.

[44] Bryngelson, Joseph D., and Peter G. Wolynes, "Spin glasses and the statistical mechanics of protein folding," *Proc. Natl. Acad. Sci. USA*, Vol. 84 (November 1987): 7524-7528

KARPLUS: Peter Wolynes. Baldwin in his News and Views article [. . .] didn't cite Wolynes, [and he blamed us for that]. **<T: 20 min>** [. . .]

EARDLEY-PRYOR: To you and your group directly?

KARPLUS: There were three people involved. Eugene [Shakhnovich] and I were the lead authors, and Andrej Šali was the one who did [the actual calculations]. I tried to say we didn't write the News and Views. In retrospect—I think I discuss this somewhere—I probably should have realized that Baldwin not mentioning Peter, who regarded himself, and rightly so, as one of the pioneers in discussing protein folding in statistical mechanical terms. I always like to have something concrete that I'm looking at, and try to understand and learn from it. He's much more a general statistical mechanician. If I had been more insightful, I would have written something immediately to say, "Yes we did this work, but as I wrote in something else, 'Unlike Venus on the half shell, [our work in] protein—science didn't develop by itself spontaneously. There are many other people who [contribute]'"—but I didn't do that.

[. . .] I won't go into more detail about that. But anyway, it was to a certain extent that I wrote this other paper called "The Levinthal Paradox: Yesterday and Today."[45]

EARDLEY-PRYOR: The one from 1997?

KARPLUS: Yes.

EARDLEY-PRYOR: And that was originally a talk you gave abroad, correct?

KARPLUS: Right, abroad. There was a meeting on protein and design, and at least some of the talks appeared in the *Folding and Design*, which was an independent journal for a certain amount of time, edited by Alan Fersht. Then it was taken over by *Structure*. You're right, this [paper] was based on a talk. What I say here **<T: 25 min>** [described] two types of items which are of interest. One refers to the change in the view of the Levinthal paradox and how difficult it is for proteins to fold. This echoed what happened with molecular dynamics of proteins. It was twenty years ago or so before this was written, this was '97, and it was '77 when the first molecular dynamics simulations came out. There was a meeting in England where D.C. [David Chilton] Phillips, the crystallographer who did the first enzyme crystal structure, wrote, "The

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[45] Martin Karplus, "The Levinthal Paradox: Yesterday and Today," *Structure,* Vol. 2 Supplement 1 (June 1997): S69-S75.

period ’75 to ’96 may be described as the decade of the rigid macromolecule. Brass models of DNA and a variety of proteins dominated the scene, and much of the thinking.”

Then in the intermediate period, since the molecular dynamics simulations, everybody realized that—as they should have anyway—proteins are not brass models, but that the atoms are connected by relatively weak springs. At room temperature, every one of them must have three kT of energy, and so they must be vibrating. Nevertheless, people saw a beautiful x-ray structure and said, ‘That’s the protein structure,” and didn’t consider the motions. It took many years for people to be aware that proteins were fluctuating systems, and so the paradigm changed from proteins being rigid systems to proteins being fluctuating systems.

My feeling as expressed here was that, again, people had always focused on the Levinthal paradox, and asked, “How can the protein fold?” Now after some of these simulations were published, the question [changed to], “Why do proteins fold so slowly?” So essentially the conceptual idea changed, and as I say here, “It’s not a great exaggeration to say that the pessimistic view of yesterday, it is impossible for proteins to find the native state, even though they do so readily in solution, has been replaced by the optimistic viewpoint of today. It’s obvious that proteins should be able to fold rapidly to the native state.”[46]

What I say here, is of more general interest, in that science has paradigms, and even without very clear reasons, it moves from one paradigm to another. That’s how progress often takes place.

EARDLEY-PRYOR: You mentioned elsewhere this really neat quote by Richard Feynman, that everything in the molecular world—and in biology in particular—could be explained by the jiggling and wiggling of atoms.[47]

KARPLUS: Right.

EARDLEY-PRYOR: Feynman had that view in the early sixties.

KARPLUS: Right.

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[46] Martin Karplus, “The Levinthal Paradox.”

[47] In his 1963 lectures, Richard Feynman said, “Certainly no subject or field is making more progress on so many fronts at the present moment than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jiggling and wiggling of atoms.” Richard Feynman, Robert B. Leighton, and Matthew Sands, *The Feynman Lectures in Physics* (online edition), The Feynman Lectures Website, http://www.feynmanlectures.caltech.edu/.

EARDLEY-PRYOR: And it took all the way through after the 1977 BPTI calculation to really show that to be done. Why do you think it took so long between this conceptual point up to—was it the ability to calculate these on computers? Is that part of the story?

KARPLUS: Feynman, he was a physicist. He wrote a wonderful three-volume set—he didn't write it, he gave the lectures and his students wrote it—three-volume lectures on physics, which talk about all kinds of things. He has a little section on biology where this quote appears. It had disappeared, until I found it, and now almost every paper on molecular dynamics has this quote.

I also found—that's in the marsupial lecture—that **<T: 30 min>** Titus Lucretius [Carus], a Roman poet wrote one poem that we know about called "The Nature of Things." He describes the motions of atoms—and you could imagine that—it says the atoms move around—I'd have to look it up exactly to have it—until finally they form everything we know today.[48] It's an amazing thing. Actually, the Greeks knew a lot about atoms. Democritus described solids and liquids—solids have very tightly bonded atoms, and liquids have very weakly bonded atoms, so they can move relative to each other.[49] This atomic model—I won't call it a theory—of structure disappeared for two thousand years, until [John] Dalton came up with the atomic theory. I'm sure he didn't know anything about Lucretius, and he did very careful measurements, including [determining] Avogadro's number. But for two thousand years, this idea was just lost, which is interesting.

EARDLEY-PRYOR: I'm fascinated to learn where your realization of some of those ancient, deeper connections to these Hellenistic worldviews of atomic structure came from. Was that part of the marsupial research, the research for that lecture on the motions?

KARPLUS: No, well, that particular part came again by accident. There's a scholar here [at Harvard] named [Stephen] Greenblatt who's written a book; it's called *The Swerve* and it talks about the development of atomic theory and other things.[50] He's a Shakespearean scholar, in addition, but he also has written a lot about ancient Greeks and what they knew. Probably—I'm just making this up—the *Harvard Gazette* maybe had an interview with him, or something like that. And I saw this, and I thought, "Hmm, that's interesting," and then I got in contact with him, and the quotes that I give are his free translation from the [Latin]. It's really amazing to see. [Greenblatt's] a very interesting fellow. [. . .] I'm not a Greek scholar as such, but I do sort of remember things, though I often don't remember all of the details. I do sort of capture—I think that's one of the abilities that I have—the essence of something, and then it comes back to

[48] Titus Lucretius Carus, *De Rerum Natura* or *On the Nature of Things*, translated to English by C.J. Thomsen in 1834.
[49] Democritus lived in ancient Thrace, Greece ca. 460 BC to 370 BC. None of his writings have survived.
[50] Stephen Greenblatt, *The Swerve: How the World Became Modern*, (W.W. Norton & Company, 2012)

me, and I can look it up, and that's basically how I looked it up— just said, "Oh, this would be great to have in the marsupial talk." I mean to give a general culture in this [lecture].

EARDLEY-PRYOR: I'm also interested to go back to the "How Does a Protein Fold" publication in *Nature* that creates this lattice, in order to try to calculate the energy within that space, and the movement in that space. Where did that idea come from? To create this sort of bounded area that you could quantify?

KARPLUS: It's, again, to a certain extent an older idea. I'm not sure who the original person was. It was probably [H.] Abe and [Naburo] Go. I refer to it here as Abe and Go, Japanese biophysicists, who looked at two-dimensional lattices in 1981.[51] [quoting from paper] "Go and Abe, 1981, made a pioneering study in this area, and they did it in two dimensions." It had some of the same ideas as we had, but they couldn't really show that it worked in a general sense, in a system that had the Levinthal paradox. But the system **<T: 35 min>** was [not] large enough to do what we did, but the original idea was theirs, and I am sure I was aware of it. I knew Go quite well. One time I went to Japan when he organized a conference. He was really a wonderful individual. So I would say if anybody should receive credit for the original idea, it was Go. He refers to the harmony principle of protein folding, that there are lots of weak interactions between the different atoms or amino acids, and that the stabilizing interactions that you get from them lead to a native state. That's why they call it the harmony principle. Yeah. As I say here, "The work of Go and Abe and Bryngelson and Wolynes contain many insights that are important for the present-day view of protein folding. However, they appear to have had rather little impact on experimentalists. As sometimes happens"—I was going to say that, but it says it here better than I could—"As sometimes happens in science, papers are published before their time has come." [Their description was not] neat and clear-cut as to what happened. Also, people weren't interested in folding. It's only now as more and more protein structures were determined. Nowadays, protein folding [is of more interest] with gene sequences because you have many gene sequences of proteins, and it would be lovely to be able to take these sequences and determine the structure of the protein on the computer, but we aren't there yet.

Maybe this is an excuse to go on to something more recent, if I can find it. This is a paper with Amedeo Caflisch, and I thought I had pulled it out. I can pull out another copy, if you want to stop it for a second.

EARDLEY-PRYOR: Sure.

[Break in audio]

[51] N. Go and H. Abe, "Noninteracting Local-Structure Model of Folding and Unfolding Transition in Globular Proteins. I. Formulation," *Biopolymers* 20 (1981): 991–1011.

EARDLEY-PRYOR: All right. You found the paper you were referencing? [. . .] This is the one titled, "One-Dimensional Barrier Preserving Free Energy Projections of β Sheet Mini Proteins"?[52]

KARPLUS: β-sheet.

EARDLEY-PRYOR: β-sheet mini proteins. "New Insights into the Folding Process," from 2008, in *J. Phys. Chem*.

KARPLUS: Now before going to that, mentioning doing things before the idea has come, long ago—I can look it up. Can you hold it off one other second?

EARDLEY-PRYOR: We'll just let it run. It's okay.

KARPLUS: Okay.

EARDLEY-PRYOR: There's plenty of space on there.

KARPLUS: [A.] Mukherji and I published a simple quantum mechanical calculation of hydrogen fluoride in 1963, called "Constrained Molecular Wave Functions."[53]

EARDLEY-PRYOR: Yeah.

