CHEMICAL HERITAGE FOUNDATION

# THOMAS C. ALBER

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Neil D. Hathaway

at

The University of California, Berkeley
Berkeley, California

on

15 March, 9 April, 16, 23, 28, and 29 July, and 15 December 1993

From the Original Collection of the University of California, Los Angeles

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UNIVERSITY OF CALIFORNIA, LOS ANGELES

Oral History Interview Agreement No. 970321

This Interview Agreement is made and entered into this 26th day of May, 1998 by and between THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a California corporation, on behalf of the Oral History Program at the UCLA campus, hereinafter called "University," and THOMAS C. ALBER having an address at University of California, Berkeley, Department of Molecular and Cell Biology, 229 Stanley Hall, Berkeley, California 94720, hereinafter called "Interviewee."

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In consideration of the mutual covenants, conditions, and terms set forth below, the parties hereto hereby agree as follows:

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If to Interviewee: Thomas C. Alber
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University and Interviewee have executed this Agreement on the date first written above.

INTERVIEWEE

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Berkeley, California 94720

Date 3/17/96

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Carli V. Rogers
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Date 5/26/98

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**THOMAS C. ALBER**

1954 Born in Tokyo, Japan on 5 January

## Education

1976 B.A., University of California, Santa Cruz
1981 Ph.D., Massachusetts Institute of Technology

## Professional Experience

Massachusetts Institute of Technology
1981 Research Associate

University of Oregon
1982-1987 Research Associate

University of Utah
1987-1992 Assistant Professor, Associate Professor

University of California, Berkeley
1992-present Associate Professor

## Honors

1975 University of California President's Undergraduate Fellowship
1976 Graduate Fellowship, Danforth Foundation
1983 Postdoctoral Fellowship, Helen Hay Whitney Foundation
1985 Fellowship, Medical Research Foundation of Oregon
1988-1992 Pew Scholar in the Biomedical Sciences

## Selected Publications

Alber, T. et al., 1976. Crystal structure of elastase-substrate complex at -55 °C. *Nature* 263: 297-300.

Alber, T. et al., 1981. Crystallization of yeast triosephosphate isomerase from polyethylene glycol: Protein crystal formation following phase separation. *Journal of Biological Chemistry* 256:1356-61.

Alber, T. et al., 1981. Preliminary x-ray data for the galactose binding protein from *Salmonella*

*typhimurium. Journal of Molecular Biology* 147:471-74.
Alber, T. et al., 1981. On the three-dimensional structure and catalytic mechanism of triose phosphate isomerase. *Philosophical Transactions of the Royal Society of London,* Series B, Biological Sciences, 293:159-71.
Alber, T. and G. Kawasaki, 1982. Nucleotide sequence of the triose phosphate isomerase gene of *Saccharomyces cerevisiae. Journal of Molecular and Applied Genetics* 1:419-34.
Alber, T. et al., 1983. The role of mobility in the substrate binding and catalytic machinery of enzymes. *CIBA Foundation Symposia* 93:4-24.
Alber, T. and J.A. Wozniak, 1985. A genetic screen for mutations that increase the thermal stability of phage T4 lysozyme. *Proceedings of the National Academy of Sciences USA* 82:747-50.
Alber T. et. al., 1986. Structure and stability of mutant lysozymes from bacteriophage T4. In *Protein Structure, Folding, and Design,* UCLA Symposia on Molecular and Cellular Biology, vol 39. New York: Alan R. Liss, 307-18.
Alber, T. et al., 1987. Contributions of individual amino acids to protein stability determined by x-ray crystallographic analysis of selected and directed mutants of T4 phage lysozyme. In *Biological Organization: Macromolecular Interactions at High Resolution,* eds. R.M. Burnett and H.J. Vogel. Orlando: Academic Press, 246-58.
Alber, T. et al., 1987. Selected and directed mutants of phage T4 lysozyme. In *Crystallography in Molecular Biology,* ed. D. Moras. New York: Plenum Press, 251-60.
Alber, T. and B.W. Matthews, 1987. The use of x-ray crystallography to determine the relationship between the structure and stability of mutants of phage T4 lysozyme. In *Protein Engineering,* eds. D.L. Oxender and C.F. Fox. New York: Alan R. Liss, 289-98.
Alber, T. et al., 1987. Temperature-sensitive mutations of bacteriophage T4 lysozyme occur at sites with low mobility and low solvent accessibility in the folded protein. *Biochemistry* 26:3754-58.
Alber, T. et al., 1987. Contributions of hydrogen bonds of Thr157 to the thermodynamic stability of phage T4 lysozyme. *Nature* 330:41-46.
Alber, T. et al., 1987. Crystallography and site-directed mutagenesis of yeast triose phosphate isomerase: What can we learn about catalysis from a "simple" enzyme. *Cold Spring Harbor Symposia on Quantitative Biology* 52:603-13.
Alber, T. and B.W. Matthews, 1987. Structure and thermal stability of phage T4 lysozyme. *Methods in Enzymology* 154:511-33.
Alber, T. et al., 1988. Replacements of $pro^{86}$ in phage T4 lysozyme extend an $\alpha$ helix but do not alter protein stability. *Science* 239:631-35.
Alber, T., 1989. Mutational effects on protein stability. *Annual Review of Biochemistry* 58:765-98.
Alber, T., 1992. Structure of the leucine zipper. *Current Opinion in Genetics and Development* 2:205-10.
Alber, T., 1993. How GCN4 binds DNA. *Current Biology* 3:182-84.

## ABSTRACT

**Thomas C. Alber** grew up as an American in post World War II Japan and had to deal with issues related to his bilingualism and biculturalism. After moving to Los Angeles with his mother in 1964, Alber was encouraged in all areas of study, including the sciences, through his involvement with the Independent Program School at University High School in Los Angeles. This unique high school experience helped Alber choose the University of California, Santa Cruz for his undergraduate studies because of its non-traditional structure. At Santa Cruz, Alber worked in Anthony L. Fink's enzyme mechanism laboratory and pursued an opportunity to perform research with Gregory A. Petsko at Wayne State University. This research experience solidified his future interests in chemistry and biochemistry over other fields, such as the history of science. With a Danforth Foundation Graduate Fellowship, Alber undertook graduate research at the Massachusetts Institute of Technology (MIT), first under Alexander Rich and later under Petsko (when Petsko joined the MIT faculty). Alber traveled as a graduate student to do research at various laboratories including those at the University of California, San Diego, the University of California, Berkeley, and the University of Oxford. After earning his Ph.D., Alber started his postdoctoral research with Brian W. Matthews at the University of Oregon. Since Matthews was involved with the interdisciplinary Institute of Molecular Biology, Alber continued his pattern of research and study in a non-traditional setting. While finishing his postdoctoral research, Alber authored "Mutational effects on Protein Stability," in the *Annual Review of Biochemistry* in 1989. In this article, he proposed departing from the traditional model system of structural protein research and instead stressed the importance of all possible hydrogen-binding sites, the external amino acids on the rigid portion of the active site, the relative unimportance of the so-called 'floppy part,' and the necessity for flexibility in a protein. Alber's movement from the University of Oregon to the University of Utah and then on to the University of California, Berkeley allowed him to reflect on the American model of university science, the ways in which that model differs at a range of institutions, and the ways in which it varies from science in other nations. Alber's oral history ends with a discussion of the ways in which Alber's laboratory life changed over a ten-month period in 1993 right after he joined the faculty at Berkeley.

## UCLA INTERVIEW HISTORY

INTERVIEWER:

Neil D. Hathaway, Interviewer, UCLA Oral History Program. B.A., English and History, Georgetown University; M.A. and C. Phil., History, UCLA.

TIME AND SETTING OF INTERVIEW:

**Place:** Alber's office, University of California, Berkeley.

**Dates, lengths of sessions:** March 15, 1993 (75 minutes); April 9, 1993 (85) ; July 16, 1993 (93) ; July 23, 1993 (83) ; July 28, 1993 (85) ; July 29, 1993 (108) ; December 15, 1993 (76).

**Total number of recorded hours:** 10

**Persons present during interview:** Alber and Hathaway.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew scholars in the biomedical sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts' Pew Scholars in the Biomedical Sciences Oral History and Archives Project. The Project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships, from 1988 through 1992.

In preparing for this interview, Hathaway, in consultation with the director of the UCLA Oral History Program and three UCLA faculty project consultants, developed a topic outline to provide an overall interview framework. Hathaway and the director of the UCLA Oral History Program then held an in-person pre interview conversation with Alber to obtain extensive written background information (curriculum vitae, copies of published articles, etc.) and agree on a research and interviewing timetable. Hathaway further reviewed the documentation in Alber's file at the Pew Scholars Program office in San Francisco, including his proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members. For general background on the recent history of the biological sciences, Hathaway consulted such works as: J.D. Watson et al., *The Molecular Biology of the Gene.* 4th ed. 2 vols. Menlo Park, CA: Benjamin/Cummings, 1987; Lubert Stryer, *Biochemistry.* 3d ed. New York: W.H. Freeman, 1988; *The Journal of the History of Biology;* and H.F. Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology.* New York: Simon and Schuster, 1979.

The interview is organized chronologically, beginning with Alber's childhood and education in Tokyo and Los Angeles and continuing through his education, his postdoctoral work at the University of Oregon, and his career at the University of Utah and University of California, Berkeley. Major topics discussed include low-temperature x-ray crystallography, protein structure and folding, and the training and funding of research scientists.

ORIGINAL EDITING:

Kristian T. London, editor, edited the interview. He checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

Alber declined to review the transcript but did respond to editorial queries by telephone.

Steven J. Novak, senior editor, prepared the table of contents and index. London assembled the biographical summary and interview history.

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**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **15 March 1993**

**HATHAWAY**: As I say on every one of these, I've given up trying to sound original. In the beginning, we start at the beginning with an easy question to get warmed up, and that's where and when were you born.

**ALBER**: I was born in Tokyo, Japan, in 1954, on January 5.

**HATHAWAY**: Child number one, two, three?

**ALBER**: Child number two.

**HATHAWAY**: Out of?

**ALBER**: Out of two. My father [Harry F. Alber], on the other hand, has been married three times, so I have two half brothers and a stepsister from his other marriages.

**HATHAWAY**: Was your mom [Florence Teplin Alber] his first wife?

**ALBER**: Second wife. Child number two and wife number two.

**HATHAWAY**: It's also in the beginning a good time to get some names, like your brother. Or actually, I'm assuming your sibling is a brother?

**ALBER**: Yeah. My brother's named Chad [Alber]. He lives in Boulder. My father is Harry Francis. My mother was Florence Teplin.

**HATHAWAY**: And you're somebody else. Your name is different yet again. Is there an explanation for that?

**ALBER**: I meant my father--

**HATHAWAY**: Oh, you're giving me middle names. Okay, I 'm sorry. Francis, of course. So his last name is Alber?

**ALBER**: Alber, yeah. My mother's maiden name is Teplin.

**HATHAWAY**: A good way to sometimes start this out, at least for some people, is to ask them what's in their first memories. [tape recorder off] As I was saying, one way to start this flowing is to ask you what some of your first memories are. A lot of people have vivid first memories or recollections.

**ALBER**: I don't recall what my first memory is. [laughter]

**HATHAWAY**: Or even some early ones. Your first consciousness of being a person, if you will, or an event that was striking, is usually what our first memory-- Or even a regular kind of daily routine, for instance being walked in a park or something like that, you know?

**ALBER**: Well, there's certainly lots of scenes of Japan and Tokyo that are striking. When I was small, we lived in a Japanese farmhouse in a part of Tokyo that's now built up and has high-rises on that spot. The house is gone, but it was a traditional house with a big thatched roof and tatami mats in the house. It was not a Western-style house. It had quite a nice garden; it was a formal garden. I can remember sitting on the wooden sort of hallway that looked out on the garden and the sun coming in, moss had grown on the stones. It's an image, I think, that's very non-Western in that sense. And growing up in a foreign country, I think there are a lot of those types of images that I have, that I remember.

**HATHAWAY**: I'm not sure I'm exactly following what you're saying. You are saying, in more of a sense of your being in a foreign place, you don't have much of-- Or you're talking about that with hindsight now. In other words, you are looking back and seeing that these are not American things—

**ALBER**: Well, I didn't think of it as a foreign place at the time, certainly. I've lived in the U.S.

for almost thirty years, so I definitely consider this home, but there are aspects of American culture that seem foreign, rather than Japanese culture seeming foreign.

**HATHAWAY**: You said it was a farmhouse in an area that's now built up. I can't imagine, though, that even a farmhouse in Japan is really that isolated from neighboring homes or people.

**ALBER**: Well, we had neighbors, but the house was on a fairly big piece of land. There were fields around it, even though it was a suburb of Tokyo. And my brother and I used to chase each other through the fields that seemed to be sometimes over our heads, play hide-and-seek and things like that with friends in areas where you could hide in growth or—

**HATHAWAY**: These were cultivated fields?

**ALBER**: Yeah.

**HATHAWAY**: I wonder what grows that high. I have no idea.

**ALBER**: I don't know. I was a little kid, so they didn't have to grow that high. [laughter] Whatever it was, I don't remember.

I went to nursery school in Tokyo. I remember bits and pieces of that. I went to an American kindergarten, or an international kindergarten school, called the American School in Japan. I guess I have good memories of that; I enjoyed it. I liked to draw, for example. But I didn't like to take my naps. And because of that, my teachers recommended to my parents that I not go on to first grade.

**HATHAWAY**: So you could learn to take naps, or because this was a behavior issue?

**ALBER**: Presumably it was a behavior issue, you know. I didn't follow directions.

**HATHAWAY**: So they would keep people back?

**ALBER**: Yeah. So we had this horrendous meeting in the dining room of the house we were living in. By this time, this was the second house, I remember. It was a Western-style house near Tokyo Tower, and I remember we had this sort of formal dining room with a big table that

seemed awfully thick when I was five years old.

**HATHAWAY**: And it was never used?

**ALBER**: No, that's where we had dinner. We used it every day. But it was on the side of the house, and the sun was coming in from the yard. It was a big, sort of Western-style yard at this point, where I used to play a lot, and we had a dog pen out there where the dog- - My parents had English pointers. My father was very serious and saying, "Son, the teachers are recommending that you not go on to first grade. What do you have to say for yourself? What are we supposed to do about this?" I don't actually remember any of my responses, but just the scene was pretty intimidating. So I ended up going to a kindergarten that was a Japanese kindergarten, so--

**HATHAWAY**: Oh, because the place wouldn't take you for a second year? Or your parents felt maybe you'd do better in a new situation?

**ALBER**: I don't really know what the reason was. Maybe they didn't feel that there was any point in me going through that again. I have no idea. I guess that's what I assumed.

But instead I went to a Japanese kindergarten, which is actually much more substantive in the sense that you learn to start writing the Japanese characters, and so you practice over and over again in these books how to write each of the phonetic characters. That school was also in my neighborhood, so it was easier to get to. But that was a difficult experience in the sense that I was the only foreigner in the school, and I felt very shy about talking. So even though I spoke Japanese fluently, I didn't really say much, and the other kids used to sort of tease me, thinking that I was stupid or that I couldn't talk. So I remember this was happening one day over our workbooks, and I sort of swore under my breath at my attacker, and one of the little girls sitting next to me sort of beamed her-- Well, she also said something. I can't remember what she said, but she expressed her active support that I was standing up to this guy. [laughter]

**HATHAWAY**: And you were swearing in Japanese, I take it, right?

**ALBER**: Yeah, it was in Japanese-- I must have been six or something like that.

And then from there I went back to the American School in Japan for first grade, and apparently I had—

**HATHAWAY**: Overcome your nap problems.

**ALBER**: --become acceptable again, exactly. [laughter]

**HATHAWAY**: Oh, Lord. I'm guessing that in both places that you lived as a young child, it wasn't "Oh, this is a community of foreigners set off from the Japanese population" or--?

**ALBER**: That's right. They were both in Japanese neighborhoods. They were very upscale Japanese neighborhoods, but nonetheless not in some kind of foreign compound.

**HATHAWAY**: And again, my knowledge of Japanese culture and history, especially post-[world] wars, is very dim and minuscule at best, but I get the sense that after the [Second World] War Americans were rather occupiers, or maybe not that-- We are now talking '58, '59 maybe--

**ALBER**: Uh-huh, '59, '60.

**HATHAWAY**: We're talking fifteen, sixteen years. I know things rapidly changed to where the Americans weren't in that position of overseeing a military presence, I realize. But there wasn't any--? You weren't aware of that situation of where Americans had recently been the conquerors of these people? I guess I still think of certain areas of Germany--

**ALBER**: Yeah.

**HATHAWAY**: --where to this day, because of the American military presence, there's a hostility or friction between the German community and the American.

**ALBER**: I guess as a child I was pretty much shielded from that. Maybe that was something that Japanese people expressed toward my parents; I have no idea. But there was a substantial military presence still in Japan. We used to go to the beach area south of Tokyo in the summers and on weekends. The family rented a house at the beach, and driving there the road went by a U.S. naval base at Yokosuka. This was a huge installation with aircraft carriers and massive ships and huge numbers of people. In some ways I guess I heard stories from my parents about this sort of ugly American syndrome that some of the naval personnel fell into.

Another type of military experience is, when I was at the beach, there were the remainders of the fortifications that the Japanese had built to defend the island from a sea

invasion. My friends and I used to play in these caves that had held artillery pieces. In fact, my father said that the first time he went down there the guns were still in place, just cut up so that they couldn't be used. Certainly when I was a kid, we never found any of the guns. But we did occasionally find ampoules and some weird things that had been left and I completely cleaned out of these sort of tunnels that ran under the hills.

**HATHAWAY**: So you are talking about maybe even like food or--?

**ALBER**: We didn't find--

**HATHAWAY**: --medications or--?

**ALBER**: It seemed like it was some kind of medications that we found. But these tunnels were extensive and, you know, really creepy for a little kid, but that was part of-- You know, it's like being on a roller coaster: it's part of the scary thing to go back in there with a flashlight, and are there going to be animals or insects, or whatever--

**HATHAWAY**: Of course you're probably not allowed to do it—

**ALBER**: Of course.

**HATHAWAY**: --which was the other part of the fun. Had you much sense then--? Were you traveling back to the States? Did you have relatives of this other, your native [culture], if you will?

**ALBER**: No, I got a sense of that only from television: *The Wonderful World of Disney.*

**HATHAWAY**: So was there a full gamut of American television in Japan at that time or just something like Disney? Were you watching *Leave It to Beaver* also or--?

**ALBER**: I can't remember if I first saw *Beaver* here or there. It's the type of show that might well have been dubbed in Japanese and presented on Japanese TV. No, I didn't come back to the States until my parents were divorced in 1964.

**HATHAWAY**: So you were ten, twelve?

**ALBER**: I guess that's not coming back to the States.

**HATHAWAY**: Well, it's actually an interesting use of a phrase, then, too.

**ALBER**: So I was ten.

**HATHAWAY**: Ten, okay, not twelve. Maybe it also implies that your parents--and maybe you knew other Americans or other foreigners. That this wasn't your-- Even if you were born there and you didn't know anything else, that Japan wasn't your, quote, "home." There was always a sense that you would always come back to the States for school, for whatever.

**ALBER**: Yeah, that's definitely true. The Japanese culture is not inclusive.

**HATHAWAY**: That's what we hear today.

**ALBER**: And I think many of my friends-- Well, certainly most of my friends were foreigners; most of my parents' friends were foreigners. And so regardless of the fact that we lived in a dispersed way, the culture itself was such that you felt like a guest.

**HATHAWAY**: How many Japanese friends did you have? Were they 20 percent, none?

**ALBER**: I don't know, it's hard to remember. Certainly when I was in a Japanese school, I had more Japanese friends.

**HATHAWAY**: This little girl perhaps, an ally or--? [laughter]

**ALBER**: Yeah, but probably most of my friends were foreigners.

**HATHAWAY**: You sort of described yourself as shy, at least in the situation in the Japanese school where there was a lot of hard work in it, and you did feel obviously marked as different without-- You had no choice in that sense. How would you describe yourself upon returning to

an English-speaking school?

**ALBER**: Well, the school experience was a pretty-- I don't know. I can't really think of one word to describe it. The problem was that the curricula of the school here and the school there were completely different. So, for example, things I would have learned about grammar in the next year in the school in Japan, I was already expected to know by the time I got to the school here. The school here was in Bel Air, in L.A.--a public school called Bellagio Road Elementary [School]--a very rich neighbor-hood. My mother specifically found an apartment in that area so that I could go to that school. She was really concerned with finding a really good public school that I could get into.

**HATHAWAY**: She thought you might be a little behind and you needed the extra--? Or that you were a bright kid and you needed the stimulation?

**ALBER**: Well, I don't know whether she thought of me as a bright kid or not, but she just wanted a good school. So what happened was, I got to the States and just the journey was bizarre. I came by myself, but that's another story.

**HATHAWAY**: We'll make sure we get back to it.

**ALBER**: So I took sort of a placement exam at the school to get into the fourth grade, and basically I couldn't do anything that was expected of me. I could do the mathematical part, I guess, but the language was--

**HATHAWAY**: Really difficult, huh?

**ALBER**: --really difficult, not because I didn't speak English but because I didn't have the sort of training that elementary school students here would have gotten.

**HATHAWAY**: I'm trying to recall my own experience at that age, whether there was a lot of grammar.

**ALBER**: Well, just identifying, for example, what a noun is. It's really hard. But I remember--

**HATHAWAY**: Parsing sentences?

**ALBER**: Yeah, you take a sentence and I was asked to write down what the noun was. Well, I didn't know what a noun was. I could speak English, I could write, but--

**HATHAWAY**: If you'd already learned grammar in Japanese, I'm assuming it's such a radically different concept. Does one even call it grammar? I don't know.

**ALBER**: I don't know. Maybe because I learned Japanese from living there, in addition to the Japanese classes that we had in school, my Japanese language was very instinctive. And so I don't remember really picking apart the Japanese language until I went back to Japan when I was twelve and went to a language school. There the training or the classes were much more formal. But the Japanese language that I knew was learned from television and learned from being on the street and learned from talking to people in a sort of nonstructured way. So trying to apply that structure to English when I came here, I just didn't have any basis for that.

**HATHAWAY**: The whole idea of what a language is and how a language functions is different for Asian-- I mean, that's my understanding. I don't know much about it. I get the impression that even psychologically it's different.

**ALBER**: Certainly, yeah. Their language is more complex; there are more multiple meanings. There are more subtleties that involve who you are and who you're talking to.

**HATHAWAY**: And that nouns and verbs aren't so much anything structurally important as perhaps images or—

**ALBER**: Well, very good and very sophisticated, but for a ten-year-old or an eight-year-old, it was still important to try to convey that you had some relationship to the listener. But those are the sorts of things that to me I felt were intuitive. I don't remember. I know that for example in second grade the Japanese course I took in school had formal drills and things like that, but I don't remember any of it. I remember certainly being comfortable speaking. And I had been told when I lived there, if someone was talking with me on the phone, they couldn't tell that I wasn't Japanese.

**HATHAWAY**: Were most of your, let's say, American or English or European contemporaries, other kids, as equally--?

**ALBER**: Certainly my friends that had been born in Japan spoke the language fluently, but there were many children who came from foreign countries and were just learning the language. I should say that the language in my home was English. That was my—

**HATHAWAY**: Did your parents learn Japanese or did they speak Japanese?

**ALBER**: They both did, but not meticulously.

**HATHAWAY**: It's a tough one, I think, for people speaking Romance languages and English.

**ALBER**: Well, it's a tough language, that's true. But I have a suspicion that the level of language skills that my parents sought was something that reflected their relationship to the country rather than an inability to learn the language. I mean certainly my father had been there since the U.S. occupation; he went over in 1945 and landed on the beach south of Hiroshima, near a navy base called Hiro, and he was in the first wave in the first group of people who went up the beach on the landing crafts. They were told that they would be shot when they went there.

He worked as a county governor. He was a lieutenant in the army. His assignment was to administer the occupation in a county in southern Japan. So he--

**HATHAWAY**: Is that like a municipality, or is the word transferable to our notion of a county or--?

**ALBER**: No, it was called a prefecture. Yeah, it's more like a county, an area that has many different cities in it—

**HATHAWAY**: So a couple of million people--

**ALBER**: It's a rural area that had a well-known artists colony.

**HATHAWAY**: What was the name of it?

**ALBER**: It was called Kurashiki. He was in charge of finding out what the people needed to live and rebuild and obtaining those things from the U.S. occupation government. I guess that's

a pretty romantic view of what he was doing then.

He has told stories about meeting with Japanese leaders and finding out from them what they would need to get, say, an industry started again in this area. And there was one particular town where there was a hill that split the town. There was a tunnel through the hill, and the Japanese had put many machine tools from all the factories in the area in the tunnel to protect them from bombing. My father tells a story of being shown this by the town leaders, and asking them, "Well, what do you need to get these machines out of the tunnel and back into the factories?" They said, "Well, nobody told us to do it." And so, to make a long story short, he wrote out an official order on the hood of the jeep, signed it, and gave it to them. And that's what they did. It got things going. In some sense, there were logistical things about food and real concrete things that he was responsible for. And in another sense, it was simply relationships; he was a public figure in that sense. He told me about meetings he would go to where the first thing he would do is take off his .45 and the holster it was in and hang it at the door, to show that he wasn't there to intimidate the people in a military way.

**HATHAWAY**: This was the reason he was there when-- You say '45, and of course you were born I think it was in '54.

**ALBER**: In '54, yeah. So, yeah, certainly that was the reason he was there. He had been an instructor in the infantry during much of World War II, so he hadn't been in combat essentially. And toward the end of the war, he was given the opportunity of going to paratroop school or going to the Pacific, and he chose the Pacific. He didn't want to jump out of airplanes. He was on his way to the Philippines when the atom bomb was dropped on Nagasaki. He was involved in, the way I understand it, sort of mopping up operations in the Philippines after the Japanese had surrendered. He was slated to be part of the invasion force when the Japanese surrendered.

**HATHAWAY**: And he never left. I mean he never went back to the [States]. Whether he went back for a month or two, but he--

**ALBER**: Right. So his military orders kept him in Japan until 1948, when he was court-martialed. He was accused of disloyalty for involvement in a black civil rights group in Tennessee in the thirties. He was involved in TVA [Tennessee Valley Authority]. He had run out of money at the University of Maryland [at College Park] and so got a job with the TVA. I think it was in Knoxville. I'm not exactly sure.

**HATHAWAY**: Run out of money at Maryland. He was an instructor there?

**ALBER**: He was in college.

**HATHAWAY**: Oh, he was a student.

**ALBER**: He was a college student--University of Maryland, majoring in chemistry--and didn't have money because of the Depression. So he got a job, and had been involved in civil rights causes when he was in Tennessee. And that was considered a communist front activity by the late forties. My understanding is that he had a formal military court-martial in which the charges were that he was disloyal, and he was acquitted.

**HATHAWAY**: For this activity in the thirties, not for anything in his military career?

**ALBER**: That's my understanding.

**HATHAWAY**: So was this generated outside of the military, then?

**ALBER**: Again, I don't know the details of what he went through. This is one part of his past that I learned from my mother rather than from him. Although I have talked to him a lot about subsequent events, I haven't talked to him about this.
I can't remember what the question was.

**HATHAWAY**: Just if there was any knowledge on your part as to where this court-martial--? It was obviously done by the military, but it wasn't about military matters.

**ALBER**: I understand there was a purge in the military of left-wing people at that time, and certainly the group of military people who were observers of the Chinese communist movement were purged. That was something I've read about.

**HATHAWAY**: I 'm also familiar with what's happened, for instance, in a lot of areas in the New York area, especially. I mean it actually had to do with anti-Semitism as well as people's membership in certain kinds of organizations. But again, from the early thirties on up--
Targeting military people is obviously sensitive--

**ALBER**: So my understanding is that, starting in the late forties, there was a purge in the military that essentially preceded the [Joseph R.] McCarthy witch-hunt.

**HATHAWAY**: But that was generated from the same group of people. Again, I think of a particular base near where I grew up, a military installation with a local history. Now it's important, you know. And again, that was all based on McCarthy and certain people in Congress and the Senate kind of practicing in the military what they decided worked so well that they would then take it on to a civilian—

**ALBER**: So my father didn't get back to the United States very frequently. He got back in 1948 for the trial, and also he brought with him pots that had been made by people in this town of Kurashiki, where he was the governor. These potters were the great potters of Japan, [Shoji] Hamada among them. He took some of their work to the Museum of Modern Art in New York and suggested that maybe MOMA [Museum of Modern Art] would want to do a show. He says that they just laughed at him, that this was crap and not art. Subsequently, these people became living national treasures in Japan, but MOMA rejected them.