KARPLUS: The hydrogen fluoride molecule. What we did there, it was because you couldn't do very accurate quantum mechanical calculations, the way you can nowadays on big computers with lots of basis sets and all that. It was a minimal basis set. I've always been interested in—and this goes back to what happened in Oxford when I was a postdoc—what I wanted to do was

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[52] Sergei V. Krivov, Stefanie Muff, Amedeo Caflisch, and Martin Karplus, "One-Dimensional Barrier-Preserving Free-Energy Projections of a β-sheet Miniprotein: New Insights into the Folding Process, *J. Phys. Chem. B, 112* (29) 2008: 8701-8714.
[53] A. Mukherji and M. Karplus, "Constrained Molecular Wavefunctions: HF Molecule," *J. Chem.Phys. 38* (1963): 44-48

theoretical chemistry that was of interest to chemistry rather than just the theoretical chemists. **<T: 40 min>**

One of the molecular quantities that one can measure experimentally and try to calculate is the dipole moment of a molecule. We did a calculation on the hydrogen fluoride [molecule], which has a large dipole moment and we realized that the dipole moment didn't come out correct, so clearly the wave function wasn't correct. We had the idea that if we constrain the dipole moment to be the correct value, then the wave function would be a better approximation. We did that but nobody was interested in the paper, as far as I can tell.

In last few years [while] doing much larger scale calculations, people have suddenly discovered the idea that doing calculations and constraining the wave function with certain approaches to do this constraint, which are rather sophisticated, more so than what we did, is a very useful thing to do. For example, if you have [a system composed of an atom, an ion, say Fe, Fe^-] and you really want to have the wave function artificially [. . .] have all the extra electrons to stay on the ion. Then you constrain the wave function, so that the extra electron is confined to this ion. And basically, they use the method that we developed in 1963, and one or two of the people—one is at MIT, name escapes me—actually refer to our paper. [. . .] But I think the essential point is, yes, it was clever, what we did, but so what? It didn't advance science.

EARDLEY-PRYOR: At the time.

KARPLUS: At the [time]. Nobody actually used our paper and said, "Ha, that's a good thing to do. Let's do it now when we can do things so much better." I mean, it just had no effect. You drop a pebble in water, it disappears unless a fish eats it. That's one of the lessons that one learns. I can say to myself, I was really clever. I had this idea. It's now fifty years ago. But as far as [advancing] science was concerned, it was not useful.

EARDLEY-PRYOR: Until later. So I'm kind of interested in your ideas on that. So the theoretical idea you came up with, why do you think it came into greater use later? And again, I'm wondering if there's a technical component to that.

KARPLUS: It certainly is true that you can do much better calculations, but my point is the idea *per se* didn't [have any effect]. None of the people who are trying to do this localizing of the charge distribution said, "This is the way we should do it," and it was a result of this. As one says, they reinvented the wheel, or Dalton reinvented—Dalton's atomic theory—in the same way [reinvented the ideas of] Titus Lucretius. I think that's an important thing to remember. There are a number of other things that I've done in that way. When I see someone who's doing it, I might write him and say, "Look," but I realize that if you have an idea before its time has come nothing will happen. That was of course a bit [the case] in molecular dynamics, where it took a while before people were really willing to accept it.

EARDLEY-PRYOR: The idea of moving—

KARPLUS: And—

EARDLEY-PRYOR: —vibrating—yeah.

KARPLUS: —I don't know whether I mentioned this, but [. . .] and one of the first lectures I gave on molecular dynamics.

EARDLEY-PRYOR: No, please do.

KARPLUS: Was in Oxford. There were mainly crystallographers in the audience.

EARDLEY-PRYOR: When was this?

KARPLUS: Must have been shortly after **<T: 45 min>** '77, maybe in the early eighties. I said, "In BPTI, there are four tyrosines." I still have a model of BPTI up there [*pointing to an encased ball-and-stick model of BPTI on a shelf in his office*]. What we find is that on a very fast time scale, they flip. And crystallographers say, "Tyrosines are the best determined because they're big flat things, they couldn't be flipping," and they didn't realize that, sure, 99 percent of the time they're like this. Then all of a sudden they flip. It's exactly the same structure. So the fact that they actually do flip was just beyond them, and they didn't believe it.

EARDLEY-PRYOR: How did they register that, during your talk?

KARPLUS: They said they couldn't be wrong. I couldn't convince them. They didn't understand what was going on. They [determine] average structures in x-ray crystallography. If you take a time average, or average [over many BPTI molecules] in the crystals, they're one way or the other way, but the two ways are equivalent. Now if it were a substituted tyrosine so that you could see that it had an OH out here, and then it flipped over, the OH was here, then that's a small energy difference in the crystal. If they do high resolution [structures], they could tell the difference between the two of them. Crystallographers didn't want to believe that [flipping can occur]. It took quite a while for them to believe it. I think the simulations and such were timely and had a lot of effect on their thinking.

And I remember there's a paper by [Robert] Huber, who was a crystallographer and won the Nobel Prize [Chemistry, 1988]. I was very amused when he emphasized that in a certain crystal structure, you couldn't see part of the molecule. And he said, "That shows motion of the molecule—." I don't think it shows motion; it showed that there was disorder. There's a difference between disorder [and motion]. To get a good [high-resolution] crystal structure, every molecule in the crystal should be pretty much the same.

EARDLEY-PRYOR: There were some other articles—finish, yes.

KARPLUS: It's the next stage in studying protein folding. For a long time, it wasn't possible to simulate folding just by molecular dynamics. However, by using relatively simple systems, such as a double β-hairpin, and using implicit solvent, [it was possible]. What do I mean by that? Most of the time, if you're simulating a protein, and you want to get a reliable simulation, you simulate it [. . .] in water with ions. Then it turns out that 99 percent of the simulation time is spent simulating water, so you could do it a hundred times faster if you didn't actually have to simulate the water. We developed a very simple implicit solvent model, which represents the solvent in a very simplified way, as an effective potential. Charlie Brooks has developed more sophisticated ones.

These are very important. Amedeo Caflisch, a former postdoctoral student, who is now in Zürich on the faculty of the University of Zürich, has done **<T: 50 min>** some outstanding work. He started doing folding simulations of this double β-hairpin in implicit solvent. You could, if you study it at the temperature where the denatured state and the native state are [equally] stable, and you do molecular dynamic simulations that take only a reasonable amount of time—reasonable meaning that you can do it with the computers that are available—you can watch hundreds of folding/unfolding transitions.

[The Caflisch double hairpin] became a model system where people tried different approaches to understand the protein folding process. There have been many more papers written by people, usually in collaboration with him, on studying this system. It's a model that's more realistic than the lattice model, and I think it's very important. Sergei Krivov, a postdoc with me—I'm still working with him on other problems, how the brain works, but that's something else we will get to—we did a paper which studied the protein folding.[54] It turns out that it's more complicated [than people had thought]. There are many pathways. But you can develop networks, simplified networks, and complex networks [to describe the folding. There

[54] Sergei V. Krivov and Martin Karplus, "Diffuse Reaction Dynamics on Invariant Free Energy Profiles," *Proc. Natl. Acad. Sci. USA* 105:37 (Oct. 2008): 13841-13846.

are] different metastable states which go from one to another. Sergei developed a method of representing this whole complex behavior in one dimension, [. . .] without losing information.

The β-hairpin was an important next step in going to more realistic models. It's only recently, in 2010, that David Shaw and his coworkers with a special-purpose computer, the Anton, that they developed, have been able to take some small proteins that [fold fast and have up to forty or so amino acids, and actually observe in a realistic description, with full solvent, many folding/unfolding [transitions]. Again people are sort of shifting to this being the paradigm systems, to try to analyze—Amedeo Caflisch gave away the coordinates as a function of time of the folding and unfolding—the Shaw group has also made all of these coordinates available. Many people are using them, sort of mining them for information with different models of protein folding, including Sergei, independently have tried to interpret what they find, and have disagreed somewhat with the original Shaw interpretation. This gives a bit of the history up to present day of protein folding.

EARDLEY-PRYOR: Yeah.

KARPLUS: On the dynamics of protein folding, there's another aspect. There are really two protein folding problems. One is, given a sequence, what's the structure of the protein, the native structure? And the other is how it gets there. If you could reliably fold a protein by molecular dynamics, you would solve the other problem, because you'd take the sequence, put it on a computer, and get the structure, but that's not possible yet. So a number of **<T: 55 min>** people, including David Baker, have developed predictive methods for taking a sequence [and predicting] what the structure is, or conversely, for what David is more famous for, is "I want an amino acid sequence that will fold up in a certain way," to predict—it may not be the only sequence—a sequence that will reliably folds up to [a given structure]. It's called the ROSETTA program, and it is very important.[55]

EARDLEY-PRYOR: And is there an idea to have that translational somehow, that it'd be able to create amino structure to one's will, and then use them in a system?

KARPLUS: This is certainly the beginning. You may want to have a certain function—[say an] enzyme function—in one case, people have taken known structures and tried to predict how they have to modify the amino acid sequence of an enzyme that hydrolyzes something else [so that it] would synthesize something. To do this by *de novo* folds is coming, but it is still in the

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[55] For early articles related to ROSETTA, see K.T. Simons, R. Bonneau, I. Ruczinski, David Baker, "Ab Initio Protein Structure Prediction of CASP III Targets Using ROSETTA," *Proteins*, Suppl 3 (1999): 171-176; P. M. Bowers, C.E. Strauss, David Baker, "De Novo Protein Structure Determination Using Sparse NMR Data," *Journal of Biomolecular NMR* 18 (2000): 311-318; David Baker, "A Surprising Simplicity to Protein Folding," *Nature* 405 (2000): 39-42.

future. The ideas are there to do this in a production way, so that drug companies would use it. It's not here yet, but it's certainly coming.

EARDLEY-PRYOR: The steps that move through these advances over time, it seems that the—I mean, increasingly more complex systems are able to be modeled. And I'm wondering about, at these early phases, these entry points where many times in your career you've been on this sort of cutting edge of where people are moving, sometimes even ahead of where people are moving. And both with the beta structure, the hairpin beta, and other things, stripping out aspects that you know exist in a system to a minimum point—where the model still seems to work—seems to be a common approach. Is that something that is a conscious thing, or is that—does that seem to be how these advances happen? Perhaps, for example, stripping out the water in a simulation to create the sort of more simplified—

KARPLUS: Model.

EARDLEY-PRYOR: —model.

KARPLUS: There are two aspects of this. One is the practical aspect, that unless you can do that, unless you can say, well, water is certainly important, but we're not primarily interested in that, so let's represent it in the simplest reasonable way, and that's what made it possible to do these multiple simulations here. That's one part.

The other part is understanding what are the essential elements. You wouldn't be able to use a simplified water model if you didn't realize that it had the properties that you needed. This gives you a deeper understanding of what's essential and what's peripheral. That's certainly an element in many things I've done.

EARDLEY-PRYOR: Also, when talking about the earlier work from '63 with the wave function and confining, and having these realizations by controlling one aspect of the process, to then highlight some knowns or some of the essential components of the other parts of the process. So I guess, is that something as well? This thought process to what would happen if we confine or limit this part of the—the system's movement or process, to then learn what's important about it? Is that also a method that you—

KARPLUS: I think that's certainly an element of—it's one way of trying to manipulate the system in a controlled fashion, to find out how it works. It's like taking apart a car engine. You want to find out what parts . . . if you want a racing car, what parts you can get rid of to get the minimum weight and the most efficient [engine].

EARDLEY-PRYOR: Yeah. Interesting.

KARPLUS: I don't think that that's anything peculiar to me. I think it's a general way that many people do science. **<T: 60 min>** I think what's a special element about me is that I like to work on something that I haven't worked on before. I strongly believe you're most likely to have original ideas if you're not encumbered by what everybody else has said and thinks about it. Obviously, you have to sort of understand what's going on, but if it's something new for you, then you [are more likely to have original ideas].

There's the father of Lionel Salem—a colleague that I worked with in France. His father was a banker when he was young, and earned enough money so he could do what he wanted, and he decided to do mathematics. People say you can't do mathematics when you're over twenty or so—that you have to be very young. He was forty, but he'd never thought about mathematical problems, and to him it was something new. His brain was a *tabula rasa*, whatever, as far as mathematics was concerned. He made a number of important contributions. He's one of the examples that I cite for my own "travels in science," where I try to look at something new. I have said after five years I want to do something else. Also after five years I moved from one university to another, until I got stuck [at Harvard]. I went to France, but I finally did come back here. Now I am dividing my time between France and here, and I have found that to be very useful.

EARDLEY-PRYOR: Yeah, new environments.

KARPLUS: I don't know whether you want to go on to some of the other subjects.

EARDLEY-PRYOR: Well, I do have one other question related to some of this, and that has to do with your trajectory over time moved from doing these simulations that were mostly theoretical and working out some sort of basic calculations on a computer, but not with a ton of visualization. And as computer programming moved forward through the eighties, through the nineties, till today, so much more of this work is done on computers, being able to control parts of the system, move things away to see what would happen. And this visualization aspect becomes increasingly more available.

So I'm wondering what was your experience with that? Are there things—certainly to be gained with that, but because you've seen these advances, and you helped make them possible—that are lost during that?

KARPLUS: I still think that having a three-dimensional model like that—

[*pointing to the encased ball-and-stick model of BPTI in his office*]

EARDLEY-PRYOR: The BPTI?

KARPLUS: —gives you insights. You can do all that on the computer, but it just is not the same. And I was—

EARDLEY-PRYOR: In what way?

KARPLUS: Maybe to me, having grown up with these puppet beads models which kids used, and John Mack made a living for a while making these very simplified but accurate models. So it's not quite the same.

On the other hand, I may have told you this story. I didn't believe very much in graphics when we first started doing calculations. We had to draw things [by hand], but there was one case where we took a protein structure, and then we folded it up to change the structure. Then we put [the new coordinates] on the computer, and we minimized the energy. We did dynamics. We did everything, but the energy stayed very, very high. So there was clearly something wrong. We looked at the coordinates and we really couldn't figure out what was wrong. We did have the VAX [Virtual Address eXtension computer] and the very crude graphics system that was developed by Evans and Sullivan [at Harvard], which we used for making the first film of a chemical reaction, H plus H2, when it was still ray graphics, much better than the pixel graphics that you have nowadays. It was really beautiful. But it's gone now, except for television. **<T: 65 min>**

We finally did look at pictures of [the structure]. What we saw had happened is that as we had changed the conformation, we had put one amino acid through the center of another one and there was no way of getting it out of there. We had spent days trying to figure out [what was wrong since] the coordinates didn't look so bad. As soon as we saw that, we realized we'd folded it up manually, and we didn't worry about something like that. We couldn't find [what was wrong] until we saw it on the graphics system. That convinced me that it's of some use.

Nowadays, the most popular program is one that is continuing to be developed by Klaus Schulten, who was a student here, partly with me, and I think partly with Dudley Herschbach.[56].

[56] Klaus Schulten, interviewed by Roger Eardley-Prior and Lee Sullivan Berry, at Beckman Institute for Advanced Science and Technology, Urbana, Illinois on 22-23 February 2016 (Philadelphia: Science History Institute, in process).

He's moved completely into the biophysical area, and he's developed the VMD [Visual Molecular Dynamics], which is the most widely used program.[57] Everybody uses it.

EARDLEY-PRYOR: For visualizing?

KARPLUS: For visualizing. And it's really very good, and you can play with it in many ways. I think it is very important. Now we do look at [our results] all the time and have learned that seeing is really very helpful in understanding what's going on.

EARDLEY-PRYOR: Klaus Schulten's work with NAMD [formally NAnoscale Molecular Dynamics, but originally "Not Another Molecular Dynamics" program], his simulating program, and then VMD, the visualizing program, did you have any connection with his development of those ?[58] Did he approach you in any way, or is there any kind of collaboration you have done since he was a grad student in the seventies? Or has he kind of taken his own path?

KARPLUS: There's often been talk about collaborating, but it never happened. At one point he thought it would be good to combine the work of both groups—

EARDLEY-PRYOR: The CHARMM group?

KARPLUS: The CHARMM group and the NAMD group and everything. And I think at that time, he was probably having trouble getting funding and such, and he thought that having it combined with [the CHARMM group], that there was a real likelihood that it would continue to exist. It turned out that he was very effective in getting funding. He had a big group, part of which has permanent people that are essentially involved both in NAMD and VMD. [James] Phillips, I think, is the person's name. We had joint meetings, but it never went anywhere.

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[57] William Humphrey, Andrew Dalke, and Klaus Schulten, "VMD: Visual Molecular Dynamics," *Journal of Molecular Graphics* 14 (1996): 33-38; John E. Stone, James C. Phillips, Peter L. Freddolino, David J. Hardy, Leonardo G. Trabuco, Klaus Schulten, "Accelerating Molecular Modeling Applications with Graphics Processors," *J. Comput. Chem.* 28 (2007): 2618-2640. See also, Mario Valle, "Visualization: A Cognition Amplifier," *Intl. J. Quantum. Chem.* 113 (2013): 2040-2052.

[58] Mark Nelson, William Humphrey, Attila Gursoy, Andrew Dalke, Laxmikant Kalé, Robert D. Skeel, and Klaus Schulten, "NAMD - A Parallel, Object-oriented Molecular Dynamics Program," *International Journal of Supercomputer Applications and High Performance Computing* 10 (1996): 251-268; Laxmikant Kalé, Robert Skeel, Milind Bhandarkar, Robert Brunner, Attila Gursoy, Neal Krawetz, James Phillips, Aritomo Shinozaki, Krishnan Varadarajan, and Klaus Schulten, "NAMD2: Greater Scalability for Parallel Molecular Dynamics," *J. Comp. Physics* 151 (1999): 283-312.

EARDLEY-PRYOR: Why is that? It seems like the two programs would be—

KARPLUS: I think he had no reason to. I don't think we would provide anything that would help him. I think he's very good, and he has been able to get all the funding, because his programs are so widely used. In calculations that we do nowadays, if we're just doing pure molecular dynamics, we will set up the problem with CHARMM. One of the things that has happened, and that we actually did work together on, was to make sure that in NAMD they had really an accurate representation of the force field in CHARMM, so that if we calculated something with NAMD rather than with CHARMM, it would be consistent with it. I think that's been an important interaction, and he'd done this with AMBER, with other programs as well.[59] I started to say is sometimes if we're just doing pure molecular dynamics, we'll set up the problem with CHARMM, do the calculation with NAMD, which is faster than [CHARMM]—particularly if you can use a large number of processors. It scales better to a larger number than CHARMM does. And we analyze the output with **<T: 70 min>** CHARMM.

So we use it, and I think many other people do some similar things. It is a community service. I think it's very good that he continues to get support. He's also done scientific work on his own, much of which is very good. It's characterized by doing bigger systems, because that's what he's able to do, and he has the [computer] time to do it. He has somebody working on viruses and [virus] capsids. The short answer is we don't collaborate on anything.

EARDLEY-PRYOR: I'm interested in CHARMM as well, since you're bringing it up as this computer program that evolved from Bruce Gelin's work and some of his early programming, and then officially was published and announced as a thing in the early eighties.

KARPLUS: Right.

EARDLEY-PRYOR: And has since continued to be developed over time. That program in particular, you need to have a license to use it, so it's commercialized.

KARPLUS: The answer is yes, but there are two aspects. The CHARMM program is licensed by Harvard to nonprofit organizations. In addition, it's sold through a company, which is now called—which has gone through many incarnations— BIOVIA, which was recently bought a year or so ago by Dassault Systems. That's a whole other story. The reason we charged originally was to cover the costs of [distributing it when made DVDs]. Also, we want to make

[59] AMBER (Assisted Model Building with Energy Refinement) is a suite of programs that allow users to perform molecular dynamics simulations on biological systems. Available here: http://py-enmr.cerm.unifi.it/access/index.

sure that because it was also sold commercially, that the people who got it, if they were honest, were really at academic institutions. I think that's basically been true, that most companies, it's just not worth their while, and it's such a small amount of their budget.

Also, originally, we did this when making tapes and everything was a certain amount of effort, to discourage people from just saying, "We want it," and they had to think [twice before asking for it]. It turned out, at first it was two hundred dollars, and then it was four hundred dollars, which had this sort of effect that they thought twice. If they didn't really need it, they didn't try to get it. Now it's six hundred dollars, and probably could be somewhat higher. That was the rationale, because it was a lot of work, and that's mainly true at Harvard in contrast to other places. You don't have permanent people who work in your labs as staff scientists. It's not the way Harvard is set up. It's changing a bit. Anyway, that's how the license arose and the charge arose.

EARDLEY-PRYOR: So essentially to recoup the cost of updating it and also replicating it for people that wanted it?

KARPLUS: Yes, making sure that they did want it. Now we have a system [though] we still charge for the full version. It's now mainly automatic, so people can just press a button, but they still have to pay one way or another. It's much more automated.

EARDLEY-PRYOR: Was this your first experience with a commercialized scientific work?

KARPLUS: Yes.

EARDLEY-PRYOR: What was the impetus at the time, then, and not earlier? Commercializing other earlier work?

KARPLUS: I never thought of it, and actually, the way it happened is that David Wales and somebody else—Andy Ferrara]—who were neighbors, **<T: 75 min>** came to me, and said, "Look, we have this idea. We think it would make a commercial entity." I thought for a while about it. The original concept was the following. One important thing was that for academic institutions, we had complete control. The second [thing] was at that time essentially people at Harvard, now it's people from all over the world; there are about forty development groups—

EARDLEY-PRYOR: On CHARMM?

KARPLUS: Of CHARMM, mainly former students, or former students of students, [scientific] children and grandchildren. The idea was that we put this tool together, but we realized that [CHARMM] wasn't a commercial program that you would expect for commercial usage. [The company, originally PolyGen, was to produce a commercial version.] They were supposed to do that, but they never did.

I didn't mention the fact, it slipped my mind. Rod [Roderick] Hubbard [. . .] visited Harvard, and he said, "You have this molecular dynamics program. Wouldn't it be nice to have a graphics program to go with it?"

EARDLEY-PRYOR: Where did he come from?