**HATHAWAY**: I think maybe they have changed their tune now about the crafts versus the high arts.

**ALBER**: I don't really know. Anyway, so he came back-- I mean he can be sort of altruistic, to take these pots to—

**HATHAWAY**: Especially when he was, perhaps, under some stress.

**ALBER**: Well, also he was just a young guy. He was born in 1916, so he must have been thirty-two. So, as a result of the court-martial, he realized that his military career was done, and actually resigned from the military when he got back to Japan. And fortunately didn't sign up for the reserves in the way that many other people did when they left the army. The reservists were called up in Korea, and many of them were killed, of course. My father sort of dodged that, simply because he felt that the court-martial had damaged his standing. So, in a sense, it was a lucky thing, although very traumatic for him at the time.

**HATHAWAY**: And again, not to spend too much time on your father-- Do you know what his upbringing, background, family situation was that, for instance, he was not only showing crafts to MOMA in the forties, but the civil rights movement in the thirties was extremely young?

**ALBER**: No, I don't really know. No, it's not like-- There aren't even stories in my family like Bill [William J.] Clinton, who, you know, went to his grandfather's-- He grew up in suburban [Washington] D.C. His father was an auto mechanic. I never knew his father, but his mother,

who I knew, wanted a girl, so that's where the name Francis comes from. But I don't really know much about his family. There was a sister who I met, but--

**HATHAWAY**: So it's not that you hang out at the family reunions. Was he close to them, perhaps, before almost sort of a forced separation and not coming back to the country?

**ALBER**: Well, certainly his mother visited Japan. When he came back to the States in subsequent years, he often went to visit his sister. I don't really know why his family is not that close.

**HATHAWAY**: Maybe they just didn't get along. A good reason not to be close. I'll ask the same questions about your mom's side of the family. As you said, you moved back when you were ten to Bel Air. Again, her background and upbringing and where she was from?

**ALBER**: Her parents were Russian Jews. Her father came from the Ukraine in 1890s on a boat to New York City. Her father and mother eloped, essentially, from the Lower East Side—

**HATHAWAY**: Economic reasons, or family?

**ALBER**: No, their parents didn't approve of the relationship.

**HATHAWAY**: Because?

**ALBER**: I don't remember. And moved to Denver. My mother was born in Denver, moved to Los Angeles. Her father did many things. He wasn't sort of a traditionally respectable individual.

**HATHAWAY**: Was he on the lam a lot, is that what you're implying, or--?

**ALBER**: No, no. He just did crazy things, you know, raised rabbits during the twenties to sell the meat and the fur.

**HATHAWAY**: He wasn't somebody who brought home the paycheck every week, and that kind of image.

**ALBER**: I don't know if he had a regular job or what he did. He had a house in a community near Palm Springs called La Quinta when I moved there [to Bel Air], so we used to go out into the desert to his little house. I don't know how he got the money to get that. He was a character.

**HATHAWAY**: So you had more--simply because when you moved back to, not back-- See, I'm doing it now too. When you moved to the States, it was mainly-- Your mother was divorced, and you were with her. So she went back to her family, in a sense.

**ALBER**: She grew up in Los Angeles, went to high school in L.A., graduated from UCLA in the late thirties. She was pretty left-wing at the time. She and a friend, who ended up becoming Herman Wouk's wife, went off to Washington, D.C., to sort of make their way in the world. That's where she met my father.

**HATHAWAY**: This is the late thirties also.

**ALBER**: Yeah. My father, by that time, had moved back to Washington, D.C., and was working in the OPA [Office of Price Administration].

**HATHAWAY**: Had he gone to college?

**ALBER**: My father didn't graduate from college, no.

**HATHAWAY**: No. He just picked up the experience--

**ALBER**: He had a couple of years at the University of Maryland, but he didn't graduate. My mother graduated from UCLA.

**HATHAWAY**: They perhaps met at some sort of gathering, whether it was informal or formal. We won't talk about anything like card-carrying whatnots or anything--

**ALBER**: No. Well, I think my mother was more into carrying cards than my father. So I don't imagine that they met at a formal gathering, but at a meeting. My father talks about social things they did at the time: going to New York and listening to jazz in Harlem, or listening to Billie Holiday—

**HATHAWAY**: A sure sign of their politics.

**ALBER**: I don't know how they met. My father at that time had been married a year and divorced.

**HATHAWAY**: You mentioned, I think, two half brothers?

**ALBER**: Yeah. This first marriage was something that lasted a year. My oldest brother Bill [William Alber] was—

**HATHAWAY**: It's his oldest child?

**ALBER**: Yeah, so he's in his fifties, fifty-four. So that would be 1939 when he was born.

**HATHAWAY**: Did you grew up knowing him, or did he visit?

**ALBER**: Not at all. I met him after I moved to Los Angeles. My father was pretty absent from his life, so he and my father didn't really get along. They didn't know each other; they didn't have much of a relationship. By the same token, when I moved to Los Angeles, Bill was active about getting in touch with me. He took me to the Sierras for the first time, took me to the mountains backpacking, things like that. So Bill was conscientious about including me in his family, or being in the same family that I was in, but I don't think he and my father spent so much time together over the years.

**HATHAWAY**: And then your other half brother is younger and from the third--

**ALBER**: He's younger, yeah. So my father was married for a third time now, after my parents were divorced. He and his present wife had a son in 1964, so he's twenty-seven, lives in New York City.

**HATHAWAY**: Not much contact? He sells what?

**ALBER**: He sells bonds. Actually, I think all the brothers are pretty close at this point, regardless of who our mothers were. We don't really draw those lines. My youngest brother is half Japanese. He really kept up his fluency in the language. And so his business is selling bonds to Japanese banks. He has a Japan niche in that.

**HATHAWAY**: I wanted to actually just check with you: Can you still speak Japanese, can you still understand it, or is it something that you just have--?

**ALBER**: I'm very rusty. It's been, like I said, almost thirty years. I speak mostly with my stepmother, and as a result my speech is pretty feminine because I hear her, and men and women speak differently in that culture. But my vocabulary is also pretty spotty, and it's pretty juvenile, because I left when I was a kid. So I'm not really comfortable speaking Japanese. I can get around. I can listen to people and know what they're saying often. I can go to movies and understand much of the dialogue without reading the subtitles. In fact, I think it's fun because I can tell when the subtitle is missing a lot of the real stuff.

[END OF TAPE 1, SIDE 1]

**ALBER**: So anyway, I'm pretty shy when I speak now. If Japanese people speak to me in Japanese, I usually try to respond in English to see if they can understand that. And then if they don't, I'll speak Japanese. [tape recorder off]

**HATHAWAY**: I guess we had a long-enough break that we decided we would just drop it there. We have spent a lot of time on your bilingualism and perhaps your biculturalism.

I guess one thing that I'm struck by is that your extended family--which includes, of course, not even blood relatives--is still very close and very much intact, considering also it seems to be spread over thousands of miles and different countries.

**ALBER**: Yeah, like my stepsister and her family in Tokyo.

**HATHAWAY**: The sister I've missed totally.

**ALBER**: This is my father's current wife's daughter, and her family--my father's wife's family--is extensive in Japan. She has a number of brothers and sisters who I've met and spent some time with. Certainly my youngest brother, when he was growing up in the Seattle area, spent summers with my stepmother's relatives in Japan. I have a confusing family.

**HATHAWAY**: No, no, it's not confusing at all. But again, it seems--

**ALBER**: Oh yeah. So for example, my father is turning seventy-seven at the end of the month, and we are having a family reunion up in Seattle, and people will be coming from Japan. It will be a big group, an interesting group.

**HATHAWAY**: Have you been one of the initiators of it, or just, "Okay, that's a good idea, I'll do this?"

**ALBER**: Oh no, this is something traditional in the family. It's a Japanese custom that every eleventh birthday is a big deal. I think we did this at seventy for my father, but maybe it was sixty-six. I can't remember the last one. But we got tickets for my parents to go to Hawaii, and then the whole family met them there. My stepmother knew this was happening, but my father didn't know. So he stepped off the plane and--

**HATHAWAY**: He at least knew he was going to Hawaii, right?

**ALBER**: Well, the funny thing was, he didn't want to go to Hawaii. Why go to Hawaii?

**HATHAWAY**: You've lived in Japan.

**ALBER**: Well, he's not one for the resorts and the tropics so much. But he felt that it would be rude to not go because the kids had banded together and gotten him this present to go to Hawaii. He didn't want to go. It was a lot of fun.

**HATHAWAY**: I seem to remember that perhaps your mother is not alive anymore?

**ALBER**: Yeah, my mother died in 1985 of lung cancer. She quit smoking the day she was diagnosed. So she smoked her whole life.

**HATHAWAY**: You still have the connections with that side of your family, too, I take it? Maybe not so much. Maybe that was a childhood thing.

**ALBER**: Well, there aren't many people on that side. Certainly I have a cousin, Laurie [Nelson], who lives in Topanga Canyon in Los Angeles, and we write and see each other as much as possible--well, not as much as possible, but certainly regularly every year.

**HATHAWAY**: Topanga is a nice place to go visit.

**ALBER**: Yeah, it is.

**HATHAWAY**: You came to the States when you were ten, to L.A., and you said something about going back to Japan--language school when you were twelve. Was that a vacation-type, couple-of-months stint, or--?

**ALBER**: I might have been eleven. I think it was for the summer, while school was out in the U.S.

**HATHAWAY**: To see your dad?

**ALBER**: Yeah. To see my dad.

**HATHAWAY**: So you came right back to L.A.?

**ALBER**: Yeah.

**HATHAWAY**: Was there much adjustment? What did you think about a place like L.A. after being in Tokyo?

**ALBER**: Well, the first thing that was really funny in retrospect was I thought the whole of the U.S. was like Los Angeles.

**HATHAWAY**: It soon will be. [laughter]

**ALBER**: Yeah, there was quite a bit of an adjustment. My impressions of the U.S. had been

almost of a fairyland or something like that.

**HATHAWAY**: You had been maybe once or twice, three times, before you moved here, right?

**ALBER**: No.

**HATHAWAY**: No, not at all? Okay, I'm sorry. You said that, and I didn't--

**ALBER**: My father didn't come back to the U.S. in the fifties because he had lost his passport in the McCarthy era of troubles.

**HATHAWAY**: The government wouldn't renew it?

**ALBER**: Well, he was subpoenaed by the McCarthy committee to testify about land reform in the Philippines, which was considered a communist activity. It happened to be run by a good friend of his. He hadn't been back to the States for some time before he was subpoenaed, and he asked Americans in Tokyo what the McCarthy hearings were about and just decided that he didn't want to be part of that.

**HATHAWAY**: He didn't really have much of an idea, then, of what was going on.

**ALBER**: I'm sure he did, but his information was based on sort of a news report, but also people who had recently moved to Japan from the States.

**HATHAWAY**: As a result of--?

**ALBER**: No. For one reason or another. You know, just what's happening--

**HATHAWAY**: Okay, because I know there was, for instance, quite a large community of people who left, who didn't testify, who went to Paris and places in England and whatnot, I believe. But I didn't know of any in Japan.

**ALBER**: No, my parents' friends who I remember were journalists--foreign journalists,

American journalists-- business people, art collectors--

**HATHAWAY**: So he would have had actually a wide variety of information and knowledge.

**ALBER**: Anyway, so he didn't go to testify. He was indicted for contempt of Congress, and that's why he lost his passport.

**HATHAWAY**: So it was actually repossessed as opposed to simply being allowed to lapse or not being used.

**ALBER**: It was canceled. Which at that time, Japan got home rule back, and so the Japanese were happy to have him as a guest. And the Americans were disinclined to try to extradite him because they didn't want to be embarrassed by the Japanese, who would presumably have--

**HATHAWAY**: Made it difficult.

**ALBER**: Made it difficult, right. The Japanese were happy to try to embarrass the Americans. So it was sort of a quid pro quo that left him welcome in Japan but without a passport to go anywhere else. That actually was an issue in a couple of ways. Japan was a nervous place in the late fifties because people feared a nuclear attack from what was then called Red China. My parents actually, I remember, had a bag packed in case they had to leave, although it wasn't clear where they were going to go.

**HATHAWAY**: Or whether your father would be able to go anywhere.

**ALBER**: Yeah, he certainly couldn't leave the country. The other thing was that I think my mother, especially, felt stuck in Japan, and it was a very heavy stress on their relationship. Japan has very much a male-oriented, male-dominated culture. I think my father got used to being the head man, but of course my mother didn't have that opportunity. So she, being an intelligent, independent-thinking woman, chafed at the prospect of not being able to leave and had more difficulty living there.

**HATHAWAY**: Did she remarry at all?

**ALBER**: She didn't remarry. No, she remained much in love with my father for her whole life.

**HATHAWAY**: And I take it, at some point, since he does live in the Seattle area, that he was given a passport or his status was rehabilitated?

**ALBER**: His indictment was renewed during the [Dwight D.] Eisenhower administration, but was allowed to lapse when Bobby [Robert F.] Kennedy became the attorney general, and he got his passport back in '63 or '64.

**HATHAWAY**: So fifteen years, sixteen years?

**ALBER**: No, it was maybe ten, twelve years.

**HATHAWAY**: I'm thinking of his service in the military and coming back from there, which is not correct.

**ALBER**: Well, it's a lifetime, if you think about it.

**HATHAWAY**: I can't imagine what it's like to not have the freedom of movement that, especially as Americans, I guess we are all very used to. I was under sort of house arrest during the [1992] riots [in Los Angeles], and you can't leave your house after sunset, or you're not supposed to. It's a very claustrophobic, strange feeling to suddenly realize you're subject to arrest for simply being outside. Again, being isolated like that, and limited in your ability to do what you want to, in a sense, must be awfully frightening or disorienting.

**ALBER**: Well, I don't know. I wouldn't go that far. He was awfully successful in that culture, in that time, so he had a good time. I think—

**HATHAWAY**: But he came back. I mean, even with the Japanese wife, he's-- When he could make the decision to come back to this country, or--?

**ALBER**: No, in fact he stayed in Japan until 1971, and sold his business at that time and moved back to the States because my youngest brother, being half Japanese, wouldn't be accepted in the Japanese culture. It's not like being half American.

**HATHAWAY**: He didn't encounter problems as a child, but as he was getting older, he just couldn't--?

**ALBER**: Right, as he grew up and would be going to school and getting older, the idea was to get him out of a culture that is racist to the point where he would be considered in the way a minority person in the United States might be considered an outcast or--

**HATHAWAY**: Or even somebody who is mixed--

**ALBER**: --biologically inferior. So my father and stepmother looked for a place in the U.S. where Japanese were accepted, and so the choice came down to Seattle, Vancouver, and the Bay Area. They fell in love with Seattle, so they moved there. But it was ostensibly for my youngest brother's education.

**HATHAWAY**: And social well-being, too. I mean instead of just sending him off to some sort of boarding school or something. They haven't gone back though. He's twenty-seven, you said, so there's obviously no need for them to. [They're] obviously settled in.

**ALBER**: Right. My father's wife, my stepmother, has a house in Tokyo; her family house is there where my stepsister lives. My father used to travel there often. My stepmother still travels there often. She was just there for a month, for example. So she goes back and forth. He retired a couple of years ago, and so doesn't have a business reason to go to Japan and doesn't go there very frequently at all.

**HATHAWAY**: We kind of got back on to the Japanese track and the family things from your response about L.A. versus—

**ALBER**: We were talking about L.A. So a few things: just physically, it's very different. Buildings and things like that in Japan--houses--were built sort of individually with a certain kind of craftsmanship, and of course L.A. is a different scene. The first day I was there, for example, I walked into a plate glass window because I'd never seen a piece of glass that was covering a space that didn't have a frame around it. And this window was just a piece of glass that looked out over the balcony at my mother's apartment. I didn't realize it was there.

**HATHAWAY**: Boy, talk about the notion of cultural displacement or something. I mean actually running into the—

**ALBER**: Yeah. The first week I was there, my mother had just bought a car, and it was raining horrendously in Los Angeles. We lived on a dead-end street, but she had just purchased a car just before I got there and she really wanted to take me for a drive. So we got in the car in this amazing downpour; there was flooding in the street. She drove all the way up to the end of the street--it was maybe a little over a mile--and all the way back in the rain, and absolutely no other car on the road. And she drove up on the left-hand side and drove back on the left-hand side, because that's the side of the street you drive on in Japan. And so even just little things: cars are not supposed to be where they are.

Certainly, politically, my impression of the States was sort of focused around the Constitution, the Bill of Rights. We were supposed to be basically fair. So that was a bit of a shock.

**HATHAWAY**: Was it something you think you were aware of also because of maybe something you studied in school? In other words, in an English school, there was this emphasis on America is great, and-- Or was this something also--your consciousness of this is what the Bill of Rights says, but this is the reality--which came maybe from your mother's political views, which may have been a little jaundiced, let's say, toward the party line, especially the Republican Party line, although I guess the Democrats were in power at the time.

**ALBER**: No, it wasn't that at all. I guess I don't really remember having political conversations with my parents when I was growing up.

**HATHAWAY**: When you were twelve or eleven or ten--

**ALBER**: When I was, you know, in elementary school or something. I don't know from television or-- Where did I get this?

My father went in the PX [post exchange] once and bought a pair of blue jeans. When I got home from school, he said, "Son, this is your first pair of American blue jeans. These things are so strong, I can't even tear the pocket off of them." Then he [pulled] the pocket of this tiny little pair of blue jeans for a ten-year-old--I don't know how old I was--and the pocket ripped right off! And so to give you an idea of how this reflected on my image of the United States-- I mean, you could say that I would have taken that and said that "Well, that proves that America isn't as great as it's supposed to be." But instead I took that as an indication of just how strong my father really was.

I don't know where-- Well, I do know where: from Walt Disney TV shows and from-- I don't know. Who knows where I got this sort of idealistic view of politics in America?

**HATHAWAY**: I would think also, just off the top of my head, whether it was a school in Japan and no matter who ran it, if it had anything to do with Americans there would also be social studies or civics-type classes that one got in those situations.

**ALBER**: I don't know. I mean, certainly the Americans, having all this military presence, seemed like a powerful nation. In Japanese culture, there's a real pressure to support your leaders or your elders or your superiors. And so when I got to the States, I was really confused by all the political dissent. Shortly after I moved here, opposition to the [Vietnam] War really took off, and the civil rights movement was in full swing. I wasn't used to this notion of public dissent.

**HATHAWAY**: Maybe in many ways, American culture wasn't either. I mean, it was as much of a--

**ALBER**: Shock? Maybe so. I remember coming to [University] High School one day, and my friends had gone to protest [Lyndon B.] Johnson coming to visit Los Angeles. Instead of arresting people, the L.A. police had just beaten people up. So my friend came to school with his head completely bandaged.

**HATHAWAY**: They're still at it.

**ALBER**: They're still at it, but I think for me that was an event that really made me decide sort of "Which side am I on?" It's one of those things that made me look really hard at this tendency in Japan to just support your leaders.

**HATHAWAY**: You're talking now about high school, so actually maybe that's not too young. And I'm a little bit younger than you, so I kind of followed this all as maybe a seven- or eight-year-old or something like that--so not very conscientiously. It seems that perhaps, even for that time, you were rather young to be aware of these, let's say, discrepancies-- Or being able to make the comparison between Japanese culture and American culture, seeing one as instructive of the other, and also vice versa. In other words, you're doing a lot of comparison here, learning an awful lot from that double view or whatever that most people don't have.

**ALBER**: Uh-huh. When you grow up in a foreign country, that's how you live, and many things are comparative.

**HATHAWAY**: This may be a rather simple or stupid question, but actually maybe not. We'll see how you respond. Do you think of yourself as an outsider here still to a certain extent, or is that something that because now it's thirty years, you are as American now as the people around you who grow up--as apple pie and Chevrolet? Or do you still see yourself as looking in from the outside sometimes?

**ALBER**: Oh sure, I look in from the outside, make those comparisons still. But being in science and being politically active at one time in my life and--what are the other distinguishing things?--being educated, having an advanced degree, there are many things that still make me feel out of the mainstream, or unusual.

[END OF TAPE 1, SIDE 2]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **9 April 1993**

**HATHAWAY**: You mentioned in your moving to the States to be with your mom [Florence Teplin Alber] that you traveled alone, and you were I think ten years old, I think, eleven—

**ALBER**: Uh-huh, ten.

**HATHAWAY**: --and you called the trip bizarre. And then you said you'd get back to it, and I didn't pick up on it. I don't know if it now is something that-- You just said it was a weird experience.

**ALBER**: Well, I can't remember exactly what I said, but there's nothing deep or pathological there.

**HATHAWAY**: No, I just thought that maybe--

**ALBER**: No, I was--

**HATHAWAY**: "I was kidnapped and held under the storage thing on the boat." I take it it was by ship. I don't know why I think that though. It was plane, right? [laughter]

**ALBER**: Yeah, Jack London and I sailed across backwards through time, got scurvy. [laughter] No, I mean, I was dropped off by my father [Harry F. Alber] at Haneda, the airport in Tokyo. It was the first time that had happened. I transferred planes in San Francisco, and it was bizarre because there was a huge storm. It was very--what?--windy and rainy and just what happened to Caesar. [laughter] It was a very violent storm, and so to travel in that, and to be by myself, was frightening.

**HATHAWAY**: I guess that's not too pathological, number one. But number two, what I was

curious about is, was it weird also? I was wondering if you had meant it was weird because, of course, maybe it was, for any ten-year-old to have to go through something like that. I mean, your parents had split up, and so I was wondering if that had colored what you, as a ten-year-old, thought was a pretty odd trip.

**ALBER**: Sure, yeah. Nothing more than what you'd expect. [laughter]

**HATHAWAY**: I shouldn't have asked that follow-up question. We did talk an awful lot about your more extended family, and I think that's where we ended up, but we had left you somewhere in L.A., kind of adjusting to things--I would say somewhere in high school. We were just talking more about your--

**ALBER**: Well, we skipped the part where I went three for four in a Little League all-star game.

**HATHAWAY**: Oh, we did skip that part. We'd better not. [laughter]

**ALBER**: High school, right?

**HATHAWAY**: Well, not unless you want to go back-- No Little League? [laughter]

**ALBER**: That's why they call it Little League.

**HATHAWAY**: Isn't it terrible? You can tell who never went to Little League, because I never ask anybody about those questions.

**ALBER**: I still have my pin. [laughter]

**HATHAWAY**: Was that something you had started in Japan?

**ALBER**: Playing baseball?

**HATHAWAY**: Yeah.

**ALBER**: Oh, sure, yeah.

**HATHAWAY**: It's also the national pastime there.

**ALBER**: I used to go to Tokyo Giants games.

**HATHAWAY**: And soon as you were old enough to play you did. [tape recorder off] If you're willing, I'd like to-- If you started playing Little League--

**ALBER**: --talk about baseball. [laughter]

**HATHAWAY**: Yeah, if you really got into it, enjoyed it a lot and played an awful lot of it--all the way through high school, I guess?

**ALBER**: No, no, no, no. I stopped after Little League. But yeah, I mean it was a big part of my childhood: playing with my father, playing catch in Japan, going to games. I had this experience when I was little that, in Japan, you're not supposed to be left-handed. I'm left-handed. So, you know, I didn't consider myself Japanese to the point where that was a stigma, but culturally it was weird. And the Tokyo Giants had this incredible hitter, Sadaharu Oh, and he was left-handed.

**HATHAWAY**: Even I have heard of him.

**ALBER**: Yeah, he's a national hero. I guess in retrospect, he was someone who sort of proved to me that being left-handed was okay, in an odd way. I don't know. Baseball, God, I've got lots of-

**HATHAWAY**: Baseball stories?

**ALBER**: --baseball stories. You know, playing catch in the morning, and catching the ball with my hand instead of with my glove, and crying and stuff like that. [laughter]

**HATHAWAY**: Oh, by accident. Not to prove how tough you were.

**ALBER**: No, no. You know, pitching in Little League, winning the championship, blah, blah, blah.

**HATHAWAY**: This is both in the States and Japan?

**ALBER**: Well, no, I didn't play in an organized league in Japan.

**HATHAWAY**: Oh, okay, that was just out in the backyard and going to the games and stuff?

**ALBER**: Just here, yeah.

**HATHAWAY**: I would have thought they would have had some sort of little league, even in Japan. I'm sure they must.

**ALBER**: Yeah, I don't really know, to tell you the truth. They must, but I didn't anticipate-- In fact, they might not, because Japanese are so serious about being studious when you're in secondary school. But they must get their baseball players somewhere, you know? In high school it's a really big thing. The high school baseball championships are televised. They are sort of the equivalent of the Final Four here in [college] basketball--national TV coverage.

**HATHAWAY**: I was in North Carolina last week, the week before, so there was quite a bit of basketball going on.

**ALBER**: Oh God, yeah.

**HATHAWAY**: You didn't play it in high school, though. You weren't on a varsity team and got a letter and all that sort of thing? You were too late for that really being a—

**ALBER**: Well, my high school sports were gymnastics, volleyball--when I was a senior, the team I was on took fourth in the nationals in volleyball--and mountaineering, rock climbing.

**HATHAWAY**: That was like a varsity sport?

**ALBER**: No, no.

**HATHAWAY**: A club-type activity?

**ALBER**: No, not at all. In an odd thing, I ended up teaching backpacking. I was in a program within the L.A. [Unified School District] city schools, which was a new model for high school education. It doesn't exist anymore, but what happened--

**HATHAWAY**: What was it called?

**ALBER**: Independent Program School, IPS. I think that's what IPS stood for.

**HATHAWAY**: Sounds pretty good.

**ALBER**: And the idea was that people could take classes for less than an hour a day. That is, courses would meet with the frequency of college courses. That would free up time for students to do independent projects. The way it was organized--it was at University High School in West L.A.--five faculty taught all the courses. And of course, California has a physical education requirement, so part of the physical education things that we did were ad hoc. So when I was a senior, I ended up teaching basic mountaineering as a P.E. part of this program. Anyway, the school, I thought, was really great. The faculty involved were fantastic.

**HATHAWAY**: And this was open to anybody at Uni High? Or you applied?

**ALBER**: It was. But because there were only five faculty, they wanted to keep the student-faculty ratio the same as in the regular classes. And so you had to get into it by lot. And there were many more people that wanted to get into it than could be accommodated by the number of faculty involved. It was also just a pilot program.

**HATHAWAY**: So you just got lucky.

**ALBER**: Got lucky.

**HATHAWAY**: By the lottery.

**ALBER**: Exactly. I mean, I was pretty bored and normal.

**HATHAWAY**: And this started in ninth grade, tenth grade?

**ALBER**: Started in eleventh.

**HATHAWAY**: So this is really new stuff.

**ALBER**: Yeah, I had been in a regular tenth grade, and was really ready for something else.

**HATHAWAY**: Actually, it sounds amazingly similar to something I was in for two years, called School within a School, where there's very little class time. And they just suspended it in my senior year, because the rest of the school couldn't seem to deal with the fact that there might be people allowed to wander the halls in between-- It was really just a rather dismal failure from that point of view, but I thought it was great. We designed our own English classes and read what we wanted to. The administration just seemed to find that really difficult. So when they found out we were reading like Faulkner, you know, his more trashy novels, they just got upset with the English teacher and whatnot.

**ALBER**: For us it was [Kurt] Vonnegut. [laughter]

**HATHAWAY**: Pretty similar time period. That's curious.

**ALBER**: Oh, this was great. I mean, I ended up my senior year working at the L.A. [Los Angeles] County Museum of Natural History, in a dig at the La Brea Tar Pits. So I started out sorting microfossils and finding out really what insects were living and got trapped in the tar thirty thousand years ago, whatever, and ended up--I was a volunteer; I wasn't getting paid--actually working in the excavation of the pit. They had this pit in the tar that they were sort of digging down, with grids and everything marked. So I would be in there chipping the tar away from saber-toothed tiger bones or sloth bones or whatever it was.

**HATHAWAY**: And you just fell into that? Sorry, no pun intended. [laughter] You heard about

it through teachers at school? You'd always go out to the museum?

**ALBER**: I can't remember how I heard about this specific dig.

**HATHAWAY**: But you turned it into school kind of credit, too.

**ALBER**: Yeah.

**HATHAWAY**: And you did that on your own?

**ALBER**: That was the most structured part of the independent thing I did. I also took math at UCLA in the time that I wasn't in high school.

**HATHAWAY**: So you still were at school the whole typical school day.

**ALBER**: No, no, no. That was the whole point. You could be anywhere; you didn't even have to be on campus. The structured courses met two or three days a week, and that left the rest of that time to do something else. You know, like one person built a Baja racer automobile.

**HATHAWAY**: Even though it was by lottery, it wasn't by students who were tracked into special classes or advanced classes already?

**ALBER**: No.

**HATHAWAY**: Somebody who was going to end up going the vocational route obviously, or had been in a vocational kind of track, was taking this.

**ALBER**: Well, some people were. The point of the population in the program was that it shouldn't be selected. The idea was to see if it could work as a different model for a general student population in this school. I mean, some people did just, you know, essentially go to the beach and didn't get that much done.

**HATHAWAY**: It's kind of like life, you know, some people—

**ALBER**: Yeah, some people go to the beach.

**HATHAWAY**: You also said it stopped. You were aware that it didn't move from pilot status to being instituted all over L.A. Did you follow it later?

**ALBER**: Not in detail. Why did it stop? I don't know. I imagine-- Well, I really don't know.

**HATHAWAY**: You had some sort of alumni sort of thing maybe, or mentor? There was no fellow--?

**ALBER**: No. I had one particular person. He was the person who got me interested in anthropology, really. And also I think from that, that's what attracted me to the dig at the [Los Angeles County] Museum of Natural History. The guy's name was Milt [Milton S.] Anisman; he's now retired.

**HATHAWAY**: He was a teacher at Uni?

**ALBER**: He was a teacher at Uni, a science teacher. He taught an anthro[pology] course. How many high schools have an anthro course? I mean, he made up this anthro course for this program. He taught biology as well, and really brought the whole field alive in terms of intellectual conflicts. He would present several sides, and present ideas as they developed, rather than just as true.

**HATHAWAY**: You weren't getting that in, let's say, history class? What they might call civics?

**ALBER**: Sure, you see that in history for sure. That may be the major part of the content of history. But the thing that Anisman added to anthro was the technical content of the field, essentially physical anthro. That was what the course was; it wasn't cultural. It was physical anthropology. You had the discoveries of bones, basically, and fossils. There was some paleontology in there, and then human evolution. So God, can you imagine teaching human evolution at a sophisticated level in public schools now? I mean, you'd get a lot of political heat for it in some communities.

**HATHAWAY**: I don't know if they're really bothering anymore. You figure the biology courses still must be the dissect-the-frog sort of situation.

**ALBER**: I did that too. [laughter]

**HATHAWAY**: No, I mean, I'm trying to remember my own. They must have to address evolution in that; they have to, right? You're dissecting an amphibian, a frog-- Start making connections and whatnot. But you're right, I'm sure that they soft-pedal the more theoretical--

**ALBER**: Yeah, I think after I moved, for example, to Oregon, I felt that this sort of frank discussion or description of evolutionary ideas that I had, even in high school, was-- I realized that it was unusual in the sense that when I was in Eugene, Oregon--

**HATHAWAY**: This is your postdoc?

**ALBER**: Yeah.

**HATHAWAY**: Had you lived there earlier?

**ALBER**: In Eugene?

**HATHAWAY**: Yeah.

**ALBER**: No. It turns out that Eugene is a small town in rural Oregon, and there's religious strength in that community. The Baptists are pretty strong in Oregon, and evolution was, well, controversial when I went there. Should it be taught in schools? This was a political battle that was actually going on in public. Whereas when I was in high school, it was something my teacher just taught and really brought to life. Anyway, he made this experience at the natural history museum sort of, I don't know, compelling to me. And actually when I went to college, I was contemplating majoring in anthro and took a number of anthropology courses in my first two years.

**HATHAWAY**: It seems to be a pretty heavy intellectual diet for a senior.

**ALBER**: In high school?

**HATHAWAY**: Yeah, even a private high school, kind of. You know, a special math class at UCLA and the fun afternoon part is spent doing paleontology and digs and--

**ALBER**: Well, I was also climbing and teaching backpacking and teaching climbing. I did my share of going to the beach.

**HATHAWAY**: Okay, then you were a workaholic or you never went to bed or whatever already at that age. It seems awfully active. [tape recorder off]

**ALBER**: We were talking about what are some of the activities in high school that didn't have anything to do with an intellectual environment. I'd say exploring the Sierras was something I did a lot, getting out in the mountains.

**HATHAWAY**: I guess I would argue, though, that if you were teaching it and stuff, it's not just fun. I mean, it was an intellectual experience as well as a physical.

**ALBER**: Yeah.

**HATHAWAY**: Again, do you know how you got interested in--? Was it just a friend or your family who went hiking with you the first time?

**ALBER**: No, it was my half brother [William Alber] up here in Walnut Creek. When I was fourteen, he took me to the Sierras for the first time, and I really got hooked. I started climbing in high school. Again, a friend [John Lynch] took me out to a place in the San Fernando Valley.

**HATHAWAY**: Angeles Crest National Forest?

**ALBER**: No, it's a place called Stony Point in Chatsworth. I didn't really have a good time, but my mother was so horrified by the whole thing, I did it again as a--

**HATHAWAY**: Sure-fire way to horrify your mom.

**ALBER**: Yeah, exactly, a way to rebel. And then I started enjoying it a lot. The places I went a lot were Tahquitz Rock in Idyllwild, Southern California. And then my friend Tim and I did some climbs in the Sierras--technical things.

**HATHAWAY**: And you do this every year, sort of? A lot of your vacations?

**ALBER**: Well, a lot less technical things now, actually. I pretty much stopped technical climbing in graduate school. When I was in high school, for example, I climbed the east face of [Mount] Whitney, which is a couple-thousand-foot wall that you hike into. You know, it was an incredible day, an incredible climb, really fun.

**HATHAWAY**: You did it in a day. I guess you have to do it in a day, you can't--

**ALBER**: Well, we started early in the morning, got to the top. It was a July Fourth weekend. When we signed the register, there were a couple hundred other people that had signed the register that day, but we didn't see anybody because we were on the technical side, on the steep side. We sort of popped up over the top. There was a crowd up there, and people had no idea where we had come from. It was really a weird thing. And then we started climbing the ropes, and it kind of dawned on people. It was a really neat thing, because you actually finish the most difficult things a little bit farther down, but the last move onto the summit from the east face is--You just pull yourself up onto it--it's not a walk--and all of a sudden you're there. It's really exciting.

**HATHAWAY**: Have you done it more than once then?

**ALBER**: I've done that climb once.

**HATHAWAY**: Just once?

**ALBER**: Yeah.

**HATHAWAY**: It sounds the way you're describing it that maybe it's happened more than once. It's made that much of an impression. You speak of it as "You do this when you do that"-- More familiarity with it than just once. I guess with something like that you would need the one experience and you're pretty familiar with it, right? [laughter] Why do it again? It was there; you

did it.

Maybe saying you were kind of intellectual or even using the word workaholic before-- You really can be because you're a teenager. You just seem incredibly active.

**ALBER**: Well, I don't know. I did my homework and I played chess. [laughter] What can I say?

**HATHAWAY**: I guess maybe that was just what other people around you were doing. You mentioned one friend so far, Tim, but I guess I'm trying to see if we can't talk more about just a milieu in which you would be doing all these different things. I even think you say something about it really wasn't that-- Maybe you said, "outside of my intellectual development." Also, maybe you said, "I wasn't really in an intellectual atmosphere," or something like that. I don't know if I misunderstood you?

**ALBER**: Well, I guess my friends were thoughtful people. My best friend was John Bennet. He went on in college to study mathematics. I felt like we talked about serious things.

**HATHAWAY**: Like mathematics perhaps?

**ALBER**: Well, no, we didn't talk about mathematics. Things about growing up, basically.

**HATHAWAY**: Uh-huh. You said something in the first tape too about just always again using-- I think you qualified very heavily the word "outsider" and didn't mean to imply anything about being forced to be an outsider or anything, but just always having that sense of maybe looking in on something because, one, you really had grown up in a different culture and you had this whole other experience and you just don't shed it. But also you used the word "thoughtful" now, that your friends were "thoughtful." Perhaps that was a smaller number of people or a smaller percentage of the high school population, that sort of thing. You didn't mean it in an elitist way, I don't think, or in a way that you were pointed out as on the outside, but just a sense, sometimes—

**ALBER**: I think that in my first year of high school, just in the regular high school curriculum at Uni, most of my friends were sort of considered nerds. Every high school has that group of people, and I find that very dissatisfying. I think that was one of the reasons that I really loved this alternative program is that there were different sorts of people. People were trying to formulate important projects--projects that were important to them--at an early age. Identify things that they wanted to do with their time, and then do them. You know, that process is quite exciting, and you see it in the people around you. The people were more diverse than the people

I had sort of hung out with before. They were more fun. So I really liked it.

The program itself of course was innovative, so it was always under threat. It was outside the standard curriculum, and so we always had a sense that it could be canceled or stopped, and-

**HATHAWAY**: It was.

**ALBER**: It eventually was, yeah. You know, it was a sense of having to prove yourself. I would say UC [University of California] Santa Cruz, where I went to college, had the same sort of mission of being outside the standard educational paradigm and being criticized just for that reason and being put always under a threat that it would be converted to a standard university, without colleges, with grades, with fewer independent projects that faculty and students arranged--basically a standard university. [tape recorder off]

**HATHAWAY**: Clearly, this was a real way of escaping what I guess you felt were a lot of silly or artificial constraints. For instance, there really was, it almost seems like, a lot of pressure to belong to certain groups, or these groups were very clearly defined among the student population. There were the nerds, there were the whatevers, and the whatevers. There was no mixing of the-- If you were this kind of a person, you were this kind of a person. Was that really a strong thing at the rest of the high school, or just something that bothered you that really was a fluid sort of--?

**ALBER**: I guess I don't really remember, you know, objectively.

**HATHAWAY**: In a way, I guess I 'm asking you more subjectively. You felt this? I mean this really bugged you, so this program that came along when you were a junior was a real godsend? Or when it came along, you were just kind of like, "Oh, wow. Great. Let's do this."

**ALBER**: I didn't know what it was going to be like. It didn't exist. I started into it in the first year, so I didn't know that it would be such a positive thing. But in terms of, you know, why I would want to do it, yeah, certainly there were personal reasons.

**HATHAWAY**: You said something about being bored, too, I think.

**ALBER**: Well, yeah. I was more of a shy person; I'm still a shy person. But I was more of a shy person then, and whether social groups were fluid or not, they weren't for me.

**HATHAWAY**: They weren't for you period.

**ALBER**: Yeah. It wasn't that I didn't have any friends, but-- I would say that my feeling about tenth grade is that it was too intellectual. It was missing exactly those things you were asking about. So by the time I get to be a senior, I don't know, I got a C in chemistry, for example. [laughter] I mean, I'm a chemist, but I didn't care about high school chemistry for some reason, and so I didn't do well; I didn't study it. I was doing other things.

**HATHAWAY**: And it didn't matter.

**ALBER**: And it didn't matter. So I didn't end up with a 4.0 [grade point average] in high school.

**HATHAWAY**: But it sounds like maybe this program was kind of like-- Not that you were sitting around worrying about it previous to that, but it was clear to you that that wasn't the goal of what you were doing, in this independent school program. You weren't there to get straight A's so that you could-- You were there to develop some skills or learn some interesting things.

**ALBER**: To learn things, yeah. I mean, I did virtually get straight A's in high school, but you can probably look that up, you know. [laughter]

**HATHAWAY**: Oh, that's understood for all of you. All the people I interview for the Pew, you all got straight A's, unless you say otherwise. [laughter]

I guess one last thing-- Again, this is not "Oh, let's do a psychological profile." You said also as a child, you mentioned the example of having to go to the Japanese school when you were-- And you said you were very shy. And of course that was exacerbated by the fact that you were the only non-Japanese child in this classroom. And you mentioned that you were shy in high school. You said, "I'm a shy person." I guess--and these are first impressions--that's not what I would say. I might say, "Oh, you seem kind of quiet," because you speak quietly, or you may be a little reserved, but I guess shy is not what I-- I wanted to ask you, was this something everybody said, "Oh, you're shy, Tom," or you just always felt--?

**ALBER**: No, I always felt shy. I still feel shy. I'm not very outgoing. In some ways it helps a lot to be shy if you are going to spend hours and hours and hours in a lab, working by yourself late at night.

**HATHAWAY**: You don't miss what's going on, right?

**ALBER**: You don't miss it, exactly right. I mean, if you can't be by yourself, you can't do biology or biochemistry. If you are sort of addicted to constantly talking with people—

**HATHAWAY**: I'm not. I do it for a living. I get around. [laughter]

**ALBER**: Well, it's funny. Then the things that are necessary to succeed change as you go through your career. In the beginning, you know, you have to be able to be motivated to go get the results, and as it goes along, you have to sell the results a lot more heavily. So you do end up being much more--

**HATHAWAY**: I was going to say shyness doesn't seem to be a quality that is going to be prized or that you are going to hang on to in a situation like this. Obviously, you aren't required to be photogenic, and, you know, always have your hair the right way and go to a lot of parties to be a good biologist and to be in a milieu in which you can communicate your ideas and keep the process going.

**ALBER**: Yeah.

**HATHAWAY**: But you certainly need to have some aggressive or social qualities that would get you out there.

**ALBER**: Sure. I find that to be a hard part of what I do now. I don't enjoy giving lectures, for example. I mean, I give a lot of lectures, and I try to be entertaining and thoughtful, but I'm always nervous and--

**HATHAWAY**: Butterflies-in-the-stomach kind of nervous before a talk or--?

**ALBER**: Not that bad.

**HATHAWAY**: Uncomfortable period?

**ALBER**: I used to get butterflies in the stomach. But yeah, just sort of generally uncomfortable

until this thing is over.

**HATHAWAY**: This is one of the downsides and responsibilities of doing what you do, and you'll do it, but you certainly won't-- And when you say lectures, you mean invited kinds of things at conferences, not about conducting part of a class here or something like that.

**ALBER**: Oh, even that. I mean, I want to do it well. Being invited to give lectures at meetings or at universities or wherever is good because it's a measure of recognition. Giving the lecture itself can be a lot of fun, especially if it's going well and you know the audience is there and you're there and there is this thing going on and you know that they're going to appreciate it-- that's fun. And then when they appreciate it, that's fun. And if you get ideas talking to people, that's something I like to do. What I don't like to do is get ready, and-- Now I find that I can do it because I sort of know how to do it. But when I first started doing it, it was difficult because I didn't have a sense that what I was doing would actually produce a product that would be something I would like.

**HATHAWAY**: Or something that they would all like too? That the selling points now are more clear in your mind and you know that because of your wider experience in the field or whatever.

**ALBER**: It's more an issue of how to tell a story that is going to make people think, and I wasn't very good at that five years ago or seven years ago. When I was looking for my first faculty position, I didn't give good job seminars, for example. It was difficult.

**HATHAWAY**: People said to you, "That wasn't very good"? Or you just felt they weren't good?

**ALBER**: I felt that they weren't very good. [tape recorder off]

**HATHAWAY**: I guess we can move on to you going to Santa Cruz. I think that it hadn't been open that long, perhaps a decade. Maybe it was just under a decade when you started going there.

**ALBER**: No. Five years, four years.

**HATHAWAY**: Oh, so you started undergrad in '69?

**ALBER**: In '72.

**HATHAWAY**: Oh, I thought it opened '65, but maybe that was just some official--

**ALBER**: I thought it was '68, but from college to college it differed when each one opened up.

**HATHAWAY**: I just want to ask about this mathematics thing. I guess you were taking undergraduate classes at UCLA as a high school student, or involved in some sort of special program to encourage--?

**ALBER**: Oh, yeah. The L.A. city schools had an arrangement with UCLA that selected students could take two classes a quarter. I just took one, and it was just calculus. It wasn't anything fancy.

**HATHAWAY**: Oh, okay. You just picked calculus because it was one of the ones offered that looked interesting?

**ALBER**: Well, no, I liked math, and it was the next thing to do in math, and why not take it at UCLA?

**HATHAWAY**: So it had really little effect on your outlook? Or made you hate mathematics?

**ALBER**: Oh, no. I thought I might major in mathematics when I went to Santa Cruz. I started taking a math course my first quarter there, and I could not understand the professor. His German accent was so thick, I couldn't understand it, and I just gave up. I mean, for the life of me, I couldn't understand what he was saying in the lectures.

**HATHAWAY**: This was like another calculus-type class?

**ALBER**: I can't remember what it was. Number theory or something.

**HATHAWAY**: So you just bagged the whole thing. Other things became more interesting.

**ALBER**: Other things became more interesting, that was the key.

**HATHAWAY**: I mean, I think we have a good explanation already on tape. People could infer why you went to UC Santa Cruz instead of, let's say, Princeton [University] or UCLA or something like that. It's a nontraditional kind of program. **ALBER**: Well, I specifically visited the places I was considering: MIT [Massachusetts Institute of Technology]-- so that will give you a sense of how I thought about myself, right. I'm going to go to MIT. So I went to MIT. My father took me around to all these places. So the few places I was considering were MIT, Stanford [University], Santa Cruz. MIT, yeah, it was fine, but at the time, it looked like there was a lot of stone, and when I-- On the plane, when we took off from Logan [International] Airport leaving there, I couldn't see any mountains, so bag that.

**HATHAWAY**: There are the Berkshires.

**ALBER**: Stanford was fine. That was the second place I visited, and it was sort of my first choice after I visited there. But what actually happened is my father had a friend at Stanford. We borrowed his car and drove to Santa Cruz just for an afternoon and walked around. And I met people there that were just very interesting. "Rick" [Cedric I.] Davern ended up being my professor for Biology 1. I met him in his lab, just walking through one of the buildings, and he was just an interesting person. I felt like this could be a very stimulating environment.

**HATHAWAY**: And what did your dad think about that? I mean, there must have been some kind of stark contrast at some point between walking around campus at MIT and walking around campus at UCSC.

**ALBER**: Yeah.

**HATHAWAY**: And certainly the reputation of the one over the other, because the other was new, never mind perhaps it hadn't quite got the reputation that it had, let's say, when I was thinking of applying there as kind of what I would call a stoner school. You really didn't have to do anything to get through.

**ALBER**: Well, that was true, but half the entering class had 4.0 high school grade point averages.

**HATHAWAY**: It had attracted some pretty interesting faculty all across the board.

**ALBER**: Yeah, and they were really committed to working with students individually, much more so than now. They got exhausted while I was there. It's an interesting place.

**HATHAWAY**: So there was no opposition?

**ALBER**: Oh, my God. Well, my father, you have to under-stand, was very supportive. He said, "Go anywhere you want to go, and I'll take you around to all the places." And you know, he never graduated from college. He's been a maverick. He did what he thought was important. So he was, I felt, generally supportive. I guess I still feel that. He was not judgmental. And if he was, he managed to conceal it.

**HATHAWAY**: Did a good job of it.

**ALBER**: My mother, on the other hand, when I made my decision to go to Santa Cruz-- I had picked her up at work; she worked at UCLA. We were driving down Sunset Boulevard, and I said, "Mom, I have decided to go to Santa Cruz." Well, this is sort of a microcosm, maybe, of my relationship with my mother. But first of all, I had been using the car that day, and so I picked her up in front of her office, but she was nervous when I was driving. So she always drove, even though she was one of the worst drivers in the world. I mean, talk about her being nervous when I drove, my God. Anyway, so she's driving down Sunset Boulevard. It's a little after five o'clock, so there's traffic, right, and I said, "Mom, I've decided to go to Santa Cruz." And she's trying to keep her eyes on the road, and just cry hysterically at the same time. [laughter] So she really was upset. She thought I was going to ruin my life and waste my life, and why am I going there, dah dah dah. So she, in fact, dropped me off in Santa Cruz and didn't visit till I graduated. So it was not something she approved of.

**HATHAWAY**: UCLA was conventional, I suppose, when she was an undergraduate there. But she had a pretty non-conventional view of the world too. It's curious-- But she also, you mentioned I think on tape, purposely moved to the apartment that you moved into when you got to the States because of the school. That was the top-- It didn't matter: price, cost, where she wanted to be, close to family or not. It was just to put you in that school.

**ALBER**: Well, it was a main consideration.

**HATHAWAY**: Such an important--

**ALBER**: Yeah. So I guess she was--I mean she didn't say this--worried that I was wasting a really good opportunity.

[END OF TAPE 2, SIDE 1]

**HATHAWAY**: I don't know if I have anything particular that I see that needs to be covered about being at UCSC, and would just leave kind of an open question of what do you think was important about that four years. I take it that you did it in four years?

**ALBER**: So Santa Cruz.

**HATHAWAY**: You already mentioned teachers, high school people, particular people influencing or just opening up your eyes to things. But other than that I don't know that—

**ALBER**: I mean, we could spend days talking about college, because it's just a formative time for everybody, no exception for me.

**HATHAWAY**: I just know how a particular-- Okay, then I would ask you, what was the most formative thing that happened to you? That doesn't work? You don't want to answer that one?

**ALBER**: No. [laughter] So you were saying, what do I want to say about Santa Cruz.

**HATHAWAY**: Sure.

**ALBER**: Okay. One of the premises, really, or one of the ideas that the place is based on is that the students are actually trusted to know what's important or find out what's important. Certainly, I mean, there are course requirements for majors and things like that, but when I was there there were fewer requirements than many other places.

**HATHAWAY**: You mean instead of five, six core courses or something to be a chem[istry] major, there were maybe three—

**ALBER**: There were fewer, right.

**HATHAWAY**: But you had to do projects or something. You would design those--

**ALBER**: Well, also there were courses that either were required or strongly recommended in each of the colleges. And in my college, which was Crown College, there was a component on science and Western civilization taught by very dynamic faculty. People who--

**HATHAWAY**: Who were they? Were they historians? I mean, a mix of philosophers, scientists, biologists?

**ALBER**: Dick [Richard G.] Olson, history of science; [J.] Peter Euben, politics; Jack [John H.] Schaar, politics. I think those were the main people.

**HATHAWAY**: That's kind of like a core--?

**ALBER**: Yeah, Schaar was in Cowell [College], or he was in a different college, but Olson and Euben taught the Crown core courses.

**HATHAWAY**: All of-- I mean, you couldn't possibly be in Crown without running into them at least once.

**ALBER**: No, you could have. They weren't required, but they were part of the college offering, part of the college identity. And a lot of people took them.

**HATHAWAY**: Do you recall what you were reading, or what they were discussing?

**ALBER**: Oh, God. Herbert Marcuse and Plato and Aristotle, Hegel, Kant, Nietzsche--

**HATHAWAY**: Their more esoteric theories of knowledge and science, or their political theory?

**ALBER**: --Thomas [S.] Kuhn, yeah. It started with the Greeks, let me put it that way. [laughter] It was philosophy and history, and the relationship of technical development and ideas to

political ideas and processes: really, the role of science in Western civilization. I remember being so immersed in this for one quarter that I didn't really do much work in the lab.

I started research in a chemistry lab in my sophomore year. A friend of mine [James Breitmeyer] from freshman year had gone out to Cold Spring Harbor [Laboratory] to be in the undergraduate program there. He came back thinking it was really great.

**HATHAWAY**: Was it just a summer program?

**ALBER**: Summer program, right.

**HATHAWAY**: Was it competitive?

**ALBER**: Competitive, yeah, really competitive. He worked with a guy who was involved in discovering restriction enzymes. It was really the early days of restriction enzymes, and he just had a blast.

**HATHAWAY**: Who was this?

**ALBER**: [Richard J.] Roberts. He came back and said, "Gee, you really ought to do research if you're at all interested in science because that's what it's about. You better find out if you like it."

**HATHAWAY**: He was more a straight biologist, as opposed to a chemist?

**ALBER**: Yeah. His major was biology.

**HATHAWAY**: And you really were a chem major? You weren't a biochem major?

**ALBER**: I was not declared--

**HATHAWAY**: You were just enjoying--

**ALBER**: --until later, yeah.

**HATHAWAY**: You would even set the lab work aside to get into reading Aristotle and Marcuse. [laughter]

**ALBER**: Well, it wasn't that. It was so threatening, really.

**HATHAWAY**: The content of the course?

**ALBER**: Yeah, the intellectual ideas that science is the enemy and is the source of problems rather than solutions to problems.

**HATHAWAY**: That was the perspective of Olson and Euben? That was what you were getting out of reading Aristotle's *Politics,* or Kant on [*Critique of*] *Pure Reason?*

**ALBER**: Well, that was certainly a lot of the content of some of the readings that we did.

**HATHAWAY**: You mean the secondary-- I mean, people writing about these folks? Or this was all just primary--?

**ALBER**: Oh, you read Marcuse, and you go, "Oh, well, this is interesting." And if you're thinking about maybe being a scientist or doing science, and you're reading somebody who says this is not anything but a socially destructive activity, then--

**HATHAWAY**: Wasn't that maybe kind of countered by other--either the writings themselves-- I mean, I don't think Kant would have really come up and said-- His concept certainly of how people even just organize knowledge, and therefore put scientific knowledge at the top--it's all supposed to be very rigorously rational. It wasn't necessarily a negative thing, right? He might have been critical of certain parts of it or whatnot, but-- There must have been some counterweight to somebody like Marcuse. I mean, even Kuhn seems to me somebody trying to be more balanced in that approach.

**ALBER**: Right, I would say that the authors that I listed were authors that I read over the course of three or four years in college. They weren't all the same quarter. So you didn't get this balanced feeling, essentially.

**HATHAWAY**: And Olson and Euben had a specific slant?

**ALBER**: Yeah. I was a sophomore in college, and I didn't have a framework really to put their perspective into. It was just what we were studying, what we were reading in class. What I was trying to do is develop that framework. You know, it seems obvious now, but I didn't really understand the difference between political decisions and uses of technology that occur in a democracy, versus the idea that there is a technological imperative that if something is possible, it happens, and therefore it's the fault of the person who developed the technology--that the events are the fault of the scientist or the engineer who developed the atom bomb, and not that a political decision was taken in a particular historical context to use this technology in a certain way.

**HATHAWAY**: Do you kind of see it as two opposed ways: one that absolves the scientist from the work and the results of or the uses of such knowledge versus one that implicates them as the major person to whom fault should go? Are you saying you kind of hang to an equilibrium, and saw those as extremes?

**ALBER**: That's an equilibrium. I would say, yes, as a scientist, you have to take responsibility for the uses of your particular research. But you don't always know ahead of time what those uses are going to be. And then as a citizen you have to participate in deciding at whatever level how the world is going to be. Whether it be the uses of technical knowledge that you had something to do with--most of it, of course, you had nothing to do with. I guess personally, I wouldn't work on developing weapons intentionally, you know, in our current political situation.

**HATHAWAY**: You pointed up the hill. We're at Stanley Hall. So up the hill is [Lawrence Berkeley Laboratory]—

**ALBER**: A [nuclear] weapons lab.

**HATHAWAY**: --a weapons lab.

**ALBER**: And you know, I don't agree with the decisions of the people who do that with their lives. But I don't anymore see science itself as the enemy, as a destructive force. I see human beings as making stupid decisions about how to use the information, but--

**HATHAWAY**: Do you see that as--? I think this is really fascinating--

**ALBER**: It's kind of philosophical though. [laughter]

**HATHAWAY**: I certainly think that that's as important as talking about the importance of certain kinds of work you did in your lab, you know. Also, just how you see that fitting into a much larger context.

**ALBER**: Well, I think that the point to make is that I was exposed to these ideas. By the time I was a senior in college, I took a course called The Sources of Anti-Science, and it was taught by Olson, the historian of science. You know, we read Tolstoy and other sources that argued that scientific rigor was antithetical to the human spirit and it was also destructive of social relations. Certainly as a scientist, you feel that. I mean all those hours in the lab, and late at night, and there aren't other people around, you feel alienated, that's for sure. So there's some resonance with each person's personal experience, and the fact that you spend a lot of time by yourself. On the other hand, by the time I took that course as a senior, I was doing the reading mostly to become informed rather than as a threat to my own day-to-day activities. When I first was exposed to these ideas as a sophomore--

**HATHAWAY**: You were kind of scared by it.

**ALBER**: I just didn't go to the lab anymore.

**HATHAWAY**: You went and thought about whether you were going to go to the lab.

**ALBER**: Right, exactly. If an undergraduate student did that in my lab now, I would be completely intolerant. I mean, I would be pissed. So I really credit my undergraduate lab and research adviser for being incredibly tolerant.

**HATHAWAY**: Maybe you said his name?

**ALBER**: No, I haven't said his name. It's Tony [Anthony L.] Fink. I didn't get much done in Tony's lab.

**HATHAWAY**: Do you think the function of undergraduates in labs anyway is productivity? Or

do you think it's kind of continuing the line? Do you know what I mean? Exposure and-- So that you kind of catch these people who may be curious at the right time and help them into the process of becoming a scientist?

**ALBER**: I don't expect undergraduates in my lab to be very productive. Maybe that's just because I wasn't. I have had very productive undergraduates in my lab. I like to have undergraduates in my lab because they are often very thoughtful.

**HATHAWAY**: You mean that they get other people to stop and think?

**ALBER**: I'm sorry, I didn't understand the question.

**HATHAWAY**: You said they were very thoughtful. Do you mean they get the rest of the people in the lab to kind of put the brakes on them so that they stop and think as well?

**ALBER**: No, they make me stop and think. [laughter] I don't care.

**HATHAWAY**: You don't care about the rest of the damn people in the lab, right. [laughter] Let them find their own way.

**ALBER**: No, it's not that. I think what happens more often than not is that graduate students in the lab, or postdocs in the lab, are more concerned with putting out the product. It's not that I'm not concerned with putting out the product, but they're not really worried about undergraduate education or concerned about what these people are getting out of their experience in the same way that I would really like them to be able to think about a problem and become more linear and start to learn how to do science rather than stuff these little facts in their brains.

**HATHAWAY**: Just to follow this through, do you have undergrads here?

**ALBER**: Well, my lab here is very new, and so we're not really set up, and I have not taken undergraduates here. But I've had really good undergraduates in Salt Lake [City at the University of Utah]. I always had undergraduates in the lab in Salt Lake.