KARPLUS: From [University of] York. He came from the crystallographic group in York. He was involved with some of the early people who worked on insulin. He had seen some of our papers. He was very interested in graphics, and so he came over and developed a graphics program, which was called Hydra, because it had seven heads. It was a lot of fun. He's very clever in graphics development. We would say, "We would like to be able to do this," and then he would work overnight, and the next day he would show us [what he had done and] and we would sort of work together to develop the program. The company, which was called PolyGen, used that as their original graphics program. And they don't use it anymore. They use other programs. [Hydra] was one of the very earliest graphics programs that was designed to go with molecular dynamics simulations, so that you could follow them in real time, and look at them.

EARDLEY-PRYOR: Did he join your your group, or part of CHARMM? How did he pay for his time? Was that something he just did on his own? PolyGen paid for?

KARPLUS: I don't really remember. I think he still had his position in York. In Europe in general they have many more permanent people. In fact, almost everybody is permanent as soon as they start, and firing them can be very difficult. So he had this position in York. I don't think I paid him anything. I may have paid some living expenses here. Basically, he came, he said, "Look, I want to do this," and it was "a heady time," as one says.

EARDLEY-PRYOR: And that was in the early 1980s?

KARPLUS: Yeah.

EARDLEY-PRYOR: Shortly after CHARMM had been commercialized as well?

KARPLUS: Right.

EARDLEY-PRYOR: Huh. Yeah, there seems to be this shift in the early 1980s, and this is moving—getting some of your experience as a result of some of these policy changes that happened, the Bayh-Dole Act that allows for universities to commercialize their work, even if it comes from funding, NSF funding, or NIH funding.[60] And—

KARPLUS: I never knew about that.

EARDLEY-PRYOR: Yeah. And so—

KARPLUS: I know you mentioned this in the write-up. Before that—

EARDLEY-PRYOR: Yeah, and before that, it was—you—

KARPLUS: When was that?

EARDLEY-PRYOR: That law was passed around 1980. So **<T: 80 min>** along with the Reagan revolution comes this kind of new idea about commercializing science.

KARPLUS: I never knew about any of that.

EARDLEY-PRYOR: Ah, so it just happened that—

KARPLUS: It just happened—

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[60] The Bayh-Dole Act (PL 96-517, Patent and Trademark Act Amendments of 1980) created a uniform patenting policy among the various federal agencies that fund scientific research. The law enabled universities to retain ownership of patents and inventions that occurred as a result of federally funded research. "Bay-Dole" has since become a shorthand way to signify a much more complex but undeniable shift to a more commercialized regime regarding scientific research in the United States. See various chapters in Philip Mirowski and Esther-Mirjam Sent, eds., *Science Bought and Sold* (Chicago: University of Chicago Press, 2002), especially Shelia Slaughter and Gary Rhodes, "The Emergence of a Competiveness R&D Policy Coalition and the Commercialization of Academic Science," pp. 69-108.

EARDLEY-PRYOR: It happened at that time as a result.

KARPLUS: I didn't think about it. Maybe [David] Wales and knew about that, and that's why they came here. We had Joyce Brinton, who headed an office, which was concerned—

EARDLEY-PRYOR: At Harvard, concerned about the commercialization?

KARPLUS: —and took care of any contracts that we might have with industry. For a while, I was working on HIV inhibitors with a company. The office made sure that we didn't violate any Harvard rules in terms of being able to publish within a certain time. Having these rules and this office was great, because it wasn't I who was being nasty. It was Harvard who was being nasty. And I could say, "I can't do this. You can't keep it secret."

And actually, Marci probably remembers this better than I do, we had developed an inhibitor for something that was useful, and it involved Merck [& Co.] in some way. And Merck did not want to make public that it existed. I can't remember the whole story.

EARDLEY-PRYOR: Remember the time frame? Nineties or 2000s?

KARPLUS: I could probably look it up. What happened was that I told them at the time would they be happy if *The New York Times* published an article saying that they were keeping this from being available. And then they said, "Fine, you can publish it."

EARDLEY-PRYOR: And allowed you to publish in scientific journals?

KARPLUS: [Yes].

EARDLEY-PRYOR: So that's actually an interesting thing. So it sounds to me like there was some work you did consulting.

KARPLUS: Yeah.

EARDLEY-PRYOR: When did that—because I know chemists especially have done consulting work for a long time.

KARPLUS: Many chemists make their living by consulting.

EARDLEY-PRYOR: Absolutely.

KARPLUS: [They earn more than their Harvard salary.]

EARDLEY-PRYOR: And I remember you had done work that wasn't quite consulting, but Bell Labs wanted you to become more full time with their consulting.

KARPLUS: Yes.

EARDLEY-PRYOR: And you said, "No, I want to do my work for me." That was in the fifties.

KARPLUS: Right. That was with [Bob Schulman, who was at Bell Labs].

EARDLEY-PRYOR: Yeah. So—

KARPLUS: I also consulted for a number of other companies. I'm still a consultant for the present incarnation of PolyGen, which is BIOVIA. We just had a huge meeting on Monday, where there were about one thousand people, where I gave a lecture in connection with the meeting. Off and on I consulted. I always had the feeling I was happy to do the consulting, but I always felt that [. . .] if it disappeared, it really wouldn't make any difference. I earned the most money was in connection with Vertex [Pharmaceuticals].

EARDLEY-PRYOR: [Yes].

KARPLUS: It's a drug company founded by Josh Boger, who was a student of Jeremy Knowles at Harvard. I and a number of other people, Stuart Schreiber, were on the science advisory board. And for that, we received stock. Then there was another company, Enanta [Drugs and Pharmaceuticals, Ltd], which all of a sudden turned out was a success. I had almost thrown away my stock, but they had records of it. Vertex was the first [company other than PolyGen] where it was a much more of a **<T: 85 min>** relationship. About five Harvard people were on the science advisory board. It turned out to be quite successful—it still exists, which in itself is successful. I think it's [now] making money. For a long time, it was just spending money, but people had faith it.

EARDLEY-PRYOR: What kind of work do they do, and what did you do with them?

KARPLUS: Well, it's, again, design work on diabetes, cystic fibrosis, and different diseases, essentially, and they've been successful in some of them, and have some things in the clinic. We received stock, but kept the stock until it went from, well, what I paid for it was nothing. At the height, it was in the one hundred dollars [or more] per share, and now it's gone down a little bit. What I've done is always sold a little bit when it was high or when we needed it, but it didn't affect our overall lifestyle. On the other hand, we had money to buy the apartment in Strasbourg, for example, that we lived in for many years, and so in that sense, it was very useful.

EARDLEY-PRYOR: When did some of these consulting opportunities arise? Was this also—time frame-wise, I'm wondering.

KARPLUS: In the nineties.

EARDLEY-PRYOR: Mostly a lot in the nineties?

KARPLUS: [. . .] I'm very bad with dates. We can certainly look it up. [. . .] One of the things that happened is that Vertex was very interested in FKBP and cyclosporin. They were interested in the structure of that. Stuart and I with a [couple of] postdocs determined the structure, and Josh Boger was very [annoyed]; we said we were perfectly happy to give him the structure, but he wanted to have determined the structure first, so we were fired from the science advisory board, and we only received half of the shares we would have gotten, because it took more years to vest them.[61] It's written up in a book called *The Billion Dollar Molecule*.[62]

EARDLEY-PRYOR: Oh.

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[61] M.K. Rosen, S.W. Michnick, M. Karplus, and S. L. Schreiber, "Proton and nitrogen sequential assignments and secondary structure determination of the human FK506 and rapamycin binding protein." *Biochemistry, 30* (19), 1991: 4774-4789.
[62] Barry Werth, *The Billion Dollar Molecule: One Company's Quest for the Perfect Drug*, (Simon & Schuster: 1995).

KARPLUS: Have you ever heard of that?

EARDLEY-PRYOR: No.

KARPLUS: For a while it was a bestseller, I think. This whole story about Vertex . . .

EARDLEY-PRYOR: Fascinating. How are you doing? Do you need to take a break, or are you doing okay?

KARPLUS: I'm doing fine. If you want to take a break—

EARDLEY-PRYOR: No, I'm great. We had mentioned the early nineties, and a couple of the papers that you were interested in talking about involved computer simulation that seems to be a combination of the quantum and the molecular mechanics.

KARPLUS: Right.

EARDLEY-PRYOR: One of them is a *J. Comp. Chem.* article from 1990 that you did with Dr. M.J. Field and P.A. Bash.[63]

KARPLUS: Right.

EARDLEY-PRYOR: It was titled "Combined Quantum Mechanical and Molecular Mechanical Potential for Molecular Dynamics Simulation."

KARPLUS: Yes.

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[63] M.J. Field, P.A. Bash, M. Karplus, "A Combined Quantum Mechanical and Molecular Mechanical Potential for Molecular Dynamics Simulations," *J. Comp. Chem.* 11 (1990): 700-733.

EARDLEY-PRYOR: What is some of that work that you were doing with Bash and Field and others?

KARPLUS: This goes a little bit to mentioning the Nobel Prize, because the Nobel Prize was in fact given for some—I can't even remember exactly what the title is. Multiscale simulation method or something like that.

EARDLEY-PRYOR: I think it is something like that. I think I have multiscale models for chemical complex systems.

KARPLUS: Right. Multiscale methods for chemical systems.

EARDLEY-PRYOR: But I've heard—in our conversations—you mention that you think the Nobel Prize was really given for slightly different reasons—

KARPLUS: Right.

EARDLEY-PRYOR: —than what is listed in their media.

KARPLUS: Have we actually recorded that already? No?

EARDLEY-PRYOR: We have not. We—

KARPLUS: Okay.

EARDLEY-PRYOR: —other than you've mentioned we'll get to it, so—

KARPLUS: Okay. So we'll,—

EARDLEY-PRYOR: Maybe this is an avenue?

KARPLUS: —this is basically all involved in that. So, again, all of us **<T: 90 min>** became interested in this multiscale modeling.

EARDLEY-PRYOR: All of us meaning?

KARPLUS: Well, [Arieh] Warshel and [Michael] Levitt and I. Warshel and I did the first study of that type, that was for a very simple system, a relatively small molecule, retinal. These are pi electron systems, where you have a part of the system that is a conjugated molecule, and then you have several chain methyl groups in retinal, which is the visual compound of the eye. Actually, Barry Honig and I did the first multiscale study of this type, which was a very simple model. Then when Warshel came [to Harvard], we elaborated the model. Then he worked with Levitt, continuing this.

This was all on a simplified scale. It was really only when [. . .] computers were powerful enough that methods like this one described in the paper where Martin Field was the lead author, [that meaningful calculation could be done].