**HATHAWAY**: They just found you, as opposed to you-- Or you really look for them?

**ALBER**: There's some of both. In Salt Lake, I would approach TAs [teaching assistants] in certain courses and say, "Who's good?" and go talk to them.

**HATHAWAY**: That was kind of an ego thing as well for them, I'm sure: "Oh, here's the big prof who's maybe even just a little bit interested in--"

**ALBER**: Well, it's a different culture there. You know, if you're at [University of California] Berkeley or if you're at MIT or someplace, the profs are considered big profs, whether they're big or little. But if you're at [University of] Oregon or at [University of] Utah, it's a medium-level state university and the people are there for very individual reasons and their culture is different.

**HATHAWAY**: They are there to teach, I mean, to be there for student education.

**ALBER**: No, I don't mean the faculty, I mean the students.

**HATHAWAY**: Oh, okay.

**ALBER**: The student culture at Berkeley may be more intellectual. Or at MIT maybe the students are thinking that they are there to learn what's at the cutting edge, and to become well-paid or famous engineers and scientists. In Berkeley, it's broader, you know: historians or whatever, deal with the great ideas. There are students like that at Utah, but it's not the dominant culture in any sense.

**HATHAWAY**: I guess I didn't mean it in the flattering sense, but just that somebody would be approached by the professor of a course, as opposed to just the TA, and, you know, "Would you be interested in work?" That must be kind of a boost. When someone notices my work or my interest-- I mean, if there was a spark there, that may ignite it. That's maybe not a good metaphor.

**ALBER**: So my undergraduate research experience was on enzyme reactions, the mechanisms.

**HATHAWAY**: You just sought this guy Fink out after your friend told you what a great time he had at Cold Spring Harbor and how you shouldn't miss this if you were really going to do it this way.

**ALBER**: Yeah. So I made a list of people that I might be interested in and went around to each of them, and Fink was the first person that said yes. And it was nothing more informed than that.

**HATHAWAY**: And you stayed in that lab for two or three years?

**ALBER**: Yeah, for three years.

**HATHAWAY**: Except for maybe a couple of weeks--

**ALBER**: Couple of quarters-- [laughter]

**HATHAWAY**: --where you were wondering about doing that.

**ALBER**: Yeah, and I worked summers in the lab.

**HATHAWAY**: Paid, I take it.

**ALBER**: It paid not very much. Enough to live for the summer, and kept me from going back to L.A.--yes!

**HATHAWAY**: You just didn't like the city compared to the country, I guess?

**ALBER**: It's hard to be independent and on your own in college and then go back and be with your parents. In my case, it was with my mother. The thought of her telling me what to do was difficult.

**HATHAWAY**: Or the thought-- Maybe she was living alone? Or maybe she was married?

**ALBER**: No, she didn't remarry. She was living alone.

**HATHAWAY**: That may have been also different from a lot of people who maybe went home with six other kids in the family and parents in and out the door. They were just one more person to be part of the family, whereas your return doubled the population in a sense.

**ALBER**: Well, the first summer in college, I did go back to Los Angeles, and she spent much of the summer in Europe. That actually made it quite easy. I worked painting houses.

**HATHAWAY**: And this is still the same apartment you moved into when you moved here?

**ALBER**: Yeah, yeah, but it was a small place--pretty small for both of us. By that time, I was off on my own. I really liked being in Santa Cruz for the summers. I worked in the lab. Tony's lab was concerned with understanding how enzymes speed up chemical reactions. The thing that was very lucky for me is that his approach involved developing a new way to study this process. Specifically, he was studying enzyme reactions at very low temperatures. The idea was that at low temperature the reactions would be slow enough, or in fact almost stopped, so that you could observe intermediates in the reactions using spectrophotometric techniques. The controversial part of the work was that to keep the whole system liquid-- Enzymes work in liquid. To keep things from freezing, he would transfer these proteins to a mixture of water and DMSO--basically water and organic solvents—or ethanol or methanol. His work was criticized because people had thought that these proteins don't work in the presence of organic solvents. There aren't organic solvents in cells to the same concentrations.

**HATHAWAY**: They are maybe temporary--I want to say fleeting, but that's not scientific either. These solvents are just there for the moment that they are needed or that they're produced--

**ALBER**: Right. Like ethanol is a byproduct of metabolism in certain cells, but you don't get to 60 percent ethanol. The cells die by the time you get there.

**HATHAWAY**: It disappears quite quickly. I take it it's there in part of the process but is immediately broken down again.

**ALBER**: Yeah, exactly. So the work was viewed with a great deal of skepticism because people felt that maybe some of the results that were being obtained were artifacts of the high concentrations of organic solvents. So that was a constant challenge in the lab that-- People did experiments to try to show that events that were being observed under these bizarre conditions reflected events that you would observe a lot faster in water alone. My interest was sort of piqued by discussions in the lab where people would say things like "Well, it's interesting that

we have the absorbent spectrum of this intermediate and this enzyme reaction, and that indicates that this chemical group is in a more hydrophobic environment in this intermediate, but we don't know exactly where it is. What we'd really like to know is what is the three-dimensional structure of this intermediate." That is, we want to know the x-ray crystal structure of this enzyme caught in the act of catalyzing a reaction. You sort of trap the intermediate by lowering the temperature enough so that there's just not enough energy for it to break down. So my senior year, I started to try to see if crystalline enzymes could be induced to start chemical reactions, then stop. That is, could you trap intermediates in enzymatic reactions when enzymes were in crystals, rather than being in solutions.

**HATHAWAY**: So you'd make them in a, quote, "normal" way that some of them were being made to crystals in other situations, in other labs, and then throw them into this supercold—

**ALBER**: The idea is you would want to have the crystal in organic solvent; you cool it down and add the substrate that normally would be broken down in a few milliseconds and then see if you could show that the reaction was trapped, say halfway through.

**HATHAWAY**: They were doing [x-ray] crystallography work in Fink's lab?

**ALBER**: Not at all. That was the problem. What I was about to say is that we had no idea how to grow crystals.

**HATHAWAY**: And you were an undergrad and you just decided you'd go do this? Or you'd figure it out?

**ALBER**: No, I mean that was the information that people in the lab really talked about. And it would come up over the years again and again: "Well, we've got this information and it's telling us this about this step and this reaction, but to really prove it what we need to do is x-ray crystallography and figure out how to do it at these low temperatures." We didn't know how to grow crystals. I didn't know how to grow crystals. And so, in fact, I didn't grow crystals.

Instead, what I did was make precipitates of proteins--where the protein was still solid but it was just an amorphous precipitate--and started doing experiments. They were pretty off the mainstream in the lab, and so I ended up getting time on the equipment late at night. I strung a climbing hammock from the rafters, and would take time points through the night basically by reaching over, taking a pipette, taking a sample out, and then analyzing it. It is bizarre. But what happened at that time was a person at Oxford [University], Greg [Gregory A.] Petsko, started to develop methods to do crystallography in aqueous organic solvents at low temperature.

**HATHAWAY**: He had read Fink's work? Or there was a whole other area of people trying to--?

**ALBER**: Yeah. It was a very small field. One of the proponents was a man named Pierre Douzou in Paris, and Petsko had met Douzou. Petsko was in David [C.] Phillips's lab at Oxford. Phillips and Petsko started to try to show that you could transfer crystals to solvent that would stay liquid below zero and that the crystals would still diffract x rays. Petsko published a paper on this in the early seventies. He and Fink communicated.

**HATHAWAY**: Do you know who initiated that? Was that Fink?

**ALBER**: I used to know. I don't remember, to tell you the truth.

**HATHAWAY**: But obviously, this small-enough group of people work in the field, and both of them realizing they were interested in an area where other people were going, "This is insane" or "This is the wrong way to go"--Certainly they would have found each other out sooner or later. Followed each others' work for a while.

**ALBER**: What happened was that I ended up going to Petsko's lab. He had moved to Wayne State [University]. I had amassed enough credits to take a quarter off and go to Wayne State. Greg was doing an experiment on a crystal of elastase--this is a serine protease--trying to trap an intermediate in a crystal at low temperature. I had done very similar experiments with these precipitates, with a different serine protease. Fink and Petsko decided that they should collaborate. So I got to go out to Detroit.

**HATHAWAY**: You were paid?

**ALBER**: No, I was an undergraduate, so I wasn't paid.

**HATHAWAY**: So you got credit?

**ALBER**: Yeah, I got credit.

**HATHAWAY**: Which you didn't need, obviously, because you had extra--

**ALBER**: Well, I did actually. I needed a course to get all the requirements for my chemistry major. I didn't need the credits, but I needed a particular course that was only offered in the winter quarter--it was physical chemistry lab--and they accepted the notion that working in an x-ray crystallography lab was equivalent to physical chemistry lab.

So I got out to Detroit. And that in itself was an amazing experience. It was sort of my urban blight experience. I lived in the inner city.

**HATHAWAY**: I guess Bel Air in L.A. doesn't count as urban.

**ALBER**: So Wayne State University is inner-city Detroit, and I lived right near campus. There was a red-light district down the street. The Burger King down the street had an armed guard behind the counter to prevent robberies, and people were definitely afraid.

**HATHAWAY**: The racial disturbances in Detroit had been later than the other ones, I think, right? I guess they still would have been four or five years earlier, though.

**ALBER**: It was earlier and people were still armed and still—

**HATHAWAY**: But they were the worst, I suppose--

**ALBER**: --very frightened.

**HATHAWAY**: --worse than Newark and worse than Los Angeles in 1965.

**ALBER**: Yeah. So I was there for a winter. Greg Petsko is incredibly enthusiastic and energetic. His style contrasted with other people I'd met. He was a great sort of research person to work with. He had a lot of faith that even though this experiment had never been done before, that it was going to work.

**HATHAWAY**: And he was looking at your coming there, not-- You weren't just going to be some sort of intermediary, somebody who carried the communication in person back to Fink. But you had already done some of what we might want to term off-the-beaten-track experiments or work. You were bringing experience to Detroit with you that he wanted to at least see, or see what you were doing?

**ALBER**: Right.

**HATHAWAY**: That's kind of an odd twist for an undergrad. I'm not saying there aren't some people who got lucky, maybe, or were in on something that happened. But this, again, seems to be something that you either developed with Fink, or you just told him this is what you thought you should do, and because you were an undergraduate he said, "Yeah, yeah, sure." I want to get a better sense of this without pushing the "Oh, wow, this is amazing: you're twenty years old, and you're doing this," as opposed to getting at what it is that affords even an undergraduate the chance to get at the equipment, even if you were forced to do it midnight and after.

**ALBER**: Well, you know, I feel I had a pretty small role in this. I guess I was useful to Greg in the sense that I had at least had this experience--although I wasn't very productive--of being around people who were studying enzymatic reactions at low temperatures in solution. These types of experiments are required to define the conditions for the crystallography. That is, you have to know what temperature and how much substrate to add and whether the methanol is going to speed up the reaction so much in the crystal that it can't be observed in the time that you had to collect the data, and things like that. There's an awful lot of work for this low-temperature crystallography that has to be done ahead of time to define how to do the experiment. And I had been in a lab that defined the conditions. Greg, on the other hand, had developed the procedures, the protocols, for doing the crystallography at low temperatures, but hadn't dealt with all the reaction side of things at all.

**HATHAWAY**: Or maybe on just the one--

**ALBER**: Elastase. No. In fact, he hadn't done any of that work at all. He'd just figured out how to get the crystals down to low temperature.

**HATHAWAY**: Without reacting with anything. In other words, he wasn't watching any kind of interaction. It was just pure elastase that he was doing.

**ALBER**: Right. The challenge is to keep the crystals from disordering. Often when you transfer them from one solvent to another, or you lower the temperature, they explode or they dissolve and you can't collect the data anymore. So he'd figured out how to do that. I wasn't in any sense an expert on cryoenzymology, low-temperature enzymology. But I had just a little bit of experience, and I could get away. That's sort of what I was doing there, and I had no experience in crystallography.

**HATHAWAY**: But neither did anybody else it seemed in Fink's lab, right?

**ALBER**: Nobody in Fink's lab did. But of course Petsko is a very good crystallographer.

**HATHAWAY**: So you were going to bring that experience back supposedly, or at least to have some exposure to it to—

**ALBER**: No, it's a very specialized area, so I wasn't planning to bring that technique back. It can't be learned by an undergraduate in a few months. But I was just there to help with the experiments, and, you know, basically make sure-- As I say, my role was small.

So Greg sort of set things up and got them going, and he would tell me what each thing was and I would try to keep the thing running. By the end, I was getting to the point where I could start to set things up with his help. We would sort of trade off being there at two in the morning to make sure the thing didn't freeze or whatever, just while the data collection was going. You read the numbers that come out of a computer printout, and then I would sit and plot them out and do some analysis. But really Greg was the person who was doing this.

**HATHAWAY**: I don't mean to suggest that at the age of twenty you really are one of the founding parents of--

**ALBER**: Of cryocrystallography? Not at all.

**HATHAWAY**: Or claiming you're finally making the first successful-- You certainly were involved in it. I guess what I meant was that it seems to me that if Fink's work is coming under a lot of criticism, and Petsko was kind of starting out from the other end of realizing that maybe it can be done and working on it, to say to the twenty-year-old, "You go there and figure this out because you're free" still seems-- Not special, not "Oh, you were recognized as the next genius in the field." It still seems to mean that you had already developed some sort of scientific repertoire, biological repertoire, chemical, whatever, at the age of twenty. That's pretty advanced, it seems to me. I'm trying to get a sense of where that came from or how, trying to get to talk more about these weird precipitants that you were doing, that nobody would let you get on the equipment until late at night, so you lived in the lab in a hammock for a while.

**ALBER**: It wasn't that bad. [laughter]

**HATHAWAY**: You didn't take a shower in the men's gym? You went home to your dorm room every once in a while.

**ALBER**: Yeah, I mean, I'm just saying I did do experiments overnight. It wasn't that I lived in the lab.

**HATHAWAY**: This was before you went to Wayne State that you were doing these things?

**ALBER**: Yeah. You know, when I applied to graduate school, I applied in history and in the sciences, so I was not at all committed to being a scientist. I thought I would probably move to San Francisco with friends, get a job, and see what it was in the world that I wanted to do next.

**HATHAWAY**: Hang out in the Haight[-Ashbury district].

**ALBER**: Exactly. Actually, it was the Mission [district] at the time. Well, that's where you could afford to live in San Francisco. [laughter]

**HATHAWAY**: Well, now it seems to be back to where it was--I was just there yesterday. Stuck in time?

**ALBER**: The Haight? Yeah. But even when I started my senior year in college, I had this set of science courses that I'd taken. I had some research experience. I had come through some math and set that aside and done anthropology and set that aside and had been seduced by certain kinds of political theory, historical fields, history of science.

**HATHAWAY**: You mean as a thing to pursue? Like just maybe for fun, or an academic degree, or even as an academic?

**ALBER**: Yeah. I mean, I had lots of interests is all I'm saying. An odd thing at Santa Cruz is the faculty in the social sciences were sort of amused and encouraging that someone with a chemistry major would take these courses. The people in the sciences didn't automatically say, "Tom, you're not focused enough." They were tolerant. It was still an idea that you're there to get a broad education, not to go to a vocational school necessarily.

**HATHAWAY**: You're in a sense coming back for the second half of your senior year from

Detroit, right?

**ALBER**: Yeah, so I came back. After the experience in Detroit, I didn't have any question of what I wanted to do. I had gotten a fellowship to go to graduate school, and that actually opened a lot of doors.

**HATHAWAY**: In any field?

**ALBER**: It was in the sciences.

**HATHAWAY**: Was that at MIT?

**ALBER**: No, it was a Danforth [Foundation Graduate] Fellowship.

**HATHAWAY**: So you could use it anywhere.

**ALBER**: Yeah, actually, I could use it anywhere. So it was in any field.

**HATHAWAY**: You mentioned you'd applied to grad school for history of science. And you get back from Petsko's lab, and that experience was, like you said, no real choice. You didn't have to make up your mind anymore; your mind had been made up because of that experience. But you still went ahead and applied to a few other programs, maybe just in case, or--?

**ALBER**: Well, it was all happening at the same time. So I had applied to Harvard [University] and Cornell [University] in history of science. It also helped that I didn't get in.

**HATHAWAY**: To either?

**ALBER**: Yeah.

**HATHAWAY**: Do you think it was the UCSC thing?

**ALBER**: No, I was pretty naive.

**HATHAWAY**: About? You went to an interview or you talked to professors in the program in both places and they just--?

**ALBER**: No, I didn't go. I didn't even get that far. My application was rejected. In retrospect, it just was very naive, the sorts of things I was writing about.

**HATHAWAY**: [Have you] saved a copy? I'm just curious as to why they-- Somebody with your background would be-- I can see how maybe you flunked the GRE [Graduate Record Examination] in history or something. [laughter] I don't know what their criteria is, especially at Harvard or Cornell. Somebody who might write a naive application as a senior in college would be still an interesting prospect, I don't know.

**ALBER**: I don't know. But anyway, I got this graduate fellowship, and all of a sudden "Gee, I could be paid to go to graduate school, so why not?" And even then, I wasn't going knowing that I was going to be a scientist. In sciences, I had just applied to places on the East Coast because I had never lived out there and I wanted to see what it was like. Maybe this will give you a little better idea of where I was coming from. My two top choices were Yale [University] and MIT. I felt the program at Yale was more supportive. But I felt that the intellectual environment at MIT was better, and in particular the fact that Harvard was right there--and there were other schools in the Boston area--would be really stimulating, because I would have time to go to lectures and—

**HATHAWAY**: Certainly for biology and chemistry and biochemistry perhaps Cambridge was perhaps the center of the universe, or one of them, let's put it that way. Two or three, maybe out here still in the Bay Area.

**ALBER**: The things that attracted me were not just those fields. I was essentially planning to go to lectures given by historians and people in politics and things like that. I mean it was really silly. I got to MIT. I picked out a set of courses in the catalog like I was still an undergraduate. I went to see my adviser and he says, "You're taking a, b, and c. Do you have any questions?" And I said, "No, thank you." [laughter]

**HATHAWAY**: Wasn't Petsko your adviser?

**ALBER**: No, Greg moved to MIT during my third year there. The adviser that I'm talking about

when you first get there is your first-year academic adviser. They tell you what courses to take.

**HATHAWAY**: This is the chem[istry] department?

**ALBER**: Biology.

[END OF TAPE 2, SIDE 2]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **16 July 1993**

**HATHAWAY**: This is our third session and you're just starting your graduate career. Actually, maybe-- You seemed a little reluctant to talk about it, or you really just didn't know, but you had also applied for the history of science program. And you didn't even get to a point-- They just kind of flat out said, "Don't bother. We're not interested." And your explanation was that what you wrote--everybody has to write this kind of "Why I want to go to grad school in"-- was naive. Actually, I kind of pushed you to talk about it a little more, and you didn't seemed interested in doing so, or willing. I'm more curious about getting some information about these history of science programs at Cornell [University] and--

**ALBER**: Harvard [University].

**HATHAWAY**: --Harvard you applied to. Especially, of course, the Cornell one, because it has such a reputation. It has a reputation depending on who you are as a very, very wonderful program or as a very, very awful program.

**ALBER**: What's the reputation of Cornell?

**HATHAWAY**: Just very dogmatic in its approach, and run by one person. That's the negative side. I won't pretend that I'm not on that side. And then there is the other side that it is almost like a scientific program. That's why it's so wonderful.

**ALBER**: Well, this was twenty years ago--

**HATHAWAY**: That's when this guy was starting to run it.

**ALBER**: You know, I wrote an essay. My application went in. People wrote recommendations. I mean, I have no idea why they rejected my application. They don't write you a letter saying why they don't want you.

**HATHAWAY**: But you had a pretty good background, and you certainly had no problem getting into a chem[istry] program at something like MIT [Massachusetts Institute of Technology] and getting a Danforth [Foundation Graduate Fellowship] scholarship, which could be used for anything, right? You could have gone to study Restoration literature. It does seem a little strange. Unless you wrote this really bizarre proposal-- [laughter]

**ALBER**: I don't have a copy of it.

**HATHAWAY**: Okay, I just thought I would try. I won't pursue it any further.

**ALBER**: Well, I think also by the time I had to make a decision about what I was going to do it was really clear that science was more interesting and would keep me up late at night, whereas history was more one step removed from what I wanted to do.

**HATHAWAY**: It's not the doing of it itself, it's the looking at the doing of things, right, which some of us are better suited for perhaps than others. I guess I have also kind of stressed that part because I don't think most practicing scientists get into science or develop an appreciation for science the way you did. A place like UCSC [University of California, Santa Cruz] was really from that--

**ALBER**: Well, it was tolerated there, and my undergraduate research adviser [Anthony L. Fink] tolerated it. And my political science professors encouraged it.

**HATHAWAY**: It's almost as if you could learn what they had to say about science as a part of culture or something—

**ALBER**: Yeah.

**HATHAWAY**: --by doing it yourself. So that's, at least so far as I know, still the beginning of this approach, or background, to your eventually going into science-- And that you went so far before your experience in Detroit as to really actually go the other way-- It's almost as if it is clear that you have some sense that you are one of those people who, while maybe you like the doing of it, you still always have this perspective of being interested or curious about how it's done--this one step removed that you mentioned.

**ALBER**: Yeah. But frankly, that's not- - Well, I used the word encouraged, but it's not tolerated within science.

**HATHAWAY**: No, not until you are eighty years old, and then you can write about your history and the great things you did.

**ALBER**: But then it's boring. [laughter]

**HATHAWAY**: Some of it's boring, but actually some can be pretty good. I 't m trying to think of an example; actually one doesn't come to mind.

**ALBER**: A famous example is *The Double Helix.*

**HATHAWAY**: Right. But that's propaganda. I guess I shouldn't be expressing my views.

**ALBER**: Well, isn't it all?

**HATHAWAY**: I don't know. I think some people have really made some effort to try to--and his name escapes me-- [Joseph Stewart Fruton] He's a biochemist who's really done a lot of publishing actually in the *Proceedings of the New York Academy of Sciences* on the history of biochemistry, that two-volume thing where he's got historians of science and scientists themselves who were involved in these events to write. And that's not tooting one's own horn or kind of doing this "This is how it happened" sort of eminent thing from on high, or very much like how they perceive science as being done: it's there to be discovered, and this is how we discover it. It's got a beginning, a middle, and an endpoint, right, with no context, if you will. It can be completely done out of context. I guess I think of [Arthur] Kornberg's autobiography [*For the Love of Enzymes: The Odyssey of a Biochemist]* in which that kind of position is taught.

**ALBER**: Yeah, and [Salvador Edward] Luria's memoir [*Life: The Unfinished Experiment],* for example, I read. I'm not sure really what function these sorts of books serve. I mean, maybe people read them and get inspired, or not—

**HATHAWAY**: I know from my perspective they usually have enough information in them that I use them for the sheer gathering of information. They have facts about what they did. And

often I read at almost cross-purposes to why they're writing it, I think. Whereas I think these oral histories are actually done in an attempt to kind of correct for that. We are very clear about what we'd like to talk about and making it--or trying to make it--collaborative. So that there is some attempt, I think, to move away from "Well, this is my discovery, and this is how it happened." I've run into a few times people expressing to me, "Well, how are you gathering this data, and what's your objective criteria, and how--?" And it's like, "That's not what this is about. We are not conducting some sort of experiment. I kind of lead them away from that, make it a subjective discussion and conversation."

**ALBER**: Well, as far as my own relationship to the history of science or politics of science, I don't read extensively in that anymore. Part of that break happened in graduate school for sure. And part of that was I walked into my first-year adviser's office, having looked at the catalog, and there was a course at MIT on science and the law, and there was a course on some other aspect of social implications of science. I basically had this idea that graduate school would be just an extension of my undergraduate training, you know? I would just be able to go and keep thinking-- You know, I had met other people. There was a physicist [Carl Cork] at UC San Diego [University of California] who was getting a Ph.D. in physics, but also did a lot of reading in historical aspects of science. So he was a person I knew. I thought, "Oh, look. People actually do this." And I walked into my adviser's office with this curriculum planned out, and he said, "You're taking a, b, and c. Do you have any questions?" Micro[biology] and biochemistry and genetics.

**HATHAWAY**: And you're working fifty hours a week in his lab.

**ALBER**: Well, actually, that's an interesting thing about the MIT graduate program in biology. It's almost bizarre considering the style of the institute. In the MIT program in biology, the students to this day don't do these rotations in their first year. And in fact, they're supposed to be completely out of the lab in their first year. In general, the students have had some lab experience. And so you get all these people-- They're smart. They're ready to go win Nobel Prizes in their rotation projects, you know. And then you tell them, "Forget it. You don't know enough." Maybe that's part of it.

But part of it is emphasizing scholarship, and part of it is that-- You take classes for the first year. What that does is it gives the people the intellectual opportunity to break with what they've done as under-graduates. You get a certain amount of breadth and appreciation for different types of logic and different parts of biology. So by the time people choose their thesis topics, or thesis advisers, we knew a lot more than when we started about a lot of different things. So it was conceivable that someone with a chemical or physical background might go into genetics, or someone with a genetics background might go into biochemistry or something. And at the same time, really emphasize that there was a body of knowledge that you had to become familiar with and learn how to become familiar with to basically do science, do your work.

And then that third component really was a particular course called Logic and Methods in Molecular Biology, which was a course where people read the literature, and we met once a week--

**HATHAWAY**: The current literature?

**ALBER**: Yeah, the current literature--and sort of cowered.

**HATHAWAY**: Classics?

**ALBER**: I remember a genetics course with Ethan [R.] Signer where we read classic papers in genetics, up to modern papers. But the course on Logic and Methods was modern papers, three a week. The year that I took it, it was just a withering barrage of questions and complexities and issues.

**HATHAWAY**: You mean the papers themselves?

**ALBER**: The papers were, but also the questions that the two faculty that ran the course asked.

**HATHAWAY**: Who were they?

**ALBER**: Phil [Phillip A.] Sharp and Malcolm [L.] Gefter. It was a course about methods. It was a course about reading. It was a course about how you actually prove a model from many different angles. And the emphasis was that one experiment is sort of weak. The question was, "How do you really know something?" So we read papers that were right; we read papers that were wrong; we read papers that were inconclusive. And we learned that Phil and Malcolm were extremely sophisticated about how they read them compared to, well, how I read them. [laughter]

**HATHAWAY**: I've gone through a few journal-club-type group meetings and just been kind of "Huh?" and walked out numbed and shocked. And these are just kind of informal gatherings where people pick apart work in their own fields. The thing is not just some sort of intellectual exercise. It's also "Where is this stuff going? What can we get out of it? How do we critique the work of this lab? Is there a competitor doing something similar? Got some interesting new technique that we might want to learn real fast?"--that sort of thing. It's amazing that I read them

at a level of naiveté.

**ALBER**: Maybe a model would be something like a business school where people read and study successful, quote, unquote, "corporations" and learn how to do management by studying real examples of management.

**HATHAWAY**: Like case studies.

**ALBER**: Right. So this was case studies where you weren't talking about your own work or dealing with your own work. You were dealing with the current literature in that way.

**HATHAWAY**: Do you know if this was a long tradition at MIT to do it this way?

**ALBER**: Yeah. It's still going on. I have an under-graduate student [Juli D. Klemm] who--

**HATHAWAY**: Is here for the summer?

**ALBER**: No, she was in my lab in Salt Lake [City] as an undergraduate and went to MIT as a graduate student and took that course a year and a half ago.

**HATHAWAY**: And so was it still being taught by the same two--?

**ALBER**: No, no, it varies. And in fact--it was maybe two years after my class went through it--the graduate students sort of rebelled. They got really pissed off at how hostile this course was.

**HATHAWAY**: You mean that it was just so hard? It was kind of like the boot camp, no matter who was teaching it was—

**ALBER**: Well, it was a good cop-bad cop scene, and it was very--

**HATHAWAY**: You mean one of the professors was a good cop, one was-- Really?

**ALBER**: Absolutely.

**HATHAWAY**: Even if it was not just Gefter and Sharp, it was other people?

**ALBER**: It tended to be very adversarial, and the graduate students took a poll and decided the course should not be taken without permission of parent or guardian. It was that bad. I mean, it was a great course, but was also very rough.

**HATHAWAY**: And it was three times a week?

**ALBER**: Once a week.

**HATHAWAY**: For like five hours or something like that.

**ALBER**: Yeah. And, you know, it was probably justified. The philosophy in the graduate program was that the admissions committee never makes a mistake. And they tell you this up front, which is sort of weird because everybody gets in there and the first day you're looking around the room going, "Gee, what am I doing here? Everybody else is so smart." But this course-- I had an experience where-- I think it was the second or third night. It met at night and let out about ten or something like that. It was just so--

**HATHAWAY**: It met at ten P.M.?

**ALBER**: Well, it finished around ten. Yeah.

**HATHAWAY**: This was boot camp.

**ALBER**: Oh God, no. But I was so agitated about it, I wasn't paying attention. I was walking near the subway, and these junior high school kids tried to mug me. And they just picked on the wrong guy because I was ready to explode. So I managed to get away, but maybe I should credit the course. [laughter]

**HATHAWAY**: For leaving you ten bucks in your wallet.

**ALBER**: Yeah, exactly.

**HATHAWAY**: I guess I was asking also about the particulars of who and whether it's still going on and that sort of thing for two reasons. It seems that it would--considering the quality of MIT graduate students, and the consistency, let's say-- I'm not saying there aren't equally powerhouse-type institutions when it comes to biology and biochem[istry] and genetics. You'd think other schools would pick up on this process. It almost seems like it's also all of you the first year. The first year you show up, you're all stuck in the same class.

**ALBER**: Everybody is in this course.

**HATHAWAY**: You have to deal with everybody. It is like intellectual boot camp. I hate to keep coming back to the same image. Do you have a sense from your other experiences, from having grad students yourself--I would assume that you taught here--why that's not--? Would you like to see something like that instituted here? Would you think about running something like that?

**ALBER**: Oh, no. Well, there are reading courses in all the graduate programs I have been associated with.

**HATHAWAY**: For first year?

**ALBER**: First year, right: [University of] Utah, [University of] Oregon, here [University of California, Berkeley].

**HATHAWAY**: You mean you've taught some of them?

**ALBER**: I taught one in Utah. I haven't taught one here yet.

**HATHAWAY**: I take it it's time-consuming.

**ALBER**: Not really.

**HATHAWAY**: Or it depends on who you are?

**ALBER**: It's time-consuming to choose the papers, and usually it's papers-- Like when I taught a course like this, most of the papers I had already read. It just required that I sort of refresh my memory about them. But then, of course, the whole style of the course I taught was completely different. The students made presentations rather than faculty just asking questions.

**HATHAWAY**: And this was the way it was done at Utah, so you did it this way? Or this was the way that you did it?

**ALBER**: No, I guess my feeling was that students at Utah wouldn't put up with it.

**HATHAWAY**: And obviously I don't mean to also suggest it has to be done this way.

**ALBER**: Yeah. I don't think it's the best style myself. I mean, I think you can be careful and critical and sophisticated—

**HATHAWAY**: Or tough even in the intellectual sense of requiring concentration and thinking. As you said, you were agitated. It seems more of a psychological aspect of the class as opposed to having the headache or that kind of knot in your brain from having to think really hard, which is another kind of stress. This reaction-in-the-subway sort of thing is much more about nerves and psyche and other things, it seems.

**ALBER**: Yeah. No, I mean people would break down crying in the class if they got pushed to the point--they didn't know, they didn't know, they didn't know, they didn't know, and then "Bam!" All of a sudden, somebody is crying. And we didn't really--

**HATHAWAY**: Men and women? Men in tears as well as women, or do you think it was more of a--? That's not meant to be a sexist question, or a gender-type question, but just curious.

**ALBER**: It happened a couple of times. The time I remember a person crying was a woman. But also there was a woman who got driven to the same point and told the faculty to fuck off, you know, quote, unquote.

**HATHAWAY**: In class?

**ALBER**: In class. Like, you know, "Go fuck off."

**HATHAWAY**: That's great.

**ALBER**: So people have different responses. But it wasn't anything I wanted to get into in my own class, right? So I felt like there are ways to let students know that you can take any area and just go deeper and deeper and deeper into it--that you don't get it in the first reading, or the first approach to something---without making them feel like they are worthless. I think I appreciate that sort of sense of craft, you know, almost like dance or something, that this course and in fact that the program at MIT inculcated in people. But I didn't appreciate the sort of roughness of the institute.

**HATHAWAY**: Do you think it was kind of a time that this program was especially effective, too? That it was maybe Gefter and Sharp? Or it really is the program in the institution itself is something that carries forward this--? No matter who is doing this, it's going to still be kind of done with this rough-and-ready kind of fashion, and that's MIT biology, regardless of who does it?

**ALBER**: No, this particular course, I know from talking to my student, is much less hostile right now. But it's still effective. The real common thread is that the program at MIT was really oriented toward teaching students to do science, rather than getting students to pick it up by osmosis, by putting students in a place where science is happening and expecting that they will get it. Or accepting the students that get it and writing off the students that don't get it. There wasn't a student that was allowed to not get it.

**HATHAWAY**: And was there a large--? I mean, did that class--? Did you see it for the first year--? Like you came back, you started the rotations the next year or whatever, and there were like half of you left? Or was it really a much slower process of elimination?

**ALBER**: No, that was the point: there wasn't a process of elimination.

**HATHAWAY**: Basically everybody got out of that class getting it, except maybe one or two, who just jumped into the Charles River. [laughter]

**ALBER**: Well, that's happened, right? I mean, you read *Natural Obsessions:* [*The Search for the*

*Oncogene]?* You should read this book.

**HATHAWAY**: Which one is this?

**ALBER**: Natalie Angier on the discovery of oncogenes in [Robert A.] Weinberg's lab. Some of the science is odd. And some of the stories of how ideas came about are more romantic than real. But the sense of competition, and the sociology of MIT in the early eighties there, is captured really well by the book.

**HATHAWAY**: I will look at it.

**ALBER**: But the only people I know, actually, that were thrown out of the graduate program got caught in something, you know, basically dark. There was a student who was publicly vocal about caution in recombinant DNA research. After six years, she was required to write a special exam, and she failed it and was asked to leave the program.

**HATHAWAY**: You mean this was like a setup, then, to get rid of her?

**ALBER**: Well, it certainly could have been viewed that way. By the same token, if she had been a star and cruised through this exam, she would have survived. But it was definitely a special thing that was done to her.

**HATHAWAY**: Because she was vocal about--?

**ALBER**: Well, you know, again, I don't know.

**HATHAWAY**: You just knew she was vocal about something.

**ALBER**: Yeah. I don't know [if] she just didn't—

**HATHAWAY**: She was the only one asked to take this? The only one you ever knew, right?

**ALBER**: Yeah.

**HATHAWAY**: How strange--a written exam by her own chair?

**ALBER**: Well, her thesis adviser was Luria, and he certainly participated in this, you know. And there was another student who was a student from physics who had a- - His thesis committee was three physicists and two biologists, or two physicists and three biologists. He got all the way into his defense. And the physicists apparently had some ax to grind that biology wasn't rigorous, and so they started into him. And his thesis adviser decided that he could show the physicists that biology was as rigorous as physics, so he went after his own student in the last exam. Boom!

**HATHAWAY**: He was like the crucible. So that person just left the program?

**ALBER**: No. That was another sort of pathology. You can imagine what this would be like going through this. You know, it's just horrendous.

**HATHAWAY**: To kind of watch it happen.

**ALBER**: You think you're finished, right? You go into the exam, and your mentor is hammering what you have done. I would have really caved. But this person was back in the lab the next week, and he worked for another year to clean up all the loose ends and he ended up finishing. But it was a very painful sort of thing.

**HATHAWAY**: Is that somebody who's gone on and stayed inside?

**ALBER**: I haven't followed his work at all.

**HATHAWAY**: I thought maybe it was somebody you still knew or a friend or something.

**ALBER**: No.

**HATHAWAY**: I wasn't looking for so much of a name but just a turnout.

**ALBER**: No. But by and large people finished, and the expectation was that you finish. That particular program was not one that anybody ever expected to fail out of. So they just said, "Look, it's tough, but we're not going to fail you. So just do it."

**HATHAWAY**: What else was there--? It was all just course work in the first year. I assume you also knew this, right? You went in knowing MIT was going to be different about this.

**ALBER**: Well, you know it's course work, but you don't know the atmosphere. There was a time like when I mentioned recombinant DNA technology was just coming on, and there was a lot of hostility on the faculty. Different people who had been friends who weren't on speaking terms anymore because they ended up on different sides of the regulatory issue.

**HATHAWAY**: Do you know what was the splitting issue? Was it people who weren't using or tending to use, or thought that they would never really need that kind of technology, who were worried about its consequences versus those who were--? Or did everybody know we're all going to use it and--? I guess I see some biochemists as not--

**ALBER**: Sure. I mean, the people who had less direct immediate need for it were more cautious, but it wasn't exclusively that way. I would say that many of those people use it now.

**HATHAWAY**: It was enough of a controversy that it involved students. And I don't mean that you were all asked to take a side or something like that, but it was a discussable kind of thing, right?

**ALBER**: Oh yeah, yeah.

**HATHAWAY**: It wasn't some sort of backroom meetings between faculty because somebody was representing MIT at some governmental-type hearing. I assume there was a lot of politics involved in this as well.

**ALBER**: Yeah. Public hearings in the Cambridge city council. A lot of craziness.

**HATHAWAY**: Local, state, federal--Was it something that you, given your kind of background, and being conscious more of these kinds of things--like how politics affects science, or how science has a context of its social-- The people who do it, and stuff like that. Was it something you were involved in directly or just watched keenly and with interest or--?

**ALBER**: Yeah, I was involved. I think it was a central thing in biology.

**HATHAWAY**: I actually have had not much success with people so far talking about it. I feel that the further we get along with the other scholars, the less and less-- They come into a situation where it's pretty much settled or where the burning issues of an unknown technology have kind of started to be answered as people do it more and more. I was wondering perhaps if you would be willing to kind of outline some of what you were involved in, or some of the things you remember? Like some heated Cambridge city council meeting? Some paper you helped draft? I don't know. I don't mean to put parameters on it either.

**ALBER**: Well, I guess there were meetings about what was being done and what experiments would give you information about how safe the technology would be. I got involved with a friend [Louis Slesin] who worked at the Natural Resources Defense Council [NRDC] in New York in commenting on NIH [National Institutes of Health] guidelines as they came out. The thing was, it wasn't really my field. Microbial genetics was not my field. I came from a chemistry background. But at one point, I wrote a literature survey of, essentially, what was not known. What was known and what was not known. And it was centered around comments on suggested changes in the NIH guidelines.

**HATHAWAY**: And those comments were--?

**ALBER**: Went to the NRDC, who sent them to NIH. They rewrote them.

**HATHAWAY**: The NIH ended up rewriting.

**ALBER**: No, the NRDC took material-- It was like they just read the paper and took the parts out that they wanted, and they put it in whatever language they wanted.

**HATHAWAY**: It was, like you say, mainly a literature survey or whatnot: what had already been done in the sense of control experiments. What was your sense? Would you say you were on the conservative side, or were you on the other side?

**ALBER**: Well, I was sort of impressed with how little was known about movement of DNA between organisms.

**HATHAWAY**: Just natural recombination.

**ALBER**: Yeah, in a way. So there were lots of claims made that making certain genetic constructions would be completely safe, and many of the claims were based on people's opinions, basically. There were even experiments at the time that show that dimers of viral DNAs could actually lead to infection, if they were injected. Whereas the monomers weren't. So the conclusion of the paper, of course, was that people construct monomers, and, therefore, this is going to be safe. But of course, anybody who's ever done a plasmid prep knows that you always get dimers as a contaminant or as a byproduct or as a small second product. It was a time when people just wanted to get into the research using this new technique. Certainly a lot of companies were springing up at the time. There hadn't been a great deal of work on whether the organisms would be safe, or how they might spread. Nobody has died from recombinant DNA technology, and that's what people were really worried about back then: Would these genetic constructions kill people?

**HATHAWAY**: Or become, I even suppose, more virulent. I guess an issue seems to me a question of, given what we know about viral replication, aren't we talking about perhaps creating situations where that replication is just incredibly powerful and--?

**ALBER**: When you change the host range of a virus or viral sequence--

**HATHAWAY**: Not even necessarily a plague of death upon everybody but just a virus that everybody got all of a sudden that was harder to transmit before, or something like that. I still think about the unknowns in viral replication, right? Why do you think it is that nothing like that has happened, given the way that viruses naturally spread? Isn't it almost amazing that you haven't seen at least one lab kind of go down the tubes with people--? Do you think it's just controls on how experiments are done, and--like any controlled situation in a lab that deals with isotopes and other dangerous material--that everybody is just careful enough?

**ALBER**: People are careful, but there are always accidents. Probably the answer is that to the extent that organisms are dangerous, or proteins are dangerous, they don't get spread when you clone them in a bacteria, when you clone the genes in a bacteria.

**HATHAWAY**: I think of HIV [human immunodeficiency virus], right? Again, with a certain kind of controls, and the notices like this room has-- There's as far as I know no reports in lab situations; certainly there may be with health care workers and needle sticks and whatnot. There's certainly no case of infection with the virus in a lab that uses HIV, at least not that I've heard.

**ALBER**: HIV, but I've asked virologists, "Do you know anybody who got sick from the subject of their work?" Many times you're talking to people who worked on characterizing viruses that had unknown properties and they were discovered by accident or whatever. Sometimes you hear people say, well, they don't know--maybe.

**HATHAWAY**: "I was really sick with this weird thing."

**ALBER**: Yeah, "I had this weird thing once, and maybe that was--" But they never chased it down.

**HATHAWAY**: Or found out that their children and their next-door neighbors all got the same illness.

**ALBER**: Or you know, in x-ray crystallography--in my area now, we're dealing with x rays. And so there's this story of so-and-so who got stomach cancer or whatever, and it's because of exposure. I mean, Curie died from radiation exposure.

**HATHAWAY**: Galileo went blind. It's a common theme.

**ALBER**: These things happen, but the direct causative links are often not searched for.

**HATHAWAY**: I take it, like with the isotopes, with the x rays, there's just certain precautions and rules that one follows, and they are pretty rigorously checked.

**ALBER**: Oh, yeah. You get trained not to put your finger in the x-ray beam, basically. [laughter]

**HATHAWAY**: And just keep me away from all that stuff, thank you. I've been known to knock over a whole tray of beakers just walking through a room.

**ALBER**: Yeah, but you have monitors and safety procedures.

**HATHAWAY**: Would you say that you felt that the controls and the resolution of the issue back then of recombinant DNA was to your satisfaction? You felt that the process was good as a scientist then, in other words, without the hindsight?

**ALBER**: Was the process good? No, the process was horrendous. Come on, it was an education in politics: how many Nobel laureates could you get on your side.

**HATHAWAY**: To kind of get the NIH to take up that position.

**ALBER**: Right.

**HATHAWAY**: Who was the head of NIH actually?

**ALBER**: [Donald Sharp] Fredrickson. People had commercial interests and conflicts of interest because they wanted to develop commercial applications, and you could see this very plainly. And yet they were taking public stands as supposedly expert scientists.

**HATHAWAY**: And meanwhile, they were working for a pharmaceutical company?

**ALBER**: Or starting their own, or whatever. That's—

**HATHAWAY**: Dishonest? Conflict of interest?

**ALBER**: Well, there's a conflict of interest there, and you can find a lot of those still going on, but it doesn't change the way the world is.

**HATHAWAY**: You mean people who were involving themselves as experts in discussions about protocols or rules or regulations having an ulterior--

**ALBER**: Oh, sure.

**HATHAWAY**: I think it's a very common situation in the insurance companies, now that they

perceive that the [William J.] Clinton administration is going to go at them, to suggest that they have not been included in the process, right? "If anybody should know about health care delivery, it's insurance companies, and why aren't we being asked to participate in the process? We're being left out."

**ALBER**: But you know, in some ways that's the way the world works, is you have advocates for new technologies or uses of old technologies or companies that want to do x, y, and z and it's new or it's polluting or it's not polluting or it's whatever. There's a regulation against it, and you have a public conflict.

**HATHAWAY**: So it needs to be resolved by all these different-- And really the best advocates seem to be the ones who, as you say, have the most Nobel laureates in a particular case that we're talking about here, but maybe the most money in another situation, or the most votes in another where you're convincing the public or a non-specialized group making decisions-- because ultimately that's who I suppose does, if you believe in representative democracy.

**ALBER**: Right. I mean, there are very few issues, or maybe no issues, in which, for example, commercial interests don't exert the maximum influence. They can, with large amounts of resources, lobby us in Washington [D.C.]. It's a big issue. I guess I felt like it was one of my first exposures to this, or a close exposure to this type of style, and you know, I was a young man. It was an education, but in retrospect, I don't think there is anything special about how that issue was played out.

**HATHAWAY**: And now looking at how other issues are decided, whether they're about the health of the nation or the proper way things get published or one's interest as an academic scientist versus being a consultant for the next start-up biotech[nology] company, right?

**ALBER**: Right.

**HATHAWAY**: I mean these are all issues that--

**ALBER**: If anything, the public hearings in city council chambers were unusual.

**HATHAWAY**: And sometimes they have their effect, right? If Cambridge had come down and said, "No. No recombinant DNA technology in our city limits--" Although, actually, Harvard would have fought it, and MIT would have fought to the very end, to the Supreme Court and whatnot--federal legislation to combat the local legislation-- Still, it could have thrown a

wrench, and perhaps did for a while, into other people's larger interests than just the community's. But it wasn't something that disappointed you. I mean, it wasn't something that made you go, "God, science is just like being in Congress," or a bunch of—

**ALBER**: Disappointed me?

**HATHAWAY**: To a certain extent, I guess, maybe it's my own buying of the myth that an academic scientist is somebody who doesn't really get paid very well for what they do, so they have to have some other kind of interest in this, you know. There is some sort of idealistic whatever still left, right? [laughter]

**ALBER**: I can see the transcript now--laughter!

[END TAPE 3, SIDE 1]

**HATHAWAY**: I guess what I was saying is more that I get this sense from talking to you that there was a certain amount of just natural curiosity and wonder about becoming a scientist for you. It wasn't, "Hey, I can get the Nobel Prize and be really famous and control a lot of people and have a big lab. And I could be a lawyer and do this, too, in a big law firm, become a big partner." Do you know what I mean? Your ambition about being a scientist seems geared toward knowledge and curiosity versus prestige and money and control, okay?

**ALBER**: Yeah, okay. Thank you. [laughter]

**HATHAWAY**: What you discovered on this educate-- Well, I think a lot of scientists' initial motivations, okay--and I stress the word initial--are that way, too. But then you get into this world at MIT. I mean, we're talking one of the highlights, one of the jewels in the crown of American science, right? And here is all this political maneuvering with Nobel laureates, no less--

**ALBER**: Well, they're people too. That's one thing you find out. [laughter]

**HATHAWAY**: Right, but that wasn't the kind of education we're talking about here that you got from this experience? No increased cynicism?

**ALBER**: Well, that's tough to gauge because part of the process of getting a degree--say getting through graduate school, doing a postdoc, starting your own lab--involves becoming more and more practical. To say that this particular experience in the politics of science was something that made me jaded--and I could even say less interested in the political side of things--I don't know, it's hard to say.

**HATHAWAY**: Do you really think you've kind of run away from that, so that issues of administration and--? I guess as an example without any particulars: just this morning, you were talking with someone on the phone. And it's a supplier of something, and this back and forth--You are being given kind of a deal, and you don't really want the deal, you just want the stuff, and what is it worth, and "We'll pay. Can you leave me alone with the rest of it?" As you said, now by taking the deal, somehow "I have to suck up to him," I believe is the phrase you used, or that "I owe him"--the relationship is not strictly scientific anymore, right? "You've got something I need, you're good at it. Thank you, here, give it to me." And vice versa. "When somebody needs something from my lab to be done, we'll just do it. And this is how much it's going to cost you because this is how much time we spent on it." Do you know what I mean? Versus this other kind of game that you seem to resent to a certain extent.

**ALBER**: No, I'm not sure what you mean.

**HATHAWAY**: But that seems political as well, maybe at a much smaller level, but it ties you to this person in a way that you really didn't particularly--

**ALBER**: I mean, to get back to the issue of recombinant DNA, the real issue is what could I accomplish. I participated in that, and I participated in it to the extent that I could, but the opinion of a graduate student in this world doesn't really weigh equally with a learned, established investigator in the battle of experts. So there was a certain amount of just piling up, like on a scale, you know, on a balance. How many people could you get to support your side versus the other side?

You know, I think in the politics of science, there is a certain amount of organization, as in any political activity. If you organize, you can accomplish something. But just because you organize, it doesn't mean you can accomplish something. If you're trying to learn how to do science-- Or maybe what I'm saying is at some point I got distracted away from the history of science by the idea of doing science. At some point I got distracted by just how hard it is, or how interesting it is, to do the scientific work.

**HATHAWAY**: By the day-to-day politics of it, and becoming involved in that?

**ALBER**: Well, no. What I'm saying is that my first instinct was to be involved in the political side of things: a responsible scientist who is looking at the societal impact of his or her work, and publicly participating in political decisions that have to do with that. My attitude now is much more that it's interesting to do the science. And if there's an impact of my work, it's likely to be, for example, a commercial impact, rather than an environmental hazard. Even that I'm less interested in than the science.

**HATHAWAY**: In other words, if the UC [University of California] in its pretty aggressive marketing and patenting mode came along, you'd just kind of hand it over to them and not become involved in the process, and just get on with something else, or continue that work and let everybody else deal with that part of that.

**ALBER**: Well, some of the work that I did in Eugene [University of Oregon] is patented, but it's not earning anybody any money. I think this business that university professors should be in the business of making products is crazy. That's not what the university is supposed to do, or should do.

**HATHAWAY**: And there seem to be two ways that univer-sities do it, right? They seem to look out for patent-able stuff, and they go ahead and do it and leave the investigator alone and maybe it will turn into something, right?

**ALBER**: Yeah.

**HATHAWAY**: Others seem to be much more aggressive about it. There seems to even be pressure on the investigators to always keep in the back of their head "Boy, this could make us $25 million a year." It's just a piece about the-- I can't even remember what it is, at Stanford [University].

**ALBER**: Cloning?

**HATHAWAY**: Yeah. The patent runs out, and there goes an immense amount of money, actually, that Stanford was funding its grad students and whatnot on.

**ALBER**: Sure. But the number of discoveries at that level are so small. The University of Wisconsin has a patent on rat poison, basically, that funded research there, and funded the university to a huge tune.

**HATHAWAY**: Apparently Johns Hopkins [University] has always been very upset that they didn't recognize what Dan [Daniel] Nathans was doing back when he was doing it. They could have patented that and made a self-sufficient little department there.

When I was relating it back to this incident this morning, I was just talking along these lines--that stuff gets in the way of just doing it?

**ALBER**: No, not at all. It's half the fun. I mean, for you to say, did I get jaded or discouraged or cynical about science because of political aspects, or learning about political aspects--no, not at all. I guess I didn't have the need that science be pure and innocent. The more I do it, the less it has to be a certain way.

**HATHAWAY**: And I guess I'm not following completely. You mean the more you do--?

**ALBER**: What I'm saying is I didn't have a model that science was conducted by gentlemen. And maybe that's in part from reading about the philosophy of science. There are lots of descriptions of how it works: [Thomas S.] Kuhn, [Karl H.] Popper, you name these people and-- There are just a lot of different styles. People have different styles. They have different things they're effective at doing. And in terms of success, if you have good ideas and do good work-- There's certainly the politics of marketing and staying funded and things like that, but I guess I find all that enjoyable.

**HATHAWAY**: So there's none of this-- I think it's still a pretty common notion that may be more steadfastly held onto or grasped by physical scientists, but people still do believe that they are uncovering truth. Even if they understand Popper, they still think that this is an incremental uncovering of layers of confusion. I won't say getting to a final truth, but an ongoing process that is somehow-- You said "innocence," but I think you also said "purity." First of all, the whole entire vocabulary of doing science, down to talking about "doing purifications" and the way we use such words-- We are really talking about an enterprise that has been conceived, at least in the past, as being different than finding out legal truth in a case in a courtroom, which has always been a matter of who is going to convince--

**ALBER**: It is different. It is different in the sense that if you repeat a given procedure, you get basically the same answer within the error of your measuring capabilities. Or if you have a theory, and it's a quantitative theory, the predictions of the theory are the same whether you run it here or you run it in South Africa or Swaziland, which is essentially the other side of the earth from here. It's different in that sense, but it's not different in the sense that--

**HATHAWAY**: In its conduct.

**ALBER**: Yeah, in its conduct, and in the fact that it's a cultural thing; there's a competition of ideas out there.

**HATHAWAY**: Kind of a marketplace of ideas. But without getting too commercial about it at all--

**ALBER**: It's done by people. Not only do you have to uncover something, but you have to convince people that it's important or it's real or it's not just what people call an artifact of your measurement--that it's useful to them or it's useful to the world to, quote, "think this way."

**HATHAWAY**: Or even just that it has explained a whole bunch of phenomena in a nice, neat--

**ALBER**: Well, that's what I mean by useful. There's an aesthetic to it.

**HATHAWAY**: You mean to the process of doing it? Or to the explanation of it?

**ALBER**: No, I mean there are things that are thought of as beautiful, right? Certain results, or your statement just now that if you formulate an idea that explains a lot of unexplained observations or unconnected facts--that's considered beautiful.

**HATHAWAY**: The old unified field theory, right? The Holy Grail of physics.

**ALBER**: Or Fermat's last theorem. I mean, how many people know anything about it, but it's in the newspapers when it's solved. It's more of a cultural accomplishment. What is it going to be used for? Nothing. It's like a painting.

**HATHAWAY**: Or a really hard crossword puzzle even, on a completely different level. Again, we do a lot of things in our lives where aesthetics--filling in a crossword puzzle and getting it all right, and that sort of thing, is, quote, "an aesthetic thing." I didn't mean to get off of your graduate--except that again these issues seem to crop up as you're learning more and more about science, so that's why we get off on these-- And plus, it may seem kind of naive to you--"Well, of course, it's done like everything else" or something like that--yet it's about repeatable, stable sorts of results: if you can get the right controls, and prove there's no artifacts, and that sort of

thing. So that it may be something different than just commercial truth--Froot Loops taste better than whatever the other things are because we put our recipe together better. [laughter] Then you take a poll and 95 percent of people agree that Froot Loops are, indeed, better than God knows what other kind of sugar-coated cereal. To me, it's a real important thing to get people to talk about, even if it's a little elementary to you from your perspective.

**ALBER**: Oh, no, it's not elementary at all.

**HATHAWAY**: I find it kind of fascinating--

**ALBER**: Yeah, I think when I was reading about different theories and models of scientific progress--to call it that-- Even the objection to the idea of progress, you know. These were things, I think I mentioned in the last tape, that really kept me out of the lab--to be confused about these things. I think the major realization, or maybe you would call it an accommodation if you were less charitable, may be—And maybe it came in part from this political involvement on recombinant DNA. That is, the view that the technology itself is different from the political decision about what society or a company or an individual does with that technology.

**HATHAWAY**: Right, we actually did talk about that before, on the last tape, on the issue of responsibility. Is it the responsibility of the inventor of the technology or of the users and employers of such technology? In other words, is [J. Robert] Oppenheimer responsible equally as the Department of Defense, or does he share responsibility in some other way? Obviously questions that will be debated and discussed forever, as long as people are doing such things.

**ALBER**: But the point is, if you feel that as a scientist-- If I felt I was responsible for some use of my work--to make weapons or to harm people or to hurt people, destroy society--even if I hadn't thought about it or conceived of it on my own while I was doing the work, then I wouldn't be able to work. I wouldn't be able to do the work. Because what if twenty years from now somebody discovers that they can use my papers to make a weapon? It's like work on the frog visual system was used to make guidance systems for smart bombs. I don't really consider the people who learned how the frog visual system works responsible for that. On the other hand, I do consider the people who made the bomb guidance system responsible for that. I would argue that people shouldn't do that.

**HATHAWAY**: Whereas perhaps Oppenheimer's case versus the guys who work on the frog visual system is a little more-- He was in a lab making a bomb, or trying to, certainly. He was taking this kind of esoteric knowledge that he had-- Nuclear fission was certainly an important issue and question regardless of what it was going to do. It certainly became more practically important very quickly in the thirties.

**ALBER**: Yeah, but let's even take that case. Now I'm going to really reveal the depth of my conservatism or something. To develop the atom bomb, right, was an effort to defeat Germany. It was a struggle for survival.

**HATHAWAY**: That's certainly is how it's-- In general, I would say I would accept that as pretty common--

**ALBER**: The decision to use it, on the other hand, I think has been criticized, probably correctly. Although the argument on the other side is it saved a lot of lives; they just didn't happen to be Japanese lives.

**HATHAWAY**: Well, that says something about our own view of perhaps Asian people versus European people, that we made such decisions.

**ALBER**: Okay, so then it was a political decision to go ahead and develop the hydrogen bomb. You can make lots of statements about the communist menace and the cold war and the perceived threat that led to that political decision to make this incredible weapon. Now political conditions are different, and people don't feel that same level of threat. And what you see is success at reversing this decision. There's more success at nuclear disarmament. That's a political process.

**HATHAWAY**: And all those people at Rand Corporation were right about nuclear deterrents: [laughter] by building more, we'll deter. And to a certain extent--

**ALBER**: So far--

**HATHAWAY**: So far, except for, I guess, Pakistan, and questions about Iraq. In the others, there seems to be certainly very little work going forward making more and new--not that the basic research isn't continuing, but that the actual production of more advanced weaponry of that sort has really slowed down or stopped.