EARDLEY-PRYOR: The 1990 paper on combined quantum mechanical—molecular mechanical potential?[64]

KARPLUS: Right. Which developed the first modern method of doing this for complex systems in an accurate way. The conceptual idea is the same. The part of the system where chemical reaction takes place, you have to represent quantum mechanically. Even that's not entirely true. Sometimes people do quantum mechanical calculations for reactions, fit empirical potentials to the way the reaction occurs, and then just do molecular dynamics. What was developed here, which in some sense is an outgrowth of—I'm kind of curious what we did reference [*papers rustling*] . . . I'm not sure. Anyway, in terms of a modern, sophisticated way of doing this, was really in this paper with Bash and Field. And it was the first paper that represented the methods of doing it that are still used nowadays, so it's not that the concepts, the central concepts are that different, but that the implementation is much more sophisticated, and led to a sophisticated part of CHARMM. I mean the QM/MM [quantum mechanical/molecular mechanical] methodology is part of CHARMM.

EARDLEY-PRYOR: Was it part of CHARMM before this 1990 work with Martin Field and Bash?

[64] Field, Bash, Karplus, "A Combined Quantum Mechanical."

KARPLUS: We had a very simple MNDO [modified neglect of differential overlap]-type model that was used, which actually may still exist somewhere in CHARMM, though I don't think it's used anymore.[65] We generally—"we" being me—don't throw things away to clean up the program. There are things there that sometimes don't get used at all [anymore]. I tried to mention papers that represent a real advance, where there are a lot of papers that grow out of them. The first application, which was a very important one, was one to an enzyme, triose phosphate isomerase.

EARDLEY-PRYOR: That's the '91 publication in *Biochem*?[66]

KARPLUS: Right, the '91 publication in *Biochem*, which involved both **<T: 95 min>** Bash and Field. Here, Paul Bash was the lead author. It was also in collaboration with Greg [Gregory A.] Petsko's group, who provided some of the crystal structures that we used. It was a pioneering calculation, which made a number of predictions, of which the most important one was that—which violated sort of all of the dogma of the organic chemists—histidine is the proton donor for certain reactions, but normally, the histidine that's a proton donor has two hydrogens at a certain position, and it gives one of them up in the reaction.

We calculated that in fact the histidine that gave up a hydrogen didn't actually have two there, but instead [had only one], and gave up this proton to become a negative ion. We showed by the calculations that if—we weren't able to show by which the reaction was catalyzed, but we showed that if it were from the protonated histidine, it would end up in an intermediate, which was so stable that the reaction wouldn't take place, while if it was from the neutral histidine, it would give a reasonable potential surface. This was a real prediction. It's one of these things that appear in various of my writings, that many of the theoretical chemists used the word "prediction" when they find something which is agreement with experiment. This was a real prediction, and it wasn't believed. Then Jeremy Knowles's group, stimulated by this [result], did some NMR experiments, and showed that this was correct. Since then, it's been shown in a number of other reactions that the [neutral] histidine is the active. So I think it was very important. There was doubt about it, but it was published. Jeremy Knowles, who was a professor at Harvard, was one of the reasons why we worked on triose phosphate isomerase. It's often difficult to get experimentalists to work with you, because they think it's a waste of time. We started working on it, and Greg was doing the crystal structure. It was a very fruitful environment where we knew if we did something, it would really be of use.

EARDLEY-PRYOR: Go ahead, please.

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[65] Modified Intermediate Neglect of Differential Overlap (MINDO) is a semi-empirical method for the quantum calculation of molecular electronic structure in computational chemistry. It was developed by a group led by Michael Dewar.
[66] P.A. Bash, M.J. Field, R.C. Davenport, G.A. Petsko, D. Ringe, M. Karplus, "Computer Simulation and Analysis of Reaction Pathway of Triosephosphate Isomerase," *Biochemistry* 30:24 (1991): 5826-5832.

KARPLUS: I was just going to say, now computer simulations [of enzymes] by QM/MM methods are an industry in biophysics. Many people are working on them. Warshel has continued to work on them very actively, while Levitt has moved to other areas. I think this was an important paper. From my point of view, it was that we really predicted something, and that didn't agree with what everybody thought . . .

EARDLEY-PRYOR: So can I ask, to push that back in terms of development, back to this conceptual time, you and Barry Honig are working on this. You and Arieh Warshel eventually work on this, and then he and Levitt kind of go off and continue to work for a time.

KARPLUS: Right.

EARDLEY-PRYOR: Where did the idea to merge the quantum mechanical and the molecular mechanical method come from?

KARPLUS: Well, I think . . .

EARDLEY-PRYOR: And again, is this part of that, sort of, scaling back to the basics of what you can get away with?

KARPLUS: Yes, to a certain extent. Even these simpler molecules, which we couldn't have handled if you really had to **<T: 100 min>** treat everything quantum mechanically. In these simpler molecules, you could [neglect] the inner shells, so you didn't worry about [them, and then] they had only had one valence electron on each of the atoms. Why did I want to work on retinal? This was because it's the visual pigment, and I was very interested in vision. This goes all the way back to when I was an undergraduate here at Harvard—

EARDLEY-PRYOR: With Wald?

KARPLUS: —with Wald and Ruth Hubbard. I don't know whether we talked about this, but there was a volume, a Pauling *festschrift*.

EARDLEY-PRYOR: We did talk about that.

KARPLUS: With this—

EARDLEY-PRYOR: That helped inspire your move to—

KARPLUS: I realized that people hadn't gotten any further than they were when that was written. And this is something we can do. It also goes back—we've probably discussed this—this actually used some of the methodology that Coulson wanted me to use, which I thought [was not interesting]—

EARDLEY-PRYOR: When you were in Oxford.

KARPLUS: —when I was in Oxford. We did talk about that, when I was just beginning to be interested in NMR. The reason we worked on the system is that I was interested in the vision, and that we could do it better, but still not perfectly. Actually, Klaus Schulten's thesis was also on that. And again, I don't know how much we discussed this, but Bryan Kohler was doing experiments here.

EARDLEY-PRYOR: In the seventies, in the early seventies?

KARPLUS: Yes, he was assistant professor here, and was doing experiments on polymers. Brian Sykes, who was also here and was doing NMR experiments. [We collaborated on] one of the first papers [that used the nuclear Overhauser effect to determine structures], but I don't think it had any effect on the rest of the world.

EARDLEY-PRYOR: The time from when you had these early conceptions of how to do these sort of multiscale—the QM/MM methods—up until these publications in these nineties, when you're working with Martin Field and [Paul A.] Bash and Greg Petsko, why do you think there's such a gap there between—

KARPLUS: You couldn't do meaningful calculations.

EARDLEY-PRYOR: In terms of the computer accessibility?

KARPLUS: In terms of basically, the computing power very early, Levitt and Warshel did a study of lysozyme. It was completely wrong, but it was one of their early studies, which are listed in the Nobel Prize thing. They just couldn't do it.

EARDLEY-PRYOR: Because they didn't have the big enough computer to calculate it?

KARPLUS: They actually had bigger computers—Israel had the GOLEM, a homemade computer, which was pretty good. But still, they couldn't do it [accurately]. In the biological area, as I may have said before, one of the very important aspects about being successful is that you don't [work on] a problem if you can't do it. Many people come to me and say, "Look, this molecular dynamics, you can do everything." But I tell them, "We can do everything, but we can't do your problem." The realization of what problems are accessible by the methods you have has been one of the essential things, why I haven't wasted more time than I have on dead ends.

EARDLEY-PRYOR: In the 1980s, in the mid-1980s, the NSF made a massive investment in supercomputers in the domestic United States and before that, there was a real challenge in getting access to computers. And you had to go in the mid-seventies to France to run your BPTI calculations.

KARPLUS: Right. A lot of the calculations we did here, there were quite a few VAXs around that—

EARDLEY-PRYOR: Here at Harvard?

KARPLUS: At the medical school, different places. And they were only used during the day. And we went around all over the place, and got **<T: 105 min>** permission to use the VAXs at night, and said we would give them credit. And a lot of our calculations were done this way.

EARDLEY-PRYOR: On just available computers at—

KARPLUS: On available computer time—

EARDLEY-PRYOR: —other institutions?

KARPLUS: —that existed, and wasn't being used. The VAXs were fairly widely distributed, so that the programs that we used, developed here, could be used, without any problem on these other computers.

EARDLEY-PRYOR: So the CHARMM program was developed in part with the VAXs in mind?

KARPLUS: Yes.

EARDLEY-PRYOR: I guess my question was going to be, did that push for supercomputing in the eighties influence your work? Because I know that there wasn't necessarily a nearby supercomputing center here, but some of those centers were eventually kind of connected through the ARPANET [Advanced Research Projects Agency Network].

KARPLUS: Right.

EARDLEY-PRYOR: Did that supercomputing push in the eighties influence your work on molecular dynamics?

KARPLUS: There's the Pittsburgh supercomputer center, but I don't know when we first started using it.

EARDLEY-PRYOR: Oh, but that's who you collaborated with, once it was established there?

KARPLUS: Right. We were able to use that. And of course, [Sir John Anthony] Pople was in Pittsburgh [at Carnegie Mellon University] doing QM calculations. That was the first one that we used.

EARDLEY-PRYOR: And would you share your material over this early ARPANET?

KARPLUS: We would send tapes, and they would run them, and then [we would] get them back [with results].

EARDLEY-PRYOR: Oh, through the mail?

KARPLUS: Mainly, yes.

EARDLEY-PRYOR: That's fascinating. This pulls us a little bit off track, but I am interested in some of these advances in computing, but especially with the rise of the internet, the increased use of personal computers, their ease of accessibility, how that has changed the way you do your work, how your science has evolved.

KARPLUS: Well, how—

EARDLEY-PRYOR: If at all.

KARPLUS: We've had computers. We used to have eight or ten computers—we had Silicon Graphics and other computers that we used here a lot. A significant fraction of our computing was done here. And then we had a small cluster of computers here.

EARDLEY-PRYOR: Was this in the nineties?

KARPLUS: This was in the nineties. And then Harvard started to have a computer center. [. . .] We would buy a certain number of computers [and add them to the computer center].

EARDLEY-PRYOR: Oh, you would co-purchase?

KARPLUS: Yes.

EARDLEY-PRYOR: Your group and then Harvard as well?

KARPLUS: Say they had one hundred, and then we would add ten of them, and we would get first priority on those ten, but be able to use the others, sponge computing when the other weren't in use, and correspondingly, when we didn't use ours, which was very rare, they could use them. [. . .]

EARDLEY-PRYOR: And just to clarify, those were essentially cluster computers?

KARPLUS: Right. Then there was a CDC [Control Data Corporation computer] in Berkeley that was outside the secret area, at the Livermore [Laboratory]—that we got access to, and it was similar to the one that had been in . . . the dates, I'm really very poor. But we knew some people there and were able to get access there, and there we used the . . . I don't know, remember whether it was still the ARPANET.

EARDLEY-PRYOR: To share your data with them?