**ALBER**: Well, Clinton was just in the news about going to the DMZ [demilitarized zone] in [North] Korea and saying, "Look, you people are crazy to be building a nuclear weapon. You are out of your mind." I mean, "Just try to use this thing." It doesn't even take having the capacity to destroy the world many times over to deter the use of a single nuclear weapon

somewhere, you know. I mean it's--

**HATHAWAY**: Simple retaliation is a good enough threat, right?

**ALBER**: Yeah, exactly. I just hadn't really thought about how simple that idea is. Anyway, so we should get back to graduate school.

**HATHAWAY**: Who knows, you were thinking about these things in graduate school too. It was high time for all of this stuff in the beginning of the Ronald [W.] Reagan era.

The first year was all course work, then. Was there some sort of rotational system going on? Or that one first year gave you an indication of what was going on in different labs?

**ALBER**: Yeah, we certainly talked with people. Then during the month of January, the faculty made presentations to first-year students. Then you were supposed to talk to those people that you were interested in and come to some decision at the end of the spring term.

Instead of doing that, I went to UCSD [University of California, San Diego] my first January and worked on the development of a low-temperature device and low-temperature crystallography, coupled with a two-dimensional x-ray detector that had been invented at UCSD.

**HATHAWAY**: By?

**ALBER**: By a physicist named Xuong Ngyen-huu who was a particle physics guy who had adapted this detector to detect x rays in two dimensions. His students, or his lab, his group, had also built a low-temperature system, and I was involved in trying to use it and test it--

**HATHAWAY**: To get it to make crystals?

**ALBER**: To collect x-ray data at low temperatures. That was a very new thing that--

**HATHAWAY**: I take it they were using an inorganic sampler, or this was strictly biological?

**ALBER**: Strictly biological, yeah. I had been involved in that as an undergraduate. I settled on a

crystallography lab at MIT: Alex [Alexander] Rich, who is most well-known, I think, for work on the structure of tRNA, and subsequently for DNA structures. I ended up working in his lab, trying to crystallize the nucleosome particle in which DNA is organized. But then I ended up getting interested in the problem of secretion: How do proteins get out of cells? Alex had a senior postdoc [Henry M. Kronenberg] in the lab who was working on this problem. Basically, I was set to switch to that problem, or I had started working on that problem when Greg [Gregory A.] Petsko moved to MIT to the chemistry department. I saw that as a way to do some interesting crystallography, and so then switched to his lab.

**HATHAWAY**: And Rich didn't care. You were still perhaps--?

**ALBER**: No, Alex has been extremely supportive my whole career. A very interesting guy.

**HATHAWAY**: I'd like to cover more than how you're doing it this way. It's good to have a summary. When you say you went to UCSD in January, you went there for a month, six months?

**ALBER**: Yeah, I went there for the month, and did experiments that didn't work.

**HATHAWAY**: I hate to tell you, but those are as interesting to me as the ones that do. [laughter]

**ALBER**: Well, it's pretty interesting, actually. The reason—

**HATHAWAY**: How you knew about going there, and who connected you up and that kind of stuff.

**ALBER**: Greg Petsko, as a graduate student at Oxford [University], had begun developing low-temperature crystallography of proteins with the idea that this was a way to trap enzymes in action. That if you could cool them enough, you could add productive substrates, they wouldn't completely react, and you could essentially take snapshots of catalysis.

**HATHAWAY**: And this was his own--? I mean, he's sitting in [David C.] Phillips's lab, right?

**ALBER**: Right.

**HATHAWAY**: Or this is something that's all over [Oxford]?

**ALBER**: No, it was something that David Phillips had talked with Greg about, and Greg was the person who got it to work, and was getting it to work at that time--early to late seventies.

**HATHAWAY**: This is a big kind of breakthrough, considering the hell that somebody-- When you just read *The Eighth Day of Creation:* [*Makers of the Revolution in Biology],* the last 250 pages, and [Max F.] Perutz's timing just this-- We're talking thirty years of working on this protein. I mean, it's dogged work. Or maybe you don't go all the way back in your head with that kind of sense of the relation to [Sir John Cowdrey] Kendrew and--

**ALBER**: The problem with crystallography is that it's a space average and a time average over the crystal and over the time it takes to collect the data. So you can't do real-time experiments. And many biological processes that you want to look at in structural terms happen very quickly. So Greg, and David Phillips actually, were people who were really concerned with how to use crystallography to get, shall we say, more relevant information, or more useful information.

So Greg was working on this in two ways. One was, his Ph.D. thesis was on the structure of triose phosphate isomerase. I think it was recognized either by David or by Greg--or both are in the lab at the time, in the early seventies--that here was an enzyme which interconverted two compounds. So you could add the real substrate, in principle, to the enzyme. It would bind to the enzyme, and it would be converted to the product. But the product was the substrate for the back reaction, so it would just get converted back, and this thing would be going back and forth.

**HATHAWAY**: So quickly.

**ALBER**: Right. Basically, if you determine the structure of such a complex, you would actually get a picture of the average of what the enzyme was doing while it was working. Whereas many hydrolytic enzymes that had been studied up to that point by x-ray crystallography, the product didn't bind very well, and that reaction didn't really go backwards very well. So when you added the substrate to the crystal, you might get a complex of the product, but you didn't get a picture of the thing working.

**HATHAWAY**: So in what you're attempting to do with structural investigations, you're getting nothing to elucidate function.

**ALBER**: Right, you have to guess at the function.

**HATHAWAY**: In other words, its whole issue of going into it that way is kind of like not being answered until you can see it, like with a snapshot.

**ALBER**: Right, see it working. It's like maybe the difference between seeing a machine sitting still and seeing it working.

**HATHAWAY**: Or seeing what comes out of the machine and never seeing the machine, perhaps even? I mean, you could just imagine what makes your automobile, or what makes that box come around the raisins, right? And not see the machine and not have any idea, right? By deconstructing that box of raisins, if you will.

**ALBER**: Yeah. The idea was the protein structure gave you a sense of what it was that was doing the job, but not how it did the job. And so Phillips and Greg were very concerned about how to do experiments--just incredible experimentalists--to get information about how that happens. And Greg's research is still directed along those lines.

**HATHAWAY**: And still based on, again, tinkering and playing around with experimental methods.

**ALBER**: Oh, he has very little patience for repeating things. He likes to do new things. It's very nice.

**HATHAWAY**: He seems to also bounce around. He's at Brandeis [University] now, right? I mean, he's not at MIT. I just recently saw some--

**ALBER**: Yeah, he moved to Brandeis.

**HATHAWAY**: It's not too far away a distance, but it's probably like night and day. Maybe not.

**ALBER**: No, he's still very active.

**HATHAWAY**: Oh no, I wasn't implying it was like retirement, or shunting aside from the big

time. You just described him perhaps as a little restless and he saw opportunities at Brandeis that he didn't have at MIT. You don't want to talk about it.

**ALBER**: No, I don't really want to talk about it. [laughter]

**HATHAWAY**: Let's move on. What I need to ask, I'll ask Greg.

**ALBER**: Yeah, exactly. I don't know how to say this. I went to UCSD and tried to repeat experiments that I had worked on with Greg, or Greg had done in Detroit in early 1976, on binding of a real substrate to an enzyme called elastase. Basically, we collected the data in San Diego. We did the binding experiment. We did this at low temperature. The nice thing about the low-temperature device in San Diego is that it was much more stable, and you could actually go to lower temperature than the one that we had in Detroit. And so we thought, "Gee, we're going to be able to repeat the experiment really easily, and then with this two-dimensional detector we'll get much more detailed information." In the event, what happened was that every time we collected the data, we could never find the substrate bound to the enzyme. And now Greg has done an experiment, that was published I believe last year, that basically showed that because we had this better low-temperature device, we were cooling the system too much [B.F. Rasmussen et al., 1992. Crystalline ribonuclease A loses function below the dynamical transition at 22 0K. *Nature* 357:423-24]. And the supposition now is that we had cooled it so much that the enzyme couldn't open up and allow the substrate to bind in the active site.

**HATHAWAY**: You were not only maybe slowing it down, you had frozen it out.

**ALBER**: Yeah. The implication of Greg's more recent work is that we had reduced the motions of the molecule so much by cooling it that the substrate just couldn't get in. And so the reason that the experiment worked in Detroit is that our equipment was not up to speed. [laughter]

**HATHAWAY**: But indeed it was, right?

**ALBER**: Exactly.

**HATHAWAY**: Was it Petsko who--?

**ALBER**: So he arranged it. Oh yeah, yeah.

**HATHAWAY**: Not [Anthony L.] Fink?

**ALBER**: Oh, yeah. So Xuong called Greg, and Greg said, "Why don't you get Alber out there?" And so I went out there.

**HATHAWAY**: And he was still at--

**ALBER**: Detroit.

**HATHAWAY**: --Wayne State [University] then, right, when this--?

**ALBER**: So then I moved to Greg's lab [at MIT]. He was a new faculty person there in chemistry. He had no equipment. So I came to [University of California] Berkeley to purify two chemotaxis receptors in Dan [Daniel E.] Koshland [Jr.]'s lab because Greg was interested in chemotaxis. So I worked for a month with one of Dan's postdocs, and just did a purification, and then crystallized these two proteins. And Greg had another student who worked on those for her thesis.

**HATHAWAY**: And that's?

**ALBER**: Sherry Mowbray.

**HATHAWAY**: Okay, because there is another person, I think, out of his lab that she worked with--Fahnestock? I don't know what her name was.

**ALBER**: Margaret [L.] Fahnestock was in Dan Koshland's lab; she was a postdoc. We had a great time doing protein purification, learned a lot. So that was here in Berkeley.

**HATHAWAY**: This all happened in the same year?

**ALBER**: Yes. So I switched to Greg's lab, and instead of ordering equipment--

**HATHAWAY**: And that's not the year in San Diego?

**ALBER**: No, that's the next year.

**HATHAWAY**: I'm sorry. We're just doing this for the record, that's all.

**ALBER**: Then I went to Oxford for the spring.

**HATHAWAY**: So you never spent any time in Cambridge.

**ALBER**: Well, this is basically an idea that-- Petsko did not have equipment. So I could work on setting it up, or I could work on science. And he was concerned that I go off and get projects started. So I started the chemotaxis work there. Then I decided in that period that I wanted to work on triose phosphate isomerase because I felt I could learn the most crystallography on that project.

**HATHAWAY**: Because it had been used before already, there was so much to work with? Or just because of Petsko's own expertise with it?

**ALBER**: It was an interesting problem, and the way that he wanted to go about it was to solve the structure from scratch. And that's what I wanted to learn: how to do that, how to start with a protein and come up with a three-dimensional structure. So I felt like I could learn all the things I wanted. I felt like the system was interesting. And so because I made that choice, I went to Oxford to Phillips's lab, and the goals were to learn my way around the triose phosphate isomerase molecule (the Oxford group, or Greg when he was in Oxford, had determined the structure of the rabbit muscle enzyme); to make heavy-atom derivatives of the yeast enzyme crystals that Greg had already grown with Demetrius Tsernoglou; to make co-crystals if I could with the substrates and inhibitors; and then also to do a low-temperature experiment on lysozyme. It turned out that the Oxford group had crystallized I think it was tortoise lysozyme in a way that the crystals had big channels in them. And so we had thought that we could get the real substrate in and freeze the reaction. Lysozyme was the first enzyme whose structure was determined in Phillips's lab in the early sixties. They had proposed a controversial idea that when the substrate binds to that enzyme that its shape is distorted. That's what we had hoped to test by actually getting an x-ray structure of the enzyme-substrate complex.

**HATHAWAY**: When you mean distorted, you don't mean the complex is distorted--that the substrate has distorted the enzyme?

**ALBER**: No, that the enzyme has distorted the substrate. And it's distorted in such a way that it more resembles the transition state for the reaction, a very reactive form.

**HATHAWAY**: And this is a real focus for our question about structure explaining function.

**ALBER**: Right. Exactly. How do enzymes work? One way is they distort the shape of the substrate. And so we had hoped to test that. But in the event, when I got there, the equipment to do that--the low-temperature equipment--wasn't built, and so I actually worked on building it in the few months I was there. In fact, we got the equipment together, but I had to leave before doing the experiment. But it was, you know, wonderful. Spring in Oxford! Learn about British science. I had a friend [Aaron Bernstein] who was in New College studying political theory. So I went to lectures by Isaiah Berlin. You know, he took me around.

**HATHAWAY**: Your friend or Isaiah Berlin?

**ALBER**: No, my friend took me around to his lectures, and we went walking in the peaks, and-

**HATHAWAY**: You didn't take him to your lectures?

**ALBER**: Well, no. I lived in a thousand-year-old building, the graduate dorm. [laughter]

**HATHAWAY**: I did that once. It wasn't a thousand years old, though.

**ALBER**: It was fabulous.

**HATHAWAY**: You were there six months or so?

**ALBER**: Oh, less. Three or four months. And then I went to China for a couple of weeks with my mom.

**HATHAWAY**: I was going to say, what were you doing in China?

**ALBER**: Well, this was fun.

**HATHAWAY**: Right, no, your mom.

**ALBER**: My mother worked for [University] Extension at UCLA, and she planned an academic trip and asked me to go. Alex Rich had done a postdoc in Linus [C.] Pauling's lab in the fifties at Caltech [California Institute of Technology], and so had the person who was the director of the physical chemistry institute at Beijing University. So I went there and gave a seminar. He introduced me to people in Shanghai. So when the, quote, "tour" went to Shanghai, I gave a seminar in Shanghai. This was '79.

**HATHAWAY**: So pretty much a closed-- Was it?

**ALBER**: Well, it was opening up, but it was a time of the Democracy Wall in Beijing, and it subsequently got shut down. Mao [Tse-tung] was being discredited. It was a politically thrilling time in China.

**HATHAWAY**: Because you had this connection, right, through Rich and this guy, you kind of got a sense of the real flavor of it, instead of being just kind of shuttled around as tourists, or as outsiders?

**ALBER**: Yeah. I met Chinese scientists who hadn't been able to work during the Cultural Revolution but who had kept up with the literature. So they knew everything that had been done, even though they hadn't done that much themselves.

**HATHAWAY**: In other words, the foreign literature too-- I mean, they're sneaking it, or maybe they could even have access to it, as long as they don't do their own work, right? They could certainly get a hold of these sorts of things. You mean like structural chemists and biologists?

**ALBER**: Yeah. Well, there was the insulin group in Shanghai that really--

**HATHAWAY**: It was just starting up again after perhaps the—

**ALBER**: Yeah. And they had gotten a lot done. They were right up there in the world in terms

of the structure of insulin. The group in Beijing was just setting up a crystallography lab. It was really a bit of an education to go through this building that was sort of dilapidated. In one corner of it was this fantastically air-conditioned room; people take their shoes off when they go in, so it doesn't get dirty. They had just purchased an x-ray data collection instrument and the keyboard had failed. This computer keyboard had failed. What do you do when the computer keyboard fails? We just call up the company and they send another one, you know. Or you trade it in on warranty. They were looking at the schematics of the keyboard, which I had no idea how a keyboard works. So I got there, and they said, "Could you help us fix our keyboard?" You know, I go, "No, I don't know. You just have to buy a new one." So it was a different—

**HATHAWAY**: But they were still doing things. I mean, that's the lesson you sort of got: that they were still accomplishing something.

**ALBER**: Yeah. How much chutzpah you have--

**HATHAWAY**: To bother, right? When you knew that it was - -

**ALBER**: Absolutely. I don't know, I met people. I met a physicist who had been imprisoned during the Cultural Revolution. It was a fantastically interesting trip. Came back—

**HATHAWAY**: Now, there's an interesting case of the politics of science, or whatever. Actually, it almost seems like the reverse, right? The political issues are outside of any kind of scientific issues. But as scientists, and as their hope, they're just being squelched without any kind of discussion and whatnot. But still, they have to become politically involved, or they become shopkeepers or dependent on somebody else and just walk away from the whole enterprise, right? I take it when you say the Cultural [Revolution], Mao, and stuff, that certain kinds of science were just considered decadent and of capitalist thinking, right? Is that what you were getting--a sense of some of these people in their work?

**ALBER**: Yeah.

**HATHAWAY**: Or was it just economic?

**ALBER**: No. Foreign contacts were suspicious, so if you-- Science is an international thing, and so people tended to get themselves into what you'd call political troubles. They tended to be persecuted for that.

**HATHAWAY**: So really it wasn't even a science content issue. I mean just simply a blanket attack, almost. It was more that they're positioned as being an outside--

**ALBER**: Well, I didn't get to know people enough. But certainly as an enterprise, the whole thing was shut down. Experimental biology stopped. It was a time when this was just starting up again in China. Through a very chance meeting, I met somebody in a post office who was an American whose parents had done a lot of medical work in China--[Mark] Seidel. It turns out that he had just graduated from Princeton [University], and a TA [teaching assistant] in one of his political theory courses [Wendy Brown] was a good friend of mine. He was sort of a character or a special person there because of his parents. So he took me to dinner.

**HATHAWAY**: So he wasn't looked upon suspiciously?

[END OF TAPE 3, SIDE 2]

**ALBER**: And so one of the people was through Mark [Seidel]. He took me to dinner at the house of someone who is very high up in the Chinese social science bureaucracy. This person had a big house arranged around a compound where his family lived. He had his own library. And he had a car; in 1979, for someone to have a car in China was a big deal. Here was this social scientist who had somehow come out of the Cultural Revolution on top, so to speak. And yet, by the same token, in a bookstore I met this physicist who had come out of the Cultural Revolution at the bottom. It was a real interesting—

**HATHAWAY**: And he approached you in a bookstore because you were American, or you were non-Chinese?

**ALBER**: Maybe I was the only non-Chinese in the bookstore. I was just walking around in Beijing. The other thing is, I was looking in a case. The bookstore was pretty crowded; I was looking in a case where there wasn't anybody there just to see what kind of books were there. So I went to basically the only case in the bookstore where there wasn't a big crowd around it, and it turned out to be Mao [Tse-tung] 's works. [laughter] Anyway, this guy took me to dinner. He walked up and introduced himself. It turned out he had been a postdoc at Harvard [University], and so I knew, for example, his old street where he'd lived. He took me to dinner at a place where there weren't Westerners. And in fact, we weren't served. We walked into this place; the waitress just basically ignored us.

**HATHAWAY**: They wouldn't go near you.

**ALBER**: Right. We had to go pour a pitcher of beer and just sit and chat for a while. Somebody came in, had a cup of tea at the table next door, listened to our conversation, and left. And at that point, we got served.

**HATHAWAY**: They knew that the third person was going to show up sooner or later, right?

**ALBER**: Right. Then by the end of the evening, basically everybody in this little restaurant was in a big circle, and we were talking about what's it like in China versus what's it like in the West. [tape recorder off]

**HATHAWAY**: Well, let's finish. I assume you still have a few more things to say about the trip.

**ALBER**: Well, I mean, come on, it's a couple of weeks in your life, and you remember it.

**HATHAWAY**: No, no. The response like that, kind of running into all these-- Obviously, some of them were willing to take the chance at every turn the few times they saw somebody from the West to approach them and then talk to them. Again, without us making any "this affected your life this way or that way--" It's just that we're trying to accumulate some sort of sense of experience here.

**ALBER**: Well, it certainly--

**HATHAWAY**: It must have affected you somehow--the scientific aspect.

**ALBER**: In terms of the scientific part-- Certainly when I went to the [Academia Sinica] institute in Shanghai-- I mean, these people were making their own equipment.

**HATHAWAY**: But you were making your own equipment back at Oxford [University].

**ALBER**: But fraction collectors, come on. And people who would have to fix their own keyboard for their computer.

**HATHAWAY**: It was a whole different level.

**ALBER**: It was a different world, and I felt that I'd better take advantage of my situation. I mean, even Oxford was suffering funding problems. British science was broke, right?

**HATHAWAY**: And they're still complaining about it.

**ALBER**: And it's still awful. The things that I could order there, or could not order, compared to what I wouldn't even think twice about in the States--it was terrible by comparison. I mean, like that trip was very short. It was very exciting. [David C.] Phillips is brilliant, no question. I had a lot of fun, but I certainly developed a bias against doing science in the U.K.

**HATHAWAY**: Just because of the trouble? Just because of the difficulty?

**ALBER**: Yeah, it's just harder. Absolutely.

**HATHAWAY**: We can maybe come back to that as we sit here in an institution run by the University of California, and talk about the future of American science, as well, when it comes up later.

[END OF TAPE 4, SIDE 2]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **23 July 1993**

**HATHAWAY**: We kind of chronologically or factually had stopped with your coming back from China, and that's really in the middle of all your years at MIT [Massachusetts Institute of Technology], right?

**ALBER**: Yeah, pretty much in the middle.

**HATHAWAY**: We had, I think, covered an awful lot of the issues around recombinant DNA, what the program was like at MIT. The only thing I wanted to kind of catch up on, because we were talking about it this morning--or I was--was Alex [Alexander] Rich, because you did mention on tape--and I kind of let it go because you didn't work very long in his lab--that he was "a very interesting fellow" and he 'd been very supportive of your work all along. So I assume you have some relation with him and are able to shed some light on him and his lab and what kind of scientist he was?

**ALBER**: Or is?

**HATHAWAY**: I mean, you must have gotten something from him.

**ALBER**: Oh, yeah.

**HATHAWAY**: I don't mean job recommendations.

**ALBER**: Intellectually. Well, he definitely sees the big picture of things. He's involved in the politics of science as well. He was the National Academy [of Sciences] liaison to the Soviet Union in the seventies, when I was in the lab.

**HATHAWAY**: And that entailed--? Did you have much sense of what it was, or it was just a

matter of keeping avenues open?

**ALBER**: I don't really know what he did in that. He was a member of the Pugwash Conference [on Science and World Affairs] involved in nuclear disarmament issues. He is a very genuine human being, interesting person, thoughtful, curious, cares about the answers to scientific questions. He had a lot of different things going on in his lab, and lots of different types of people doing them. People were different enough, and the lab was big enough, that there was a part of the lab that listened to the Boston Red Sox on the radio, and there was a part of the lab that listened to classical music. And you could go from one part to the other. These were people who normally wouldn't be together.

**HATHAWAY**: You mean just as a personality thing as opposed to their scientific interests?

**ALBER**: Yeah, Very sort of--I don't know how to say it--disciplined, genteel people to people who are—

**HATHAWAY**: Rowdy.

**ALBER**: --rowdy, yeah, exactly. I ended up going back to Alex's lab for most of my last year of graduate work with Greg [Gregory A.] Petsko. I worked on the crystal structure of yeast triose phosphate isomerase. Our assumption was this enzyme would be conserved enough that we could interpret our structure in terms of the known [DNA] sequences of triose phosphate isomerases from other organisms. In the event, it turned out that the fold of the yeast triose phosphate isomerase is similar to the fold of the chicken enzyme.

**HATHAWAY**: I guess it was chicken that Petsko had been working on, and some other people had been doing bovine?

**ALBER**: Well, Greg had worked on the chicken enzyme in the early seventies--or determined the [x-ray crystal] structure in the early seventies in David [C.] Phillips's lab. I think, at that time, they had also worked on the rabbit muscle enzyme, but the problem was less tractable.

**HATHAWAY**: Do you know why they were after that? Well, I guess the particular enzyme-- I mean, I understand why they would be after an enzyme, because, of course, it was Phillips's lab that was the first one to do the enzyme structure.

**ALBER**: Well, I think we talked about it last time, and that is that David and Greg were both interested in trapping enzymes in action. And so the isomerase was a particularly good system because in theory you could just add the substrate and look at the complex of the enzyme in a real substrate, rather than the enzyme and an inhibitor or a product.

**HATHAWAY**: But the chicken was just because it was available?

**ALBER**: I don't know the history of the work on why they chose chicken. Rabbit muscle had been studied because there was someone at Cambridge [University] who purified most or all of the glycolytic enzymes from rabbit muscle. So these proteins were all available, or they were purified, and people were trying to crystallize those.

**HATHAWAY**: Maybe I'm wrong to assume this or expect it in a particular area in which you are working in, or with these particular enzymes, but the yeast was such a well-worked-out system, it seems, compared to others, that usually that's where people started, as opposed to--?

**ALBER**: No. In fact, it was just the opposite. People didn't know much about yeast TIM [triose phosphate isomerase] . [Fred C.] Hartman had purified the protein. [Demetrius] Tsernoglou had found crystals readily. I managed to crystallize it with transition state analogs bound while I was in Phillips's lab in Oxford [University]. Also in Oxford I found heavy-atom derivatives, screened them by precession photography. And so when I got back to Cambridge that January, I started collecting the x-ray data. I got back in the fall [of 1979], and by January I was collecting the data. I remember we calculated the first electron density map on July 4.

**HATHAWAY**: You should have had a barbecue.

**ALBER**: Exactly. [laughter]

**HATHAWAY**: Science waits for--

**ALBER**: It seemed like Independence Day, in a way, because it was a first view of the molecule.

**HATHAWAY**: And the year--just again I want to make sure I get this--it's 1980?

**ALBER**: Yeah, '80. The pressure was that Greg Petsko was going to a meeting on glycolysis and glycolytic enzymes in London at the end of the summer. He had already agreed to give a talk on triose phosphate isomerase, but--

**HATHAWAY**: In yeast?

**ALBER**: Well, it turned out that we didn't have the structure determined, and so there was some pressure. I'd say, to his credit, Greg was helpful and encouraging and taught me a lot, but he never took over the project. He never sort of sat down and did it. So for example, when we saw the first electron density map, he said, "Oh, that can be traced." But he didn't sit down to try to trace it.

**HATHAWAY**: "Get out of my way, I've got till August 5," or something. That's good.

**ALBER**: It was really an amazing display of patience, and also his--what?--practice of teaching people in the lab, rather than just doing everything for them. He, I think, really sees that as a big part of his role--that people that come out of the lab should be independent scientists, rather than just technicians. Anyway, I guess I was supposed to be talking about Alex Rich's lab, but we'll come back to that. I was fitting [the election density]; Greg was doing phase refinement on our derivatives that summer to try to improve the electron density maps. I had never traced a [polypeptide] chain through an electron density map before, and I kept making mistakes and mistakes and mistakes.

**HATHAWAY**: As a matter of fact, if I can even get you, since you are going to be the first one who's going to talk to me about any kind of the steps with the purification and the crystal structure-- Would you mind telling me what you were doing wrong, or the steps that one--? Pretend I'm totally-- Don't "pretend." I really don't know what you're talking about in the sense of the steps involved. If you could take a couple of minutes, obviously not--

**ALBER**: So the goal is to get the position of every atom in the molecule, and these are big molecules.

**HATHAWAY**: So you pick different angles, and--?

**ALBER**: Well, the first thing is to purify the protein or molecule--it could be DNA or whatever. In the triose phosphate isomerase project, that step was accomplished by Hartman. His group basically just sent us the protein. And so then you take the purified protein sample at

several milligrams per milliliter, say twenty milligrams per milliliter, and add salts or alcohols or long-chain alcohols.

**HATHAWAY**: And this is the mother liquor?

**ALBER**: Well, this is what's call the precipitant, and it's just to make the protein insoluble. If you find conditions correctly-- That is, we have to make a crystal. And if you set the pH correctly, or the salt concentration correctly, or the protein concentration correctly, and you have all the right counter-ions and the temperature right and all those sorts of things, you'll get a crystal. The idea is that the molecule prefers to associate with itself rather than with the water, rather than being dissolved. If you set up conditions just right, there's only one orientation of the molecules that is more stable or favored, compared to the molecule being dissolved in water. And that one orientation ends up being, hopefully, a three-dimensional crystal. You could get two-dimensional crystals, which I'm sure you've talked to other people about, or may talk to other people about.

The idea of the crystal is that all the molecules are sort of lined up like tile in your bathroom. So every one is--

**HATHAWAY**: Is in order.

**ALBER**: Is ordered, right. The molecules are still moving, but they're intrinsically ordered in the crystal. Because they're all lined up, when the x rays hit each molecule, the x rays are scattered in the same direction by every molecule. So the crystal is an amplifier. And a typical crystal may have $10^{15}$ or so molecules in it. So the x-ray scattering signal that you get from a crystal is amplified about $10^{15}$ times compared to a single molecule. So that gives you a signal that's strong enough to measure.

**HATHAWAY**: Kind of also aesthetically really cool, I think. It's pretty amazing--a powerful tool, I guess, in the sense that it's able to show you something you can't see.

**ALBER**: Yeah, absolutely.

**HATHAWAY**: I guess I'm saying really obvious things.

**ALBER**: Well, it's not the same as having a picture of a single molecule. It's a space average and a time average. So maybe in the future, technologies will be--

**HATHAWAY**: Its accuracy must be-- It's a pretty safe average, right? It's a pretty large sample in the sense of what you're averaging, and you're really not off that--

**ALBER**: Well, one of the controversial areas in crystal-lography now is how to deal with the problem of these averages. Typically, the product of a crystallographic study is a set of coordinates for the atoms. And if the study is at high enough resolution, if there's enough information about how much each atom is moving, that doesn't tell you much about the ensemble of structures that the molecule populates in time.

**HATHAWAY**: Which is the most favored or--

**ALBER**: Right.

**HATHAWAY**: --kind of ideal.

**ALBER**: Right. So it's like reading *U.S.A. Today* doesn't tell you about individuals that are covered. So you end up with the average. If you consider enzyme reactions, for example, as reactions where this substrate binds, and then the reaction happens when the enzyme-substrate complex adopts a reactive conformation, it may be that conformation is populated for $10^{-12}$ seconds or something like that. Basically, you never see it. You wouldn't see it in an x-ray crystal structure. And so the question really arises, what do these averages mean? How do you represent them technically, in the sense of crystallography? That is, what is the best way to model your data? How do you interpret them biologically? Does the average hide the most interesting conformation, which may be there in just a small fraction of the molecules for a small fraction of the time?

**HATHAWAY**: Are these pretty much issues--? I want to say ideological, but it's not the right word--

**ALBER**: No, ideological--

**HATHAWAY**: Some of the intellectual controversies that have come with crystallography since they were able to start crystallizing organic structures or organic molecules? Or is this something that's really relatively--?

**ALBER**: No, it's a long-standing controversy that tends to get expressed in the simple question of, are crystal structures really relevant for the biological functions of these molecules? That question has been addressed in a number of ways. And Petsko and Phillips are people who are very seriously involved in that question.

**HATHAWAY**: Because the question bothers them, too? I mean, because they think the raising of the issues is legitimate, or they just want to put it to rest? I mean, they're convinced of its usefulness and utility and they just want to nail that down?

**ALBER**: That's right. For example, Phillips's group had determined the structure of lysozyme in many different crystal packings --

**HATHAWAY**: To show that--

**ALBER**: --and shown that the structure is basically the same. It's not a function of how it's packed in a crystal.

**HATHAWAY**: Right, it's a function of the atoms, of itself. Is that what you were part of?

**ALBER**: I was involved in another attack on a similar challenge, really, and that is to show that crystalline enzymes are catalytically active. I guess it was-- Well, I don't know.

**HATHAWAY**: Do you mean the crystalline form, right?

**ALBER**: Right. So you could take a crystal of a protein, add the substrate, and you'd get the product. So whatever conformation was there--

**HATHAWAY**: Was really there.

**ALBER**: --it still worked.

**HATHAWAY**: You weren't just making up a kind of in vitro--if you will, just to use the analogy--situation of, "Well, this is what it looks like, at least when I put in this thing." Because

I realize that some of those issues are long-standing, and perhaps have been addressed more readily, about the use of solvents and what are you exactly doing to samples. Even in the purification process, it seemed to be that experiments have been done to check the fact that "Yes, we are recapitulating what's going on in vivo," and not inventing something else that--

**ALBER**: Yes. So after you make a crystal, you shine the x rays on it. X rays are detected by some kind of photon counter--a Geiger counter or an x-ray sensitive film or x-ray sensitive phosphor--there are new detectors now that have speeded this up quite a bit. And then the problem is that when you collect the data, you get only half the information you need to calculate, with a computer, the distribution of electrons that gave rise to that pattern of x-ray scattering. To get the missing information--independent of any model--for large molecules, [Max F.] Perutz and others worked out a method called the isomorphous replacement method, where the basic procedure is to bind metals, large atoms, to the protein in the crystal. You make the assumption that the crystal without the metal is exactly the same, it's just missing the metal, and then you compare the x-ray scattering.

**HATHAWAY**: In sync and not a mirror-- I'm sorry, but what's the term that is used? To refer it back to the nonmetal: they have a relation that's always the same, right? The displaced one and the replaced one.

**ALBER**: Well, the metal-containing crystal is called a heavy-atom derivative. It's a term I used earlier. By making the assumption that the difference in the scattering is coming from the metal alone--

**HATHAWAY**: Yeah. That's what I was attempting to talk about.

**ALBER**: --you can basically get the scattered amplitudes for just the metal atoms that are in there, okay? It turns out it's fairly simple to solve the structure, or to determine the position of a distribution of atoms that's that simple--just a few atoms in a unit cell. That's a simple problem now. The approach that's taken is to determine the position of the metal atoms, and then from those positions to bootstrap the information that was missing when the scattering from the protein alone was measured. By using several different heavy-atom derivatives that have different metals bound at different sites, you basically improve the consistency of this information that was missing from the individual measurement. And so by comparing the scattering from the heavy-atom derivatives with the protein alone, you get the metal positions. You bootstrap the missing information. You do this several times, and the more times you do it, in general--although that's not always the case--the more certain or the better your information is that you're using to calculate the electron density map, okay?

Greg, actually, was someone who sort of drummed into people in the lab that in

crystallography virtually the only experiment that you do is to collect the data, and so this is something you had to do well because every subsequent step depended on the quality of the data. It was interesting that he had identified the key experimental step.

**HATHAWAY**: No matter what you were working on? It was going to be this--?

**ALBER**: Yeah, exactly. And he said, "Look, you have to learn how to do this, and you have to do it well because that makes everything else more believable." Anyway, so we did that with triose phosphate isomerase--calculated the first electron density map based just on one heavy-atom derivative. That was July 4, and by the end of the summer we had calculated maps based on up to three heavy-atom derivatives. It's a simple thing that one of the mistakes I kept making was to lose track of where the polypeptide chain was going through space. One of the reasons for it was that we were displaying the maps so that they didn't cover a whole molecule. We just carved out a region of space and displayed that.

**HATHAWAY**: Just because it's a smaller space and easier to work with?

**ALBER**: No, it was big enough to cover a whole molecule. It's just that the boundaries of our display didn't coincide with the boundaries of the molecule.

**HATHAWAY**: This was a computer-type--?

**ALBER**: No, it wasn't a computer thing. It was a physical map.

**HATHAWAY**: Oh, okay. So it's something you were constructing, if you will, from--

**ALBER**: Well, what it really is is a stacked set of plastic sheets, and each sheet has a contour map on it. The more contours there are there, the more electrons there are. So it's like each sheet is an altitude map, and it's altitude in electrons.

**HATHAWAY**: Sure. I was just curious what sheet you were using to- -

**ALBER**: Yeah, I know. It was a physical map in those days. And then you stack those up, and you look and you see where the molecule is. I kept having to go across the boundaries of the maps--go off one edge and come in the other edge--to get the whole molecule, and I kept losing

track. So Greg wrote a routine toward the end of the summer where we could specify that we wanted to look at the electron density corresponding to a single molecular dimer, okay? So that was one important step.

And then the other important step, in terms of mistakes, is that I kept following the chain where it was clear and then when I got confused I would go somewhere else in the molecule and start somewhere else and follow that until it was clear, and do this over and over again. I would end up with a bunch of pieces that were disconnected. The problem with that approach is that it's very hard to check the consistency of all these different little pieces.

And so finally we had an improved map, we had an improved display. I took the strategy that I would start somewhere in the chain, not knowing where it was, and follow that continuously without jumping anywhere. And I would follow that continuously until I definitely came to an end, and then I would go the other direction. I think I started that in the afternoon one day at the end of the summer, and essentially by four the next morning I had the whole molecule. So this was, you know, in a few hours, by just changing a few subtle things.

**HATHAWAY**: And this decision to keep going in-- It seems like that maybe--and correct me if I'm wrong, because it would be an important mistake I make--that at first you were kind of doing more sampling because going straight through you thought it was kind of like doing a lot of extra collection of information that you just didn't need?

**ALBER**: No, it's that when you're following the chain through this map there are lots of ambiguities, because there are places where the electron density gets very weak, or it might do just the opposite. You might have something like a freeway interchange, which is coming from errors in the map, and so you have to decide which way to go without knowing what the right answer is. And so basically you have to try out all these different possibilities.

**HATHAWAY**: You just tried them all out, then? In other words, when you came to a freeway interchange and you didn't know whether you were-- You just went all the directions to see where it would lead?

**ALBER**: And then if I found something that was completely inconsistent, then I would pick the one that was consistent and follow that.

**HATHAWAY**: Okay, I see. Now this is a typical situation anybody doing this kind of work might come across or have to deal with? Although maybe it's easier now because it's all done on computer or this can be done in a different way, but I'm talking about at the time. Or this was a particular problem that you were facing with particular fact--?

**ALBER**: No, it's a common thing. It's a problem you face in every structure determination.

**HATHAWAY**: Every grad student starting out doing this is going to also kind of be facing the same sorts of issues about "How do I follow this through?"

**ALBER**: Yeah.

**HATHAWAY**: One thing that has really amazed me is-- And I guess one of the places where it's put down the most clearly is in [Horace F.] Judson's book [*The Eighth Day of Creation: Makers of the Revolution in Biology]*. And that's the doggedness with which someone like Perutz would keep going after getting--I mean, what?--we are talking some thirty-plus years to solve the structure of hemoglobin. And while I think things are done a lot more quickly today, and there are a lot of methods, and some more rules have been found out for doing this sort of thing, it still seems to be very much an art, and not a—you use the word "science." It seems like you need a knack, and you need to know a lot about biochemistry and recipe-making and mixing and matching and that sort of thing. That again, I think, we'll talk about as we go along here and there. I think a lot of the efforts in the area have regularized that, right?

**ALBER**: Oh, sure.

**HATHAWAY**: To get away from that. But at the same time, it's still very much this kind of a-- It's almost like an artisan working, you know, or a woodworker or a furniture maker who gets-- Each thing is going to turn out different and be unique. There are still some lessons that can be handed down to an apprentice, and that sort of thing. I don't mean to make it sound too medieval, but that seems different than a lot of other areas of biological investigation. And again, I'm not meaning it in a pejorative sense.

**ALBER**: Well, there are lots of pieces to macromolecular crystallography. So everything from purification to understanding activities to crystallization and dealing with heavy-metal chemistries, and there's computing and keeping the instruments running. I find that's one of the things that makes it exciting. I think if you talk about Perutz, one of the biggest things that he had to overcome was just developing the methods, and the instrumentation was pretty unreliable. So now, I would say, the instrumentation is much more reliable, the computers are much faster. We could talk about a revolution in methods, which has certainly happened.

**HATHAWAY**: Also while you were at it really. I mean, some of it happened before-- I'd very much like to know, if now is the time? Or do you want to get through all of your work?

**ALBER**: Well, I think we'll come back to that.

**HATHAWAY**: Okay, yeah. Because I have a list I'm compiling here of things I want to talk about, so if you want to just go over your--

**ALBER**: Yeah. But I think there are parts of all experimental work which have art involved in it. How careful are you? What is your aesthetic about how the result looks, that you're willing to accept it? How carefully do you look at the result to figure out what it means? How do you get clues about what you should do next based on the result of each experiment? How do you know when to ignore an experiment you think might have some flaw?

**HATHAWAY**: And have enough sense to say, "Oh, I will add a little bit more of this" or "That was a really weird result I got. Instead of throwing it out I'll throw it in the freezer for twenty-five years or two months" or whatever.

**ALBER**: Yeah. I think the other thing about being in Greg's lab that was just part of the atmosphere that he created was, in addition to doing the experiments well, you had to-- Well, his attitude was that the crystal structure was just the beginning. Many people that were working at the time felt that crystal structures were the end, and once you determined the structure--

**HATHAWAY**: Then you throw it out there, publish it, and now you go on to the next one.

**ALBER**: --and then you move on, yeah. But Greg, in a sense, made his career studying proteins whose structures in general were already known, and doing crystallographic experiments in general on those. So triose phosphate isomerase was one example where he certainly did determine the first structure but then went on to determine the yeast enzyme structure as well because it was a better system for studying activity. But certainly the work on myoglobin and the work on ribonuclease--that was very exciting. That was happening in the lab at the time I was there. These are all proteins whose structures had been published over a dozen years before. [laughter]

**HATHAWAY**: It seems like you always double the term or the name to make the point--"the protein crystallographer's protein crystallographer." In other words, instead of doing it for the sake of getting as many structures out there so that people can start looking at structure-function questions, he seems to be constantly looking at the tools and instruments and theories behind doing it to see if you can't improve them or understand their limits or perhaps, instead of their

limits, what their potential power is.

**ALBER**: In fact, I think, he's not the protein crystallographer's crystallographer. I mean, in the sense that he's an excellent crystallographer, that is true. But people in macromolecular crystallography, I think, view him with suspicion or sort of as an outsider in some sense, a maverick.

**HATHAWAY**: Because of the chemistry?

**ALBER**: Well, no. Because he's not out there in general, you know, taking new snapshots of new molecules. He's studying how molecules work, in gory detail.

**HATHAWAY**: For--? And maybe that's what I am not—

**ALBER**: Well, after [John Cowdery] Kendrew and Perutz determined the structure of myoglobin, one of the realizations was the extreme disappointment that the molecule was much more complicated than they had envisioned. And then, of course, lysozyme was completely different--second structure. And that sort of--

**HATHAWAY**: The third one was different also.

**ALBER**: Yeah, exactly. So it led to the idea that the solution to the problem of how proteins fold and function wasn't going to be available by solving one or two structures. That led people to think, "Well, there are these different sorts of substructures--like α helices and β sheets and turns--and maybe certain [amino acid] residues specify, in a sort of hardwired way, what structures will form." The idea came about that, if protein folding was a problem that wasn't solved by determining the structure of myoglobin, maybe it would be solved by determining the structures of one hundred proteins or fifty proteins or ten proteins—some number--just to get a database that was large enough to find out statistically what kind of shape does each amino acid specify. And so that led to the drive, or the goal, that people would just go out there and determine structures. It didn't matter what it was; it was just building up the database.

**HATHAWAY**: If it was a product of an important gene, "Go do it," right?

**ALBER**: It didn't matter. It could have been toenail grease or something. [laughter] As long as you could crystallize it and get the shape, it was fine. That effort meant that basically, if you

purified a protein and made a crystal, and showed that it diffracted x rays, you could get funded to solve the structure. Once you determined the structure, you could publish it in an important place. So for example, Brian [W.] Matthews tells a story that after they determined the structure of chymotrypsin in the sixties, the editor of *Nature* phoned them up on a Friday and said if they had the paper in London by Monday it would be out essentially immediately. So that's what they did.

**HATHAWAY**: Is this [John] Maddox? No, he hasn't been the editor that long, has he?

**ALBER**: No. This was 1960s.

**HATHAWAY**: I wish I had the time. I could go back and find all these little questions that irk me.

**ALBER**: Yeah. But the basic idea was any structure was interesting, and that was because it was building up the database. And folding would be solved in a statistical way.

**HATHAWAY**: Is that still true?

**ALBER**: Now that a few hundred structures have been determined, and people have analyzed the database, there certainly are statistical preferences for what each residue would like to do, where it would like to be, or what shape it would specify. But that hasn't led to a reliable predictive method, and people have pretty much abandoned the idea that yet another structure will be the straw that breaks the camel's back. So now the situation is quite different where if you crystallize a protein, basically-- To be funded to work on a structure, you have to show that it's interesting and novel and it is worth determining that structure as opposed to a bunch of other things. Anyway, so how did we get on to that? I guess by saying that Greg's view is to analyze structures—

**HATHAWAY**: This also seems important because this was the milieu in which you learned to do all this, or to care about it or that sort of thing.

**ALBER**: And I would say that my bias for that developed in Petsko's lab at the time. Certainly that's what I did during my postdoc. I went to [University of] Oregon and worked on structures and properties of variants of a protein called T4 lysozyme. That structure had been determined, God, almost ten years before I got there.

**HATHAWAY**: And by those folks, by Matthews?

**ALBER**: Yeah, exactly. So it wasn't like I was determining a new structure. I was analyzing the structural elements, or the elements that gave that structure its strength or specificity of the fold.

**HATHAWAY**: This being after you were after the stability part of it--because, of course, that's what you are crystallizing, as we were talking about just a little while back: the kind of ideal or the conformation of the molecule at its strongest?

**ALBER**: Yeah. I mean, we can come to sort of the details of what motivated that work and what questions we were asking. I think the point that I was trying to make is that in Petsko's lab it was a given that the way to do science, in the sense that it involved crystallography, was that the structure was the beginning, not the end. That it was perfectly acceptable to go analyze a known structure rather than to solve new ones. That wasn't true in every lab at the time. That's all I'm saying.

**HATHAWAY**: But you think that most crystallographers are now doing this? That would have actually been my impression.

**ALBER**: Yeah. Many people are just focused on trying to understand new molecules, or determine the structures of new molecules. I 'm not saying that's bad or it's not good science or anything like that. I 'm just saying Greg's strategy included that but also included analysis types of experiments.

So the type of analysis that we did right away was to soak the substrate into triose phosphate isomerase. This was done in a device called a flow cell that-- I think Tsernoglou was the first person to use it in [Frederic M.] Richards's lab in the sixties to make heavy-atom derivatives. But Greg had adopted it to be able to soak substrates into crystals. For triose phosphate isomerase, the reason that we needed to do that was that there was an intermediate in the reaction process--a short-lived state that was unstable. So we couldn't just add the substrate to the enzyme, as you would think you could do on paper, because at a very slow rate the enzyme broke the substrate in half instead of just interconverting two molecules.

**HATHAWAY**: Back and forth, back and forth.

**ALBER**: We kept needing to add fresh substrate. So we did that with the flow cell. Unfortunately, when we added the substrate, the motions that the molecule underwent corrupted

the order in the crystals. So basically, it was like putting on glasses that were somebody else's. All of a sudden, you couldn't see any of the details. So we went from a situation where the normal crystals were such that we could image every atom, essentially, to a less intrinsic order. What that means is the molecules are all slightly out of register and so they don't scatter the x rays in exactly the same directions and so all the details are lost. But nonetheless, we did get a medium resolution picture of what the enzyme looks like in action. That was, I would say, a really exciting time in the lab. It was exciting just to see the thing happen, obviously. It was exciting because we sort of beat the deadline for this meeting by about two weeks.

I ended up going to the meeting as well, and took our data in a box, and went through customs in Heathrow [Airport]. You probably know customs in Heathrow: You just walk through if you have nothing to declare, and they pull you out of line if you look suspicious or something. So here I was this long-haired, bearded, wild-looking graduate student with a box. I went through with nothing to declare, but they got me and said, "What's in the box, kid?" I said, "It's an electron density map." They didn't know what that was, so I showed it to them. They said, "What's this worth?" I said, "Do you mean how much did it cost to produce this?" He said, "Well, yeah, okay. How much did it cost to produce this?" I said, "Well, maybe $500,000." [laughter] It was the wrong answer.

**HATHAWAY**: The value-added tax. [laughter]

**ALBER**: Yeah, the whole thing is worth like $15.99, the pieces are $15.99, but the information-

**HATHAWAY**: "How much is this worth?" "My life," you know.

**ALBER**: Yeah, exactly. So, anyway, that was fun.

**HATHAWAY**: Selling it to the Russians for--

**ALBER**: Well, unfortunately, I knew graduate students at MIT whose thesis projects were classified. I mean, can you imagine?

**HATHAWAY**: Do you mean biologists?

**ALBER**: No, physicists.

**HATHAWAY**: There was somebody like a censor or a government official constantly deciding what came out of their--?

**ALBER**: No, they couldn't talk. They couldn't talk about what they were doing.

**HATHAWAY**: So you mean they knew that that was going to happen, and so they submitted it? Or there's literally somebody at MIT or some government--?

**ALBER**: Yeah, they're doing classified research, and they're graduate students getting degrees.

**HATHAWAY**: Right. So they knew they were in a classified lab or something?

**ALBER**: Oh, yeah. So it's not such a joke.

[END OF TAPE 5, SIDE 1]

**ALBER**: I was just saying it was an exciting period. So the most exciting aspect of the result--even in this blurry image--to me was that part of the enzyme that was very floppy in the absence of the substrate became rigid when the substrate bound. We saw that as, essentially, new electron density in the map. So where there had previously only been islands of disconnected density which represented a floppy loop, now in a new position--sort of leading like a bridge to the banks of this sort of dispersed region, or unclear region--was clear density for a loop of ten residues. So this was a case where the enzyme wasn't this rigid template, like a lock-and-key situation that you often hear. It wasn't that the lock was all sitting there waiting for the key. It's that the lock formed when you put the key in. And that's a very special sort of thing. Another way to say it that is more technical but leads to my postdoc is that the enzyme finished folding only when the substrate bound.

**HATHAWAY**: Which means that the structure-function issues are obviously very, very important or basic to the protein transport, protein code--just the whole function of the cell?

**ALBER**: You're asking why is that important? Or who cares? What's general about that? [laughter]

**HATHAWAY**: Or what's great about--? You know, people talk about this molecule and this

one and this binder and this receptor and this ligand. You're kind of like, "Okay, but really what's--? It's just a bunch of goop." Here you're talking about a bridge kind of going through this "mook." Here's this connection, as you say, like just the key, and boom! it goes, right? So, yeah, I guess I'm trying to-- Okay, why is it important? Who cares? [laughter]

**ALBER**: Why is it important?

**HATHAWAY**: To get a nice bridge in the middle of all this chaos or murk or something like that? Not "mook"!

**ALBER**: Well, so this was a case where we basically looked at the results and noticed, "Ahh, the protein folds in the active state."

**HATHAWAY**: But all this talk about protein folding--

**ALBER**: It's not finished until it-- Okay, so then we thought, "Well, are there any other examples of this?" And it turns out that there are lots of example of this. Things that we knew about at the time are, for example, the coats of viruses don't finish folding until the nucleic acid is assembled inside. So nucleic-acid-binding parts are not these rigid things, like coat hangers, that the nucleic sits on--

**HATHAWAY**: Hangs on--

**ALBER**: --hangs on. They become intertwined with the nucleic acid as the whole thing assembles. Some other examples that were known then include genetic repressors, which seem to have disordered bits or arms, that in general wrap around the DNA. So the first question was, "Okay, part of triose phosphate isomerase folds. Is this an isolated thing, or is it something general?" And it turns out it's general. So then we thought about, "Why could this be designed this way? What are the advantages to the molecule, or what are the properties of the molecule that arise from the idea, or from the fact, really, that part of it's unfolded in the absence of substrate?" I think this was something actually that I thought about more than anybody in the lab. It was one of those situations-- I mean, it happens to all graduate students that you end up thinking about one thing so much that you end up getting to a different level.

**HATHAWAY**: That's the point of the whole business, right?

**ALBER**: Yeah, exactly.

**HATHAWAY**: Then you finally have enough--?

**ALBER**: And so--I don't know--I really felt like this was something that I keyed on.

**HATHAWAY**: This was yours.

**ALBER**: Yeah. It turns out that there are advantages in terms of thermodynamics, or consequences in terms of thermodynamics. The connection was simply that to get the protein chain to sit still--in other words to fold--the interactions had to contribute energy.

**HATHAWAY**: The process of the folding?

**ALBER**: Right. That is, just to pick one possible conformation out of the many, it takes energy that favors that one over all the others, okay? That energy of inter-actions comes from all types of molecular interactions you can think of--hydrogen bonds and charges, and getting rid of water, and all the things that people think give rise to interactions. But the point is that this type of coupling of binding and folding meant that the binding energy had to be weakened compared to a situation where the protein was already folded before the substrate caught on, okay?

So that makes things more reversible. In other words, it's something that keeps binding from being too tight. That is, let's take triose phosphate isomerase. If the protein was completely folded to start with, then the substrate might get on, but not get off as easily. It turns out that the slowest step in that catalytic reaction is the release of the product, that the enzyme itself has evolved to be so fast that all the chemical transformations are rapid. What slows the reaction down is just letting go.

**HATHAWAY**: Okay. And it really is a reversible process in vivo, and then it just gets done again? And it's just kind of sitting there to be used as the--?

**ALBER**: Right, as the catalyst. The thing that was sort of shocking was that here was a mechanism that people hadn't really appreciated that had evolved to allow things to be released. Now, in the case of viruses, for example, there's an obvious application or ramification there. When the virus gets into its host cell, the thing has to fall apart. So if it binds to the nucleic acid too tightly inside the [virus's] head, it will never uncode and allow infection.

Anyway, this was an idea that, I don't know, I guess occurred to me. I talked to Greg about it, and he said, "Oh, it's a great idea. Write a paper." And it's one of these twists in science. This was to me one of the most important parts of my research. I wrote a paper and submitted it. It was rejected from the *Proceedings of the National Academy* [*of Sciences USA]* by someone who worked in this area before, and said, "Oh, this is completely obvious," although he couldn't point to a place where it was in the literature before this.

**HATHAWAY**: In other words, he just didn't bother to point to a place, or you actually resubmitted? Was there an actual exchange, or you just couldn't see anything?

**ALBER**: When you submit to the *Proceedings,* you pick someone who is in the National Academy and you send it to them.

**HATHAWAY**: Oh, I see, okay. It's not a review process that's anonymous. Or they send it off then, finally, to be reviewed.

**ALBER**: So I felt it wouldn't be right to send it to someone else to get around that judgment of the first person.

**HATHAWAY**: Oh no, of course not. I mean, it wouldn't, would it? They would be highly-- Who was it?

**ALBER**: Oh, it's all right. No, really.

**HATHAWAY**: Oh, come on. You're just making some poor historian do some extra legwork here.

**ALBER**: No, it was someone, you know, who I think is a great scientist anyway.

**HATHAWAY**: Oh, I 'm not saying that you're right and he's wrong.

**ALBER**: I'm not being critical.

**HATHAWAY**: I'd be curious actually to know whether you did discuss it with him? Name or

no name.

**ALBER**: No, I didn't know him at the time. I just knew his work. I sent him the papers. He had worked on this idea with respect to the question that when substrates bind to enzymes, they have to adopt one shape as opposed to many possible conformations. So part of what weakens the binding of substrates to enzymes is the fact that the substrate has to adopt a unique shape. I just sort of turned the coin over and said, "Ah, well, the enzyme also has to do that, and that weakens binding." And he said, "Oh, pfff. It's obvious."

**HATHAWAY**: He decided it's tautological or something?

**ALBER**: Well, it was something I think that was obvious from his work, just that he'd never emphasized it.

**HATHAWAY**: Or bothered to demonstrate. Or suggest that it could even lead anywhere or was worth investigating—

**ALBER**: I guess I was disappointed because I thought, "Look, not only here is this small turning over of the coin," but in the paper that I wrote, which is in my thesis ["Structural Origins of the Catalytic Power of Triose Phosphate Isomerase"] –

**HATHAWAY**: Which I've got.

**ALBER**: --yeah, which you've got, which has never been published, I demonstrated a concrete case with triose phosphate isomerase, and then generalized it to other biological molecules and sort of discussed the general implications of this. So the paper was rejected. Greg, on the other hand, thought it was a great idea, so when he would give lectures, he would mention this. Then he said that probably we should submit it to the *Proceedings of the Royal Society* [*of London],* and David Phillips would be a great person to receive the paper. He'd be real excited, because it was about triose phosphate isomerase. So I did some rewriting and sent it to Phillips, and Phillips sent it out for review. The reviewers came back-- One of the reviewers said that it was all fine but this was Petsko's idea. Greg wasn't an author on the paper. I should have said that at the beginning: it was just me.

**HATHAWAY**: Okay, it was just you, right? And as you said, this was your-- I mean, we've already established the fact that Petsko wouldn't have-- You didn't ask him to put his name on the paper, and he didn't offer.

**ALBER**: No, I asked him to put his name on the paper, and he said no.

**HATHAWAY**: "It's your idea."

**ALBER**: I thought that he should definitely be on the paper, and he kept saying, "No, no, no."

**HATHAWAY**: There comes that time--

**ALBER**: Yeah, the irony is that if he put his name on the paper, it would have been published.

**HATHAWAY**: Because he had probably heard one of the lectures, you think? The reviewer perhaps had heard--?

**ALBER**: Absolutely, exactly.

**HATHAWAY**: Oh, that is irony.

**ALBER**: So it was this funny catch-22, you know, and I became so discouraged that I gave it up. But on the other hand, it led to some lasting friendships, because I did circulate the paper, essentially privately, and got to know some people. Peter [S.] Kim read it, liked it.

**HATHAWAY**: Which is, I hope, a collaboration we can talk about, because we'll get to get the other side of it, I hope, if he's willing. You make sure he is, right?

**ALBER**: Oh yeah. He was a graduate student at the time. So anyway--

**HATHAWAY**: Is it something--we'll cover it, I think, in more detail later if it is--that is manifested in later work? Or is it maybe manifested only in the sense that it's a way you think, or a kind of--? A coin turning is something you constantly do with the work you look at? In other words, you kind of do a reverse take on what people are saying. This man told you, "This is obvious." But indeed, the opposite was obvious or had been demonstrated in his work. What you were saying is almost the other side of the coin indicates not the same, right? Related, but

even opposite. So I'm kind of curious about the results of this work beyond the fact that it's led you to collaborate. Does it focus--?

**ALBER**: Well, it's certainly something that is part of how I view proteins and motions and dynamics. Just the question that Greg addressed in his work was really, what are the functions of protein motions? He was working on that when I was a student, and that's why I thought this was important. And he's still working on that question.