KARPLUS: To share the data. And most recently we've been using NERSC, [National] Energy Source Computing Center, which is a very big computing center, and they always [have] state-of-the-art computers, and they give us lots of computer time, [in part for the science and in part] because, well, they like to have the computers fully used so they can ask for bigger ones. We, and some of the other people doing molecular dynamics simulations, are some of the largest users there.

EARDLEY-PRYOR: Of this [. . .] group?

KARPLUS: Yes.

EARDLEY-PRYOR: And is that a private—

KARPLUS: No, **<T: 110 min>** it's an Energy Resource.

EARDLEY-PRYOR: Oh, it's part of the DOE funding?

KARPLUS: That's right. It's out there, because electricity is very cheap. Also that's why Intel is out there. I don't know the exact reason, but that's certainly why they have the big—

EARDLEY-PRYOR: Yeah, water was a big reason why they went to Portland, [Oregon].

KARPLUS: Yes.

EARDLEY-PRYOR: Or have a big factory there.

KARPLUS: For the electricity and the cooling together. So is this big resource, which is—other than maybe at Livermore, for the defense-related computers—it's probably the biggest, and we use that. We do some computing still at Harvard, which actually isn't at Harvard now, but it's somewhere downtown, where, again, it's cheaper to control the temperature. We do almost all of it at NERSC.

EARDLEY-PRYOR: And was getting access to those computers or the clusters, over time, was that difficult initially?

KARPLUS: You had to write proposals. At a certain stage, getting large amounts of time was difficult. There were insight proposals where you got money for a year or two. Nowadays our computer demands are less, because my group is much smaller, and there's no problem in getting what we need.

EARDLEY-PRYOR: Something, in terms of proposals, that has changed over the course of your career as well, is NSF proposals increasingly, or over time, started requiring a social impact aspect. Are you familiar with those changes?

KARPLUS: [Yes].

EARDLEY-PRYOR: How has that changed how you have written proposals, or how you think about the purpose of your work? Has it?

KARPLUS: It hasn't changed the purpose of my work. This is relatively recent that it's been both NIH and NSF outreach. Now with the Nobel Prize, I give so many lectures to young people and such that there's really no [problem]. That's actually one of the ways that I've used the Nobel Prize. It is to accept invitations where I speak to young people. The first invitation that I accepted was to go to Houston, Texas, where there was the annual meeting of [the Beta Kappa Xi honor society and National Institute of Science]. For students at traditionally black colleges, like Fisk [University, Lincoln College, and the University of the District of Columbia].

Apparently, [. . .] at a certain [time in the twenties], black students weren't allowed at some of the meetings of the American Chemical Society. I think it wasn't the policy. It may just have been when the meeting was in the South [. . .] so they started this parallel honor society, and annual meeting, where the students could go and give talks and listen to lectures and such. And they invited me in 2014, but for end of the program [to be the Summa Lecturer]. They had some very good speakers, all of whom were black, and they try to invite somebody who gives the Summa Lecture at the end.

A woman, [Kim Fenwick of UDC] called me up, and it was clear to me that she didn't expect me to say yes. I looked into [the organization], and called back to say, "I'd love to do it." It was really a fabulous experience for me. I gave again my Marsupial lecture, more or less. The students were just so excited, and, of course, everyone wanted to have their picture taken with me. That was a wonderful experience for me, and from what I heard afterwards, I think it was really a great experience for them. I've tried to do things like that. There's also the Harlem **<T: 115 min>** Children's Society which tries to take students from the poorer neighborhoods. They arrange for them to work in laboratories for six months and then they have a sort of graduation ceremony, and they invited me to give a lecture there [in 2015].

So, in terms of outreach it is something that has naturally happened. It has been sort of for me the thing I wanted to use my Nobel Prize for. It's probably the only science-related prize everybody recognizes, whether or not they know anything about science. So I think I can do a lot of good with it . . . well, that's what I've tried to do.

EARDLEY-PRYOR: Have there been any challenges that have arisen as a result of the Nobel Prize? I mean, these are some beautiful opportunities, and it sounds like you've leveraged them in some really lovely ways. But have there also been some challenges that have arisen because of it?

KARPLUS: You have to learn to say no. After I received the Nobel Prize, then here there was a celebration that morning, that was organized [in Chemistry]. There were two other—E.J. Corey and Dudley Herschbach—both of whom won the Nobel Prize. E.J. said, "Come and see me afterwards when you have a chance." He told me, "You won the Nobel Prize, and you can do what you want." This was true in the whole Nobel Prize celebration, where they urge you to go [to the universities in the neighborhood of Stockholm]. I decided I would go—I had a former student who was at Umeå [University], where nobody goes. So I said, "Well, I'd rather go up there than do that."

But also in trivial things—as far as he was concerned, after he came back, he was willing to devote two weeks to things related to the Nobel Prize, and then he had just gone back to work. He also said that I was very lucky that I got it when I was so much older, because I had so much more time to work without being faced with so many decisions. I think what he said was very important, in making me realize, I have the prize, and I use it where I think can do something good. There are lots of invitations. I keep getting invitations that I say no. There were some climate change conferences where they always try to invite Nobel Prize winners, and I thought a little bit about that. Of course, I don't really know anything about climate change, but I finally decided I have several experts on atmospheric physics here at Harvard, Steve [Steven C.] Wofsy [and Mike McElroy], and so I said, "If you want somebody who can talk about that, you invite them." I actually asked them whether they were invited, [but I think not]. I decided if it’s a topic that I don’t know anything about, [I would not go]. One that I did finally accept, was the OPCW [Organization for the Prohibition of Chemical Weapons] anniversary.

EARDLEY-PRYOR: The Chemical Weapon Convention?

KARPLUS: Yes. Thanks to you and [David] Caruso, I had something to say. In general, I don’t. Marci and I get these email invitations, and I think they’re becoming more and more obvious that I should say no. I keep getting them from India [in particular]. **<T: 120 min>**

EARDLEY-PRYOR: Can you take—go ahead.

KARPLUS: I was actually going to say, so the short answer is no. Certainly I think about it. I have a much broader field of opportunity to do things, but making the decisions is not that difficult.

EARDLEY-PRYOR: That’s nice. Can you take us back to when you were told that you were awarded the prize?

KARPLUS: [Yes].

EARDLEY-PRYOR: Where were you? What was the context? How did you hear?

KARPLUS: Well, I was in bed because I was in the US, rather than in France. And probably it’s worth saying that I knew that I [was] being nominated for the prize for at least twenty years, maybe more than that. For a while, particularly when we were in Europe, I knew [when it was going to be announced—at 11:30 a.m. on a certain day]. I would sit by my computer. Of course, I would have been notified before then, but anyway, to see whether this was my year.

I’d sort of given up, decided, well, okay, I’m not going to get it. Then we were here in the US, so it was 5:30 in the morning, and we were in bed, and Marci was closer to the phone, so she picks up the phone. This was 5:30 in the morning, 11:30 [a.m.] there. And my first reaction was I had a daughter in Israel, and she often has called to to reassure us when there’s been a terrorist attack at odd hours like that, since they’re seven hours ahead. So that was what I thought. But she said, “No, somebody wants to talk to you. They have a foreign accent.” I then go to the phone.

EARDLEY-PRYOR: Did you have an inclination as to—since it wasn't your daughter— what it might be?

KARPLUS: No, I didn't. I wasn't awake, really.

EARDLEY-PRYOR: Yeah.

KARPLUS: Then the whole committee gets on [the line], one after the other, and finally, the secretary of the committee, who was a biophysicist that I'd known for a number of years. When he said it I really believed that it was true. Very shortly after, we were hardly up, somebody rings at our doorbell. And Mischa happened to be there, though he's been in New York for most of the time. And he goes to the door, and so he calls, "There's somebody at the door." And so Marci goes and looks. It's a young woman, Stephanie [Mitchell], who is a local reporter for the *Harvard Gazette*, who happens to live right around the corner from us. And she said she was from the *Gazette*, and could she take some pictures? And—

EARDLEY-PRYOR: And you were just getting up.

KARPLUS: I was hardly up, so Marci said, "You just wait here." Then I got dressed and we allowed her to come in. She started talking to me and taking pictures. I said, "Look, we're going to just go ahead and have breakfast." And though I almost always make breakfast, Marci made it—she reminded me just recently when I was writing this up, that she actually had made breakfast. All of this was recorded, what this Nobel Prize winner has for breakfast. There's one very nice picture of me sitting in the armchair where I often sat. Then there was [the call from Harvard] which said, "Are you available at 11:00 [a.m.]?" And so there was a celebration.

A number of people said very nice things. George Whitesides made a nice review [of my career]. He's very good at that. One that I appreciated very much was from Stuart Schreiber, who said that he had been invited—he was at Yale—to become a Harvard professor, to carry on the synthetic organic **<T: 125 min>** chemistry [tradition]. He'd worked with Woodward and gone to Yale, and was supposed to do that. When he started going into biological work, like [studying] FKBP the organic faculty really didn't like this, but that I had encouraged him, that he had very much appreciated that. The other thing was that Alan Garber, who was the provost, came. He had no idea who I was. He had some flowers, and he was looking around what to do with them. So I said, "Well, that's my wife over there." Then but he asked, "Is there anything I can do for you?" I think people often ask that, [just as a formality, but with me it's] sort of a mistake. So I said, "Well—"

EARDLEY-PRYOR: Why is it a mistake?

KARPLUS: Because I always have something in mind. What actually had happened is that [there is always a] shortage of space. [Eric N.] Jacobsen was the chairman [of the Department of Chemistry and Chemical Biology at Harvard University] at the time, and I proposed that I wanted to keep certain parts of it. Other parts I didn't need anymore, and I was happy to give up. But then the statement was that no space belongs to anybody, and it's departmental space or the university space. He said he had talked to the dean, and asked about that, and was told he couldn't promise me that I could keep the space.

So when Garber was there, I said, "Yes, there's one thing you can do for me, and that's to guarantee me that as long as I'm working here I can keep space that I have." And he said, "Yes." And I said, "It's important to have it in writing, and—" because I know that even if I do get it in writing, sometimes the dean's administration says that they didn't mean what they said, which actually has happened to me. So I did get this statement, and I think there is no problem about my keeping the space. It does come up that they tried—I have an extra room that I really don't need, but it's still nice to have. And [there is repeated] talk about somebody using it—but nothing has happened so far. So E.J.'s comments, Stuart Schreiber, and my interaction with Garber, were the initial events before we went to Stockholm. And then we went down, and had a visit with President Obama.

EARDLEY-PRYOR: Before we talk about your visit with Obama, did you go to Stockholm to accept the award—

KARPLUS: Yes.

EARDLEY-PRYOR: —next? Was that the next step?

KARPLUS: The visit with Obama was before we—

EARDLEY-PRYOR: Oh, it was?

KARPLUS: —left [for Stockholm].

EARDLEY-PRYOR: So, yeah, go ahead, and then please tell us about that.

KARPLUS: We got invited. I knew the science advisor, his name is [John] Holdren, he's still the science advisor. I called him and said if this is just going to be a photo op, I wasn't really interested in going, after having received the invitation, which was for November. He said, "If you receive an invitation from the President, you can only refuse for two things: if you're dead or if you're dying, or if a relative has died." So I said, "Okay, what do you think? Is there going to be anything more?" He said, "He's the President. If he's interested in what you're [talking] about, then it can be longer. It's up to him what to do."

[. . .] Once we were in the Oval Office, we formed a line. Normally, physics would be first, then chemistry, then physiology and medicine, and then economics.

EARDLEY-PRYOR: Is that how they always do it?

KARPLUS: That's the Nobel order. Within each prize, if there's more than **<T: 130 min>** one person, it's alphabetical. That's how you give your lecture. Everything is done this way. Since the physics prize was given to Europeans [in my year], the chemistry prize was first. Since my name is first, I was first in the Oval Office—actually, Marci was first. [. . .]

EARDLEY-PRYOR: In the office, in the Oval—

KARPLUS: That's very impressive. When Marci came in first, [President Obama] said, "Hello, Marci. It's really nice to see you." Even though he'd been in a very important meeting before, he just switched, and that was what he was focusing on. When I went up to him, I said to him, "You're the second president I've ever met. The first president was President Truman in 1947. And he was the first president to try to institute universal health insurance." And Obama thought for a second and said, "No, that's not true. It was Theodore Roosevelt." And then he thought again, and he said, "No, you're right. Roosevelt did propose it, but he wasn't elected. It was just the campaign promise for a second term"— where he wasn't elected in between."

Then I said, "Well, but you're the first president to have actually done it." Then I gave him a copy of my photo book, which I had . . .[67]

EARDLEY-PRYOR: Yeah. What did he say to that, when you told him he was the first to have done it?

[67] Martin Karplus, Sylvie Aubenas, Nathalie Boulouch, Jean-Pierre Changeux, *Martin Karplus: La Couleur des Annees 1950* (Paris: Editions de l'Oeil, 2013).

KARPLUS: He didn't really say anything, just smiled. And then I gave him a copy of the photo book, which I had dedicated to him and Michelle [Obama]. He looked at it a little bit, and then gave it to an assistant. As an aside, in France, in contrast to my going to see the president, the president came to see me.

EARDLEY-PRYOR: In France?

KARPLUS: Yeah. He came to Strasbourg. It was not only to see me, but he also then used the occasion to make a talk about science and the importance of science in France. I also have lovely pictures with him. I gave him a copy of the photo book, and I said, "You're going to see President Obama in two weeks. Ask him if he's looked at it." Hollande is a very charming individual personally. I think no president can really do anything much about the economy. Obviously he has not been very successful.

EARDLEY-PRYOR: So after visiting President Obama, and then you traveled to Europe, did you go directly to Stockholm for the ceremony, or did you travel through or did you spend some time in France?

KARPLUS: At that time, I went direct [to Stockholm]. You're allowed to have ten people [as your guests at the ceremonies]. So Marci, Mischa, Reba, and Tammy, Rachel, my granddaughter, and Beverly Karplus, my oldest niece, [and Andy Karplus, a nephew who is a protein crystallographer], and then various friends.

EARDLEY-PRYOR: What was the experience like for you?

KARPLUS: Mixed.

EARDLEY-PRYOR: In what ways?

KARPLUS: I worked very hard on my lecture. There's a dinner of thirteen hundred people in the grand hall. It's a little bit too organized. Some things are nice. The nicest thing is that you have a chauffeur who's essentially there any time of day or night for you. You have a car and chauffeur. And you have somebody from the Foreign Office, to make sure that you do what you're supposed to do, and also to help **<T: 135 min>** you to do it. They were very good and we learned how to work together. Sometimes when there was an occasion that neither Marci nor I wanted to participate in, [e.g.] some of the big dinners, we just said, "Look, we'd like to go to a nice restaurant." And the chauffeur had good contacts in the restaurant world and would suggest a nice restaurant. I said, “If it’s so nice, will there be any room?” He said, “Don’t worry, there will be room.” So we tried to do things the way we wanted, and it worked out well.

EARDLEY-PRYOR: When you had these ideas about your winning the Nobel and being awarded for something that you think might have been for different reasons, how did that shape the lecture that you gave there?

KARPLUS: I don’t know how much you’ve read. There’s the Nobel lecture, and then there’s the article that [I wrote] for *Angewandte Chemie* [published by the German Chemical Society]. What I did in the lecture is, well, it was awarded officially for what we’ve already discussed. But [in the lecture], I talked about the origin of molecular dynamics, and how early work, looking at the H plus H2 reaction in the sixties, realizing that if classical mechanics could describe these light atoms, it should certainly work for proteins and how that led to the development of molecular dynamics. I mentioned RA, that work we had done and such. But basically, it was about molecular dynamics and its applications, rather than about what it had been given for. The lecture is supposed to be about what you were awarded the Nobel Prize for, but I didn’t do that.

Afterwards, I discovered I’d been given a book called *The Politics of* [*Excellence*], which talks about the Nobel Prize. Specifically, it points out that fifty years after the Nobel Prize has been given, the books are opened and the whole discussion of what the people who gave you the prize went through is documented and made available.[68] It talked a lot about [Albert] Einstein and how much opposition there was to giving him the Nobel Prize, and specifically, for giving him the Nobel Prize for general relativity, which had already been proved. Obviously, it was his most important work. They gave it to him finally for the photoelectric effect, and he was furious about that. I think he was in Japan when he heard about it, and then he didn’t go to Stockholm. He gave his lecture in Gothenberg, [Sweden]. He talked about general relativity rather than about the photoelectric effect. In the written version of my Nobel lecture, which is mainly the Nobel lecture, but towards the end, it talks about Einstein. Also it talks about what I think is true, that although the Nobel Prize is officially given for that, if there hadn’t been any molecular dynamics, there wouldn’t have been a Nobel Prize. That was the really important thing. But somehow, they wanted to have some [criterion by which] they could give it to three people, because they liked to give it to three people. There are so many that nowadays to delimit the subject is why it was given for this. I talked a number of times with the head of the committee. There are these five people who really make the decision, even though finally it’s officially voted by the Swedish Academy.

And he kept telling me, “You have to remember, the Nobel Prize wasn’t given for molecular dynamics.” And I said, “I know.” We had this discussion **<T: 140 min>** back and

[68] Robert Marc Friedman. *The Politics of Excellence: Behind the Nobel Prize in Science* (Henry Holt & Company: 2001).

forth, but that's my feeling. As I said, there wouldn't have been a prize—nobody would have cared about these multiscale modeling, if you couldn't really apply it. For that, you needed to do molecular dynamics. So that's the story on that.

EARDLEY-PRYOR: Yeah. There are a few other questions of work that we haven't covered. Maybe just reference to—how are you feeling right now as far as where you're at?

KARPLUS: I'm beginning to get tired, not surprisingly, and maybe we can skip them, or—

EARDLEY-PRYOR: Sure.

KARPLUS: I don't know.

EARDLEY-PRYOR: I'll just make brief mention, if there's something that comes up for you.

KARPLUS: Okay.

EARDLEY-PRYOR: One of them had to do with the acidity constant or the acid ionization constant of groups in proteins, and the details of the continuum electrostatic model.[69]

KARPLUS: There were all papers where what we did with my students and postdocs—this was with Don [Donald] Bashford, who actually had been a student with David Weaver. Where a simplified model had existed before, which was an average model for calculating the pKa's. We realized that this was similar to Hartree theory in quantum mechanics, that under certain conditions each group is more or less independent and it would work, but it doesn't work if the groups are strongly interacting. Don Bashford developed it for the first time, and it was carried on by Michael Schaefer afterwards. He considered all the groups. The problem with that is that if you have ten titratable groups in a protein, each one can have a proton, or not have a proton, then you very quickly get a very large number of possibilities.

So people had avoided this, but Don Bashford set up the calculation so you included all of them. We realized that most of them didn't titrate in a given range, so you only had to include a few at a time, which made the calculation possible. Now lots has been written [on this, but

[69] Donald Bashford and Martin Karplus, "pKa's of Ionizable Groups in Proteins: Atomic Details from a Continuum Electrostatic Model," *Biochemistry* 29 (1990): 10219-10225.

Don's] was one of these pioneering papers and it was at the right time, because then other people like Barry Honig in particular have done a lot of work on titration.

EARDLEY-PRYOR: There's another collection of articles that you were interested in talking about, essentially on energy surfaces and protein folding, which I think we touched upon there.[70]

KARPLUS: I think that we can skip that.

EARDLEY-PRYOR: And then lastly, something that I actually am interested in hearing you talk a little bit about is some of the work with crystallographic refinement with molecular dynamics, work that you have done with Axel Brünger or John Kuriyan.[71]

KARPLUS: Yes.

EARDLEY-PRYOR: Can you talk a little bit about how that work—that seemed to be something that happened really in the mid-eighties.

KARPLUS: Right.

EARDLEY-PRYOR: Axel Brünger was initially Klaus Schulten's student in Germany, and then came over to work with you as a postdoc.

KARPLUS: That's right. He spent a number of years here.

EARDLEY-PRYOR: That was also kind of picking up on some of your magnetic resonance work.

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[70] Ron Elber and Martin Karplus, "Multiple Conformational States of Proteins: A Molecular Dynamics Analysis of Myoglobin," *Science* 235 (1987): 318-321; Oren M. Becker and Martin Karplus, "The Topology of Multidimensional Potential Energy Surfaces: Theory and Application to Peptide Structure and Kinetics," *J. Chem Phys.* 106:4 (1997):1495-1517; Sergei V. Krivov and Martin Karplus, "Hidden Complexity of Free Energy Surfaces for Peptide (Protein) Folding," *Proc. Natl. Acad. Sci. USA* 101 (2004): 14766–14770.

[71] J. Kuriyan, G.A. Petsko, R.M. Levy, and M. Karplus, "Effect of Anisotropy and Anharmonicity on Protein Crystallographic Refinement: An Evaluation by Molecular Dynamics," *Journal of Molecular Biology*, 190:2 (1986): 227-254; A.T. Brünger, J. Kuriyan, and M. Karplus, "Crystallographic R Factor Refinement by Molecular Dynamics," *Science* 235 (1987): 458-460.

KARPLUS: Right.

EARDLEY-PRYOR: But then pulling in the simulations. Is that correct?

KARPLUS: Yes.

EARDLEY-PRYOR: Could you talk a little bit about that, how that evolved?

KARPLUS: The original studies that John Kuriyan—who was a student of Greg Petsko, officially, but he spent all this time here. It happened, as Greg describes it, that John said, “I really want to do theoretical work,” when he went to work for Petsko, [who] was at MIT at the time. So Greg said, “I know just the person.” Greg brought John over, and basically, John spent all of his time here. At a certain stage in his career Greg said, “Look, if you’re going to be my student, you have to do a crystal structure,” so he finally did refine a crystal structure of myoglobin. But what he actually worked on was to try to use molecular dynamics to test whether the average **<T: 145 min>** structure determined by x-ray diffraction was the correct average.

He did molecular dynamics simulations on myoglobin, and then built a—let me look at this to make sure. Ron [Ronald M.] Levy was a very good postdoc who came from medical school. But—I guess it doesn’t really matter. The essential idea was that we would represent a crystal and the motions of the protein in the crystal by doing molecular dynamics calculations, and then we would put the average structure into the standard crystallographic program and refine that structure and see whether we got out the average structure that we put in. Normally, people just do their refinement. We used molecular dynamics to [describe the motions]. It may not have been the correct model of the motions, but we knew exactly what they were. And in this way, we were able to test whether the standard crystallographic programs were correct in particular. People tried to estimate the anisotropy of the motion, whether the temperature factors—which are an assumption of how the atoms are moving around—are actually spherical, or whether they are cylindrical. We could test all of these assumptions of x-ray programs. We found that under many conditions, the results were good approximations, but if there were too large motions, then they broke down.

I don’t think this had a huge effect on crystallographers. Actually, Tom Blundell, who gave the Weaver lecture about ten years later, he is a crystallographer, picked up this idea and started discussing the same thing, but I don’t think he referred to us at all, so whether—

EARDLEY-PRYOR: What about the—oh, go ahead, please.

KARPLUS: The next thing was—that's what Axel is really mainly responsible for, with John [Kuriyan] as well— we had been doing NMR refinements, and the idea was whether one could do refinements using molecular dynamics. Basically, in the NMR refinement, you use molecular dynamics to cover the space, and then use the NMR data as constraints on the motion.

EARDLEY-PRYOR: Because you know it's going to make that form.

KARPLUS: That's right.

EARDLEY-PRYOR: Or at least it will touch that form.

KARPLUS: We didn't know exactly what it would do, whether it would actually determine the structure. We start out with it just an unstructured protein in NMR, and then put in all the distance constraints, approximate ones, between different hydrogen atoms or for whatever atoms you have NMR data, which is mainly hydrogen atoms, and if you have lots of distance constraints, and you turn these constraints on slowly, then finally, the structure will, if there are enough constraints, will actually go to the true structure, because it's over-determined. If you have N-squared distances, and you only have N atoms, you have a lot of data. So that's the idea. People used [the method] for a while a lot. Now there are other programs that people use, which have **<T: 150 min>** similar ideas, but are different.

EARDLEY-PRYOR: What Axel was working has merged into the XPLOR program?

KARPLUS: Then the same idea, except there, it wasn't actually for structure determination, but rather for structure refinement. But it's the same idea, that you do molecular dynamics, and you use the x-ray data as an additional [constraints]. Basically, what we did in the NMR was to take the normal potential function, the CHARMM potential function, and add to it the distance constraints, and do dynamics with the whole [potential]. In the x-ray refinement, you use molecular dynamics [in the presence of the CHARMM potential, plus] the data from the x-ray analysis to constrain [the system]. You slowly turn it on to do this. We published the first paper [together].[72] It appeared clear that this was something that required a lot of work to make it really useful, it was sort of a whole field by itself. Axel is very interested in doing that, and so I said, "You go ahead." When he went to Yale, he took [the program] with him. I did [actually] invent the name XPLOR.

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[72] A.T. Brünger J., Kuriyan, and M. Karplus, "Crystallographic R factor refinement by molecular dynamics," *Science 235* (1987): 458-460

[. . .] I don't know whether XPLOR is still the most-used program. It was for a while. Then again, other people that were more interested in the technology, have done more work on it. For a long time, Axel didn't do any crystallography. Now he spends most of his time doing crystallography, and has done some very interesting work on SNARE [S(oluble) N(-etheylmaleimide Sensitive Factor, or Fusion) A(ttachment) P(rotein) RE(ceptor)] proteins and other systems. And I think he's very happy doing that. He has really moved into that area, and he's spending less time on the program.

EARDLEY-PRYOR: When you both had collaborated on what became XPLOR, why not try to commercialize it in the same way that CHARMM had been done?

KARPLUS: Well, it was.

EARDLEY-PRYOR: Oh, I thought XPLOR was open access.

KARPLUS: That's a big story in itself.

EARDLEY-PRYOR: Okay. Do you mind telling it?

KARPLUS: XPLOR was commercialized as a separate program, by Accelrys, but Axel got so annoyed with them, quite reasonably—similarly, I guess [to the way] I've been annoyed with them—that they didn't do anything for the program. They just sold it.

EARDLEY-PRYOR: They didn't do any development for it?

KARPLUS: They didn't do any development for CHARMM, as I told you—that the initial idea of making the agreement was that they would [do something to improve the program for commercial use]. Actually, he wrote another program [. . .] called CNS [Crsytallographic and NMR System software].

EARDLEY-PRYOR: Oh, yeah, CNS. That's right.

KARPLUS: Yes. I always think has something to do with central nervous system, which I'm more interested in nowadays. But anyway. [. . .] **<T: 155 min>** [. . .] There's been a question—

since all of the different companies have not lived up to their obligations as far as CHARMM is concerned, should one try to do something? There's a group of core developers for CHARMM, which are five people, Charlie and Bernie Brooks and Leonard Nilsson and Alex MacKerell and now Michael Feig. We are trying to get the next generation people involved, but it's a very small group that decide about the future of CHARMM. We do this together, though it still turns out that I make the decision if there's any argument. Some of them have said, "Let's get rid of Accelrys. They don't do anything for us." But my feeling is [. . .] I certainly don't want to go through [with what it involves]. I don't think it's worth it. [. . .]

[Phone ringing]

KARPLUS: That's probably Marci.

EARDLEY-PRYOR: You need to get the phone? Yeah.

[Break in audio]

KARPLUS: Where were we? We must be close.

EARDLEY-PRYOR: Yeah. We were just wrapping up some of your discussion about the commercializations and future meetings.

[. . .] Well, the last things that I'm interested in, if you have the energy to talk about it, is some of the family aspects, that Mischa came around in the early eighties, and if there was some sort of change in your work as a result of a new child, a young child, or how did that challenge some of the work that was being done?

KARPLUS: Not at all. He was a very easy child, and when Marci—you know, Marci's always been my secretary/administrator. When he was home, I would often stay—I always liked to work at home in the morning, and then come in in the afternoon. I discovered by accident when we were living in Brooklyn, that traffic was bad in the morning, so I'd come in in the afternoon. Then I suddenly realized doing work at home in the morning when nobody bothered me was really a great system. So even when we moved back to Cambridge, I kept this system, and would work at home in the morning. So, [when Mischa was sick], I would take care of Mischa. Then he was in the crib, and he was a very easy child. I'd say hello to him every so often and I'd give him something [to do]. So it had really no effect on my life, or maybe too little effect. According to Marci, she says I work all the time, and I guess in a sense it's true, when I'm working, I work. When we go off somewhere, like we're going off to Newport for her birthday for a couple of days, and then I'm **<T: 160 min>** happy to do other things.

EARDLEY-PRYOR: Are there any other things that you wanted to talk about?

KARPLUS: In some of the things that you had listed, there was one thing about science support and its effect on me. This has come up in terms of my coming to Columbia. We talked about that, and the Watson Lab. This also happened later on, where at a certain stage, the Atomic Energy Commission—I was getting support mainly from NSF in those days, not from NIH and mainly working chemical reactions.

EARDLEY-PRYOR: While at Columbia?

KARPLUS: This was mainly while I was at Columbia.

EARDLEY-PRYOR: So in the fifties?

KARPLUS: [No, in the sixties.]

EARDLEY-PRYOR: Okay.

KARPLUS: I was working on chemical reactions and getting support from NSF. The Atomic Energy Commission asked me if I wanted them to support me. They said that I wouldn't have to write long grants, that they would just give me money, so I said, "Okay."

EARDLEY-PRYOR: They came to you.

KARPLUS: They came to me, because they were interested in the calculations about chemical reactions that I was doing. What it had to do with, I never realized. But then after a few years, they decided they weren't interested anymore. So then we had to negotiate to get my NSF grant back. I think this theme that you want to be sure that you're working for an organization that is interested in what you're doing, and it's important for them, is something for people to keep in mind. As I probably have said earlier, it also has to do with working in industry, that you may find out that they hire you when you [get your degree], they treat you royally, and then their interest shifts, so you [have to] do something different. [Also, often,] you can't advance unless you become a manager, which you don't have to do in a university. That's another great thing.

I also urge my students that if they're interested in science, even though the beginning may seem easier [in industry], the first few years, when they get support and they're treated royally, it's much better to work in the university, where science is what they want for you to do well, as well as teaching.

One last thing I will say against universities and Harvard [in particular] is that you only get paid for teaching in classrooms. With my travels back and forth, I finally went to half time and then stopped [teaching] and then [became] emeritus. Harvard doesn't pay you anything, even though you spend more of your time teaching graduate students and postdoctoral fellows. It certainly counts whether they're going to promote you, whether you're doing science, but they don't pay you anything for that. I objected to that, but of course, that makes no difference. But I think it's really sort of . . . I can't quite think of a word for it. But it's—

EARDLEY-PRYOR: Unpaid labor. [laughter]

KARPLUS: That's one. Inconsistent is a mild version of that. Of course, the university gets tuition because you're teaching classes, but I still think it's inconsistent or worse that they don't do that. So maybe leave it at that.

EARDLEY-PRYOR: That sounds good.

KARPLUS: Even though I'm very supportive of university research. Nothing is perfect.

EARDLEY-PRYOR: [Okay].

KARPLUS: Okay?

EARDLEY-PRYOR: That's very good. Thank you again so much for your time.

KARPLUS: Well, it's been a pleasure, and **<T: 165 min>** [I] recalled a lot of things.

EARDLEY-PRYOR: Yeah.

KARPLUS: And I look forward in the course of time—

EARDLEY-PRYOR: See how it emerges?

KARPLUS: Yes.

EARDLEY-PRYOR: Thank you.

[END OF AUDIO, FILE 3.1]

[END OF INTERVIEW]

PUBLICATION LIST

Books

M. Karplus and R. N. Porter, *Atoms & Molecules: An Introduction for Students of Physical Chemistry* (Benjamin, 1970).

C. L. Brooks III, M. Karplus, and B. M. Pettitt, *Proteins: A Theoretical Perspective of Dynamics, Structure, & Thermodynamics,* Adv. Chem. Phys. **LXXI** (John Wiley & Sons, 1988).

O. M. Becker and M. Karplus, *A Guide to Biomolecular Simulations* (Springer, 2006).

M. Karplus, *Images from the 50's* (Martin Karplus, 2011).

M. Karplus, *La Couleur des Années 1950* (les Éditions de l'Œil, 2013).

Scientific Papers

M. Karplus has published over 800 articles.

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