**HATHAWAY**: This is one aspect of it, or one chapter.

**ALBER**: Yeah, exactly. And the fact that that's a problem I take away from having been a student in that lab. So sure.

**HATHAWAY**: I can't imagine what the results of it would be in an applied sense of knowing these things, or conceiving of, or having a much better picture of protein-protein interaction, or protein-substrate interaction--all of that. But is it one of those issues--it's a "why" question and a "how" question--that perhaps a lot of labs and a lot of scientists and a lot of people funding science aren't necessarily--? "We really don't care why and how; we just want to know if we can redo it or we can insert something in to alter the process to deliver a drug."

**ALBER**: I think you could be a little more generous—

**HATHAWAY**: I know, I 'm sorry.

**ALBER**: --to say that it's a question that is hard to address experimentally, and that's been the hang-up. It's not that it's not important. It's that it's not obvious what to do.

**HATHAWAY**: I guess what I was wanting to oppose is-- There are scientists who--and I'm not saying one is better than the other or has got the wrong idea about science or is doing it for the reasons--just want to know some answers to questions because the questions are there--without getting into the Mount Everest routine of "Why did you climb it? Because it's there!" sort of thing--but who are doing science regardless of its potential outcomes as-- This question you learned about in Petsko's lab, and you've been thinking about it since then, without regard for its marketability or its tractability?

**ALBER**: Oh, no. I mean, on the contrary, I could list a set of practical applications in knowing

the answers to these sorts of questions.

**HATHAWAY**: But that's not what's driving you to ask the questions. Or maybe I'm still not being generous enough for you? Or it's not something--?

**ALBER**: If you are asking me personally what motivates me, I would say it’s curiosity. On the other hand, as I get on in my career, I'm starting also to see that there are more and more practical applications of the work in the lab. Part of that is that the technology for making the applications has exploded since I was a student.

**HATHAWAY**: So it's just more interest of all sorts, and because it's more accessible perhaps?

**ALBER**: No, I mean, it was hard to do everything compared to now. It was hard to sequence a gene. People were killing themselves because they couldn't--

**HATHAWAY**: And you wrote a whole twenty-page paper about it, right?

**ALBER**: Okay, so we sequenced triose phosphate isomerase, right? And I'll come to that; that was the next thing. But that was a time when labs couldn't sequence. And it was because you just couldn't get commercial reagents that worked, and you had to be careful, and you--

**HATHAWAY**: Postdoc caliber, right? Fifty to--

**ALBER**: No. That wasn't it. Now you don't even think of sequencing as-- You buy a kit, you know, and you do it, or you send it to the sequencing facility--you send your plasmid. Then it was a major technical thing, and I'll come back to that. But making a peptide? Forget it. Who could do that? Making a gene? Oh my God, that was unreal.

**HATHAWAY**: Now of course, you could do it from a keyboard, really.

**ALBER**: Yeah, send the graduate student downstairs, and they plug in the sequence. I mean, it's crazy. So it's a different world. I think that's in part why I tend to think a little more about practical applications, just because they're so much easier to accomplish.

**HATHAWAY**: I guess I want to make one thing really explicit for anybody listening to that: I'm not looking for you to justify on a practical level what you're doing. I'm actually rather interested in the--

**ALBER**: Oh, yeah, I understand that. No problem.

**HATHAWAY**: Okay, because that would be like getting Galileo: "So why did you really push this heliocentric universe? What good--?" It probably did help us get to the moon, now, didn't it? [laughter] But, you know, the practicality of-- I'm trying to think of good examples, anyway. I like just to make that [clear]. I'm not really challenging you on that issue. My bias being I kind of admire the person who is willing to answer that they do their science because it is there. Like you say, the success of your graduate education is getting good enough at things and asking questions and looking at particular things well enough and long enough and with collaboration of others to finally see something that nobody else has seen.

**ALBER**: I don't know. I think it's not that simple. I mean, it may be that simple when you are a graduate student, right, because you have very little responsibility except one thing.

**HATHAWAY**: That's your opportunity to maybe be that selfish and focused, or whatever.

**ALBER**: Right. And it may be that you have to have this curiosity to be dogged, as you say. But if I had to tell you what motivates me to do each task each day, the first thing that comes up would not be curiosity. It would be to practically keep my own lab running I have to do x, y, z. I have responsibilities to people in the lab. I'm trying to teach them things. I want them to learn how to do science. So that's why I'm doing this. It's not because I'm curious about something.

**HATHAWAY**: You're going to doggedly pursue these questions, right?

**ALBER**: Well, there are other motivations. There are other outcomes or goals or products. People are part of the products in an academic situation. It's not the same as just turning out the answer, although--

**HATHAWAY**: Or asking the hard question, maybe, or something like that? Although they can be done together, right? Certainly Perutz had had the same kind of "products as people" and whatnot by asking the same questions, or going after the same answer for a very long period of time, if we can use him as an example.

**ALBER**: Right. So this is a good example of what I'm talking about. I mean, I can't do science the way Perutz did science, because--

**HATHAWAY**: God knows if he's even doing science the way he used to do science!

**ALBER**: Right. One sort of simple way to say it, in addition to the fact that he's that much smarter than I am, is that—

**HATHAWAY**: Well, no, I was not inviting--

**ALBER**: What I meant is that I can't get funded to do something for thirty years and tell you that in the year 2020 I'm going to give you the answer. Or maybe not. I can't do that. There isn't a person in this country who can do that.

**HATHAWAY**: Not even the Pew is going to-- Three, four years, right? [laughter] But not thirty. Which is, I guess in this world, in this current day and age, very generous of them on that level, I suppose?

**ALBER**: Oh, it's great, yeah. But you know, there are examples from that time--Barbara McClintock is maybe another example.

**HATHAWAY**: Who, at the same time you turn around, was poorly remunerated for it. I mean, she was not supporting a whole lot of people, and she wasn't necessarily paid even well. She certainly was given the opportunity for years and years and years to pursue the same-- And she had the space and the time, you're right, to do it. Her colleagues recognized her abilities as that kind of "never stray from the path," and they gave her the opportunity to do it. You just said there's not a place in this country where you could do that anymore. You couldn't find anybody--and maybe you couldn't do it at the level you're doing it without all these people as well. In other words, you couldn't really go off like Barbara McClintock and be on your own some summertime.

**ALBER**: Well, maybe I said it right the first time: I'm just not that smart. I don't have that much insight to be able to say, "Okay, here is a problem that is very hard, and I'm sure I can solve it if I just work hard enough."

**HATHAWAY**: I won't do the asking or prognosticate the next ten years of protein crystallography, then, either. If it comes up, and you bring it up, then that's fine, but I won't ask you to do that.

**ALBER**: Anyway, so to get back to the chronology, the meeting in London was at the Royal Society, which is in a beautiful part of town. In that building there is a drawing of Dorothy [C.] Hodgkin's hands, and she's got crippling arthritis, so they're very distorted. Just the whole idea that this is something that is done by people, that is connected to culture, that has meaning in that sense--aesthetic meaning. I don't know, I think it's something I assume now. I find it a distracting thing, actually. It's not very useful in terms of, as I just said, turning out the product. I think some people would be shocked. I mean, I hope my study section doesn't listen to the tape or read the transcript where I'm saying, "Well, the whole point is not to turn out the product." That's heresy, I think, among some people. I'm sure you have come across different attitudes in your interviews?

**HATHAWAY**: Oh, as many as there are people, right. There are entrepreneurs, and they're real-- I mean, they call themselves on tape-- This is a business, and they are-- They'd be really good, I suppose, marketers of cameras, if that's what they had got into. And there are others who are like, you know, "No, this is a religious experience akin to taking vows in an order," and that sort of thing. [laughter] And of course all those--if you want call them--stereotypes or myths or types and paradigms of the scientist exist as well. I'm not saying everybody is a mere stereotype and stick figure of this type, but that's what we- - I mean, those are the parameters within which everybody who has a job that they think of as more than a paycheck--and even, I think, some people who think of their job as a paycheck, right--there is the whole issue about what is that in your life, and how you--?

**ALBER**: Well, yeah, and people go through different times in their lives where there is a lot of change.

**HATHAWAY**: Where all they need is a paycheck, right? [laughter]

**ALBER**: Exactly. Okay, so I got back from London. The major thing that had dawned on us was that the sequence of the yeast triose phosphate isomerase wasn't close enough to anything else for us to interpret the details of our electron density map. And at that time-- This is a story about luck in science. It turns out one of the features of MIT is that there are few or no intercollegiate sports teams, and as a result the intramural program is very strong and very serious.

**HATHAWAY**: Kind of takes the place of maybe the--? Is there a fraternity/sorority system on

campus?

**ALBER**: Yeah, there is.

**HATHAWAY**: Oh, then it won't take the place of it.

**ALBER**: No, it fits right into it. The biology department had a volleyball team, and the championships were coming up. I had played in college at [University of California] Santa Cruz--

**HATHAWAY**: You even said that--

**ALBER**: --NCAA [National Collegiate Athletic Association].

**HATHAWAY**: You guys had done really well when you were--That was at [UC]SC right, where you were second?

**ALBER**: UCSC? Oh, no, that was in high school. Yeah, at Santa Cruz we were pretty bad.

**HATHAWAY**: Oh, okay. I thought it was NCAA. The Sea Slugs? They weren't Sea Slugs then?

**ALBER**: The Banana Slugs, yeah. We'd get in games against [University of California] Santa Barbara, which was the national champion at the time, because we're in the same league. But they'd put in their third team, and we'd score two points, and so that would be the game. The levels were quite different. But nonetheless, I had played. I was recruited into the championship game for the team, and one of the other people that was recruited had played for [University of California] Berkeley. He was a postdoc in Dan [Daniel G.] Fraenkel's lab at the Harvard Med[ical] School, and so we played the game, and won. We were in the locker room afterwards, and were introducing ourselves, "What do you do?" It turned out he had just cloned the genes for basically most of the glycolytic enzymes from yeast.

**HATHAWAY**: From what?

**ALBER**: From yeast.

**HATHAWAY**: "It just so happens I met him on the volleyball court." That's very funny.

**ALBER**: Right, when we were sitting there taking showers, I go, "Oh, my God, you've got this gene. By the way, I just solved the structure of that enzyme, and we really need the sequence." It turned out he was enough of a biologist that he wasn't very good at sequencing. His name is Glenn Kawasaki. I was more of a chemist. Back then we were using [Allan M.] Maxam and [Walter] Gilbert's method of sequencing; it was all chemical sequencing. So we immediately started a collaboration. He would teach me how to make the plasmids and use restriction enzymes and things like that.

**HATHAWAY**: True collaboration, right?

**ALBER**: And then we would sequence this thing together. So to do that I went back to Alex Rich's lab because he had a little group of people led by Hank [Henry M.] Kronenberg, who was working on parathyroid hormone, and they had been sequencing. It turns out that parathyroid hormone-- The whole gene is only a few hundred bases. So they were using methods where they could read on their gels maybe eighty bases at a shot, you know. Triose phosphate isomerase was like fifteen hundred bases, and we were going to get killed. But nonetheless--

**HATHAWAY**: The time, and how long does it take to get the gel to read eighty, right?

**ALBER**: So we start into this, and Hank was really wonderful to work with. Of course, Alex was very generous to let me in the lab, and, you know, I did things--broke equipment and things like that--some crazy things.

**HATHAWAY**: But not on purpose.

**ALBER**: Anyway, Hank Kronenberg had been sequencing the way that he had always done it, or had first done it, but he had kept up a knowledge of what other methods out there were being used. And he didn't really want to try them because he thought if they didn't work, he wouldn't have gotten those eighty bases. But he was perfectly happy to tell me, "Oh, maybe you should try this." [tape recorder off] So Hank made suggestions, and then I sort of walked around MIT to the different labs that were sequencing at the time and said, "How do you do it? How do you do it? How do you do it?"

**HATHAWAY**: "Get out of here."

**ALBER**: Eventually, you know, I'd get ideas on how to change the standard procedure, and so we slowly made improvements to the point where we started to read two or three hundred bases at a shot. The sequencing went pretty well. We got most of it done really quickly and then got stuck in a region where there were no restriction sites, no places to cut the DNA. We really got stuck. It was really frustrating because getting the last little bit was quite hard.

To give you the setting, this was a time when Bob [Robert A.] Weinberg's lab was discovering restriction oncogenes but they couldn't sequence them. They collabo-rated with people at Cold Spring Harbor [Laboratory] to sequence them, and this is another lab at the [Massachusetts] Institute [of Technology]. There was a very highly recruited graduate student [Judy Swan] at MIT who ended up in David Botstein's lab, and basically her project failed because she couldn't sequence the gene that she was after.

**HATHAWAY**: And that's what she was being brought in to do, was to sequence the gene?

**ALBER**: That was the key part, yeah. So it was something that people had trouble with. It was considered hard. It was really wonderful working with Hank because he would say, "Oh, just try this. Just try this." These things would work. And then, of course, Hank would do it, and would apply those improvements to his projects. So it was very good. It was a fun time. We got the sequence in. It was pretty funny because we used the fit of the sequence to the electron density map to add a little bit of support to the idea that we'd gotten the sequence right. And that was, of course, very unusual. The sequencing labs weren't doing it for crystallography. But nonetheless, to do the sequencing, I learned some of the basic rudiments of cloning and handling plasmids and sequencing.

**HATHAWAY**: Which would do you in good stead when you got to [University of] Oregon, right?

**ALBER**: Exactly.

**HATHAWAY**: It's interesting you mention the difficulties of sequencing. One of your colleagues talks about doing a grad student project, basically a protein purification lab where they wanted to learn to purify proteins. She was set the task of sequencing a gene, without anybody to be found anywhere--and this is in St. Louis--until [Shirley M.] Tilghman showed up to give a talk and actually overnight saved this person a lot of time and trouble and showed her a few tricks on some of the splicing part, which is basically-- So it was an interesting time to just

hear about these kinds—

**ALBER**: Well, it's something that you take for granted. But it was hard. There was an article that Maxam and Gilbert wrote for *Methods in Enzymology* [A.M. Maxam and W. Gilbert, 1980. Sequencing end-labeled DNA with base-specific chemical cleavages. *Methods in Enzymology* 65:499-560] that had very detailed protocols, and most of what we did was straight out of that.

**HATHAWAY**: And it's still good-- I know that it's the [Tom] Maniatis and [Joseph] Sambrook [and Ed F. Fritsch, *Molecular Cloning: A Laboratory Manual* (1982)] that really gets cited. But you go back far enough in the literature, you still see that--

**ALBER**: That paper--

**HATHAWAY**: --was cited right before it was taken over by the other one.

**ALBER**: So anyway, I think it was because of this work on folding, or the recognition that triose phosphate isomerase had to fold, that got me interested in the problem of folding. It was a problem that Greg wasn't interested in, and also maybe that was another reason that I was attracted to it.

**HATHAWAY**: Not uncharted territory, but--

**ALBER**: It was more individual or something.

**HATHAWAY**: And obviously grew out of your background. But as you said, it had a lot to do with your own thoughts on the subject, to the point that he wouldn't even put his name on the paper.

**ALBER**: So when I was finishing, I applied to three labs for postdocs: Richard Henderson, to work on bacteriorhodopsin; Lyle [H.] Jensen in Seattle [University of Washington]; and Brian Matthews in [University of] Oregon.

**HATHAWAY**: Where's the first guy?

**ALBER**: Cambridge.

**HATHAWAY**: Harvard [University], then. Or not?

**ALBER**: No, MRC [Medical Research Council].

**HATHAWAY**: Oh, Cambridge [University]. Sorry.

**ALBER**: It's kind of weird. Why do people make decisions to go to places? I talk to my own graduate students about this now. How do they decide where to go? I had some strange criteria. One of the things I wanted to do was to be closer to my family. So that led to a bias against Cambridge, and then right around that time three-dimensional crystals of the reaction center were published [R.M. Glaeser, J.S. Jubb, R. Henderson, 1985. Structural comparison of native and deoxycholate-treated purple membrane. *Biophysical Journal* 48:775-80]. In the event, had I gone to Cambridge, I would have gotten killed on the problem of membrane protein structure. But that was the issue: Could you determine the structure of membrane protein?

**HATHAWAY**: And that's what you were--?

**ALBER**: Well, that was to me one of the most exciting things in structure, the other one being folding and stability issues. Brian Matthews had published a small number of papers at the time where they had used mutants, and compared the properties of mutants--viral mutants hadbeen screened for by sort of traditional genetics methods-- to try to understand where the properties of proteins come from in the system T4 lysozyme. I think I went and visited Seattle and Oregon, and I felt like the work in Oregon was the most exciting.

**HATHAWAY**: Your dad and your stepmom--they were in the Bay Area, right?

**ALBER**: No, they had moved to the Seattle area. So that was one of the attractions of going to Seattle. I'd be in the same place. In the event, I felt like Oregon--the work was more interesting. And I could always jump in my car and be up in Seattle in six hours.

**HATHAWAY**: Yeah, I'm from New England, so everything is really close. I mean, originally-- But it's still close. It's only a day's drive.

**ALBER**: So anyway, I ended up going to Oregon.

**HATHAWAY**: So you visited it? I mean, you visited all three?

**ALBER**: Yeah.

**HATHAWAY**: Okay. And they said, "Sure, come if you want." Was there any kind of heavy breathing down your neck by any of them?--"Aren't you coming?"--and lots of phone calls?

**ALBER**: I don't remember, to tell you the truth.

**HATHAWAY**: If there was, it didn't make a difference. You made up your own-- You had found three places then, and you checked them out and you picked the one you wanted.

**ALBER**: Anyway, so out in Oregon-- The thing that happened when I got out there was serious decompression, and I hadn't really realized how intense maybe it was at MIT and finishing had become, and so--

**HATHAWAY**: If the postscript of your dissertation is any example, I mean, I can see that it must have been very-- I almost thought, "I wonder if he had the Ph.D.'s equivalent of postpartum depression after getting all this work done?" It's just an acknowledgement of all the help. It seems like a very intense experience being expressed in your postscript, and so—

**ALBER**: I'll have to go back and read it.

**HATHAWAY**: You're kind of recapitulating that, if you will.

**ALBER**: Well, the effect was I didn't work that hard. Basically, I went through a period of sort of hanging back--built some furniture.

**HATHAWAY**: And this was something that worried you? Or it's something that you felt really great--?

**ALBER**: No, it was quite different. Well, it didn't really worry me, but knowing what I know now, it should have worried me.

**HATHAWAY**: Knowing what you know now? You mean that you see how that hurts other people?

**ALBER**: Well, no. You have to be dogged to get anything done at some level.

**HATHAWAY**: You think it slowed you down, then?

**ALBER**: Oh, definitely.

**HATHAWAY**: How many years were you in the lab there?

**ALBER**: Seven? Long time.

**HATHAWAY**: That is a long time.

**ALBER**: Six? Six.

**HATHAWAY**: Yeah, I was going to say I think it's more like six.

**ALBER**: Yeah, but that is a long time. And I didn't really realize it at the time, but it's a long time. Part of it is I couldn't find a job when I was looking for a job.

**HATHAWAY**: I was going to say, seven years today is-- You might as well shoot yourself in the foot, right? I mean, isn't that almost like you're going to automatically be questioned on your job interviews, "Why were you there seven years?"

**ALBER**: Sure. Yeah.

**HATHAWAY**: Isn't it supposed to be two to four?

**ALBER**: Yeah, I didn't know that.

**HATHAWAY**: Maybe it wasn't so true then, either?

**ALBER**: It was only six anyway. [laughter] I think the other thing is by the--

**HATHAWAY**: Maybe Matthews was a laid-back kind of guy, too?

**ALBER**: Yeah, he's laid-back. He's very competitive scientifically. Personally, he's very easy to get on--

**HATHAWAY**: And he didn't push you out?

**ALBER**: No.

**HATHAWAY**: He wanted you to hang around forever then, maybe? Very competitive when you think about it. [laughter]

**ALBER**: No, it wasn't like that. I did have problems getting a faculty position. And then when I took a faculty position, it takes quite a while to renovate a lab. It took over a year to move after I had decided to move.

**HATHAWAY**: To [University of] Utah, you mean?

**ALBER**: Yeah.

**HATHAWAY**: Because I know when I first met you here at Berkeley, you were also setting up here. Then you were kind of, "This is taking too long, and there's no--" I don't think you had electricity or something at one point?

**ALBER**: No equipment, yeah.

**HATHAWAY**: It was very frustrating for you then, right? Perhaps this is a reason why: it had already happened a couple of years before, and it was frustrating.

**ALBER**: Right. So anyway, I ended up doing a long postdoc. But by the time I got to Eugene, the easy things that I had proposed to do were already being done by other people in the lab. And, you know, I was not very highly motivated.

**HATHAWAY**: At first. Was this a personal--? You were burned out a little, maybe?

**ALBER**: I was burned out, yeah, definitely.

**HATHAWAY**: So it was a matter of R and R [rest and relaxation] to get going again. You certainly did a lot. We say it here: it was a long postdoctorate, an immense-- On my lap, I have a lot of work that came out of it. It seems that it was collaborative, in many ways outside of the direct kind of work you were doing, as well as full. It had breadth and depth.

**ALBER**: It took a long time to gel--that was one of the things.

[END OF TAPE 5, SIDE 2]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **28 July 1993**

**HATHAWAY**: All right, before we jump into the T4 lysozyme, I want to just follow up on a few quick things. At first you weren't sure if you spent six years or seven years in [the University of] Oregon, but it's six years, right?

**ALBER**: Six years.

**HATHAWAY**: Now, you met your wife in Oregon?

**ALBER**: That's right.

**HATHAWAY**: And it's this person you call Julie [A. ], whose name is Juli [D.] Klemm on some of these papers, correct?

**ALBER**: No.

**HATHAWAY**: Darn. I thought I was a damn good detective. You didn't meet her till the end?

**ALBER**: Till 1985.

**HATHAWAY**: And you got there in '82, '83?

**ALBER**: Yeah.

**HATHAWAY**: Okay, so we'll put that off until the right time, and we'll talk about it if you want

to. The other thing was, you also said that you had a hard time getting a job, and that was maybe some of the reason you stayed another year. I was wondering: The job market was just real stinky, right? Is that what you were saying? Or you went out to look for jobs, and people said, "We don't want--"? I wasn't quite clear on that.

**ALBER**: I think it was a combination of factors. Structural biology was not the fad that it is now. Many of the jobs that I interviewed for, people couldn't decide whether they wanted a *Drosophila* geneticist or an x-ray crystallographer or a--you name it.

**HATHAWAY**: It was that open and wide?

**ALBER**: Right.

**HATHAWAY**: At places like--? Do you remember any encounters?

**ALBER**: Name a place I didn't go. [laughter]

**HATHAWAY**: Okay. There were at least that many jobs to apply for and be interviewed for. So you got interviewed for a lot of jobs?

**ALBER**: Oh, yeah, I got interviewed for a lot of jobs. Then I think the other factor is I probably didn't give a very good talk, didn't give a good lecture.

**HATHAWAY**: You just didn't have enough stuff, you thought? Or you just didn't give a damn?

**ALBER**: Well, I was always very nervous about speaking, and wasn't that well organized sometimes in the way that I laid out the work, and also the work itself had some ambivalence to it. Well, we were making some progress in terms of technical accomplishments, right? We were making mutants at will, and determining structures at a rate where the structure became a useful experiment--an assay, if you will. So technically it was something new, but the answers were still pretty complicated. I imagine, although I don't know, that people might come away from some of the early work, especially when we were just right in the middle of studies without having tied conclusions, saying, "Gee, this is interesting, but what have they learned?"

**HATHAWAY**: So you're applying for jobs over a period of years. I mean, we're not talking just one year?

**ALBER**: Yeah.

**HATHAWAY**: We're talking about maybe you started in '85, and then went on to '86, or whatever?

**ALBER**: I think '86, '87, starting in '85. The other thing that happened at a couple of places is, basically, the university decided they were interested in the area and went out and tried to hire Brian [W.] Matthews, whose lab I was working in. So Brian got a lot of job offers.

**HATHAWAY**: From your talks?

**ALBER**: Well, no. He would have to go down and give the talk. The people would say if they could get Matthews, why not get Matthews instead of Alber?

**HATHAWAY**: Because he was at Oregon, and that wasn't quite--?

**ALBER**: Well, this is the odd sort of hubris of these places, of [University of California] Berkeley and Caltech [California Institute of Technology]--you name it, go down the line--Stanford [University]. They think, "Why would anybody want to live in Oregon?"

**HATHAWAY**: "He's been there forever," right? "Since he was a postdoc," right? Didn't he--?

**ALBER**: After his postdoc, he went to Eugene. He was a postdoc at Cambridge [University].

**HATHAWAY**: "And he's not making much"?

**ALBER**: Right, exactly. And so they sort of wondered what he was doing there. He's very good, you know, a brilliant crystallographer. "Let's get Matthews."

**HATHAWAY**: He's not the only person up there at this Institute [of Molecular Biology,

University of Oregon] or in the chem[istry] or biochem[istry] department that is good. I mean, there are other people.

**ALBER**: Oh, no, it's a very well-known group up there. A lot of people in the National Academy [of Sciences].

**HATHAWAY**: So I mean, they must have-- Maybe hubris is the right word. They were just being ignorant, or-- Well, I guess they figured most people would want to move from Eugene to the Bay Area, or Eugene to Pasadena--I don't know. That's interesting that all of a sudden that kind of made them click and think. He went and did a lot of-- He went at least to check it out?

**ALBER**: Oh yeah, he got interviews at Stanford and Berkeley and Caltech and ETH [Eidgenossische Technische Hochschule] in Switzerland, and lots of places.

**HATHAWAY**: And he didn't take any of them because they didn't offer him the moon and the stars and the sky as well, or--?

**ALBER**: I think he and Helen [Matthews], his wife, very much like Eugene, and there's a lot of loyalty there, and their kids are raised there. To get the details, you should talk with him. I think the closest place they considered going was Stanford, and my understanding of that was that the financing wasn't tight enough or wasn't organized enough. So they didn't offer to set up the lab.

**HATHAWAY**: "We'll recruit you, but that's kind of iffy."

**ALBER**: So then they realized what kind of mistake they had made and got the money together, but by that time he had lost interest.

**HATHAWAY**: Yeah, and it's clear that this is your understanding. You're right, it's not Brian; you're not speaking for him, and I'm not asking you to. If I ask you about a lot of these people, I guess I'm asking for your opinions. But at the same time, we're getting a picture of the milieu you're working in, right: What was Oregon like? And that's what I'm-- Not just what a catch Brian might be or how he deals with job offers. I do want to get something about him in this. As I explained off tape, we're kind of cheating and using you guys to get at your mentors as well or maybe some of the personal details.

We know you applied for a lot of jobs. You just had said that this was a situation that made you stay longer in the lab up there. Did you interview at biotech[nology] firms? Or was

that like you just weren't going to do that? You were going to either get an academic job or you were going to wait tables somewhere?

**ALBER**: I don't know. It wasn't that. Or write novels, I think, would have been more interesting. Let's see. One thing that's happened to me in the last few years is the process of becoming mortal. It happens to different people at different ages, and it happened to me pretty late. What that translated into is that until I was mortal, there was infinite time to do everything, right? So there wasn't any rush to leave Eugene. Sure, I was there six years. I didn't have a grand plan for my life, in the sense that I had to do certain things by a certain time. I was being productive there, and I felt that I could continue to do good work. And I really didn't need to leave; Brian was happy to have me there.

**HATHAWAY**: So you could have maybe just stayed there forever and a day as a kind of a lab-- Maybe until an academic position opened up there, or a research position, or grants would have kept you going there for a decade. You didn't worry about that; there was good work going on there, and you were doing it. Is that the kind of a sense you want to--?

**ALBER**: Certainly by the time that things were going well. I was happy with the work that was going on and the work I was doing. So intellectually I wasn't in a rush to leave. I didn't contemplate staying forever. First of all, it's very hard to stay in a place where you do your postdoc. I think personally, I was sort of going crazy living my life on residential streets and discovered that Oregon is charming but left some things to be desired.

**HATHAWAY**: You mean cultural--?

**ALBER**: Well, cultural, or just the energy level or something was-- Eugene is a pretty small town. By the time I left, I was happy to be moving to a larger city.

**HATHAWAY**: Do you think that maybe having more going on around you makes you more active, too?

**ALBER**: Oh, yeah. I love New York [City], for example. Not that I don't like to climb or go hiking or go to the mountains or ski or be outside in the wilderness, but I also enjoy cities.

**HATHAWAY**: This is maybe a good compromise here, and maybe Salt Lake [City] was--?

**ALBER**: Salt Lake was really good that way, too. But anyway, I was pretty frustrated, I think, by the process of not getting an academic position easily, although I had lots of interviews. The effect of it was that I really lost a lot of self-confidence during that period.

**HATHAWAY**: In the work you were doing? In a sense of facing the lab work you were doing, and the way you were thinking about doing things? Or just in this kind of, "I've got this drive, this thing that makes me--" I think there's another part one has to worry about in a very competitive world; I think basic biological research is very competitive. Was that kind of the--?

**ALBER**: Yeah, just in terms of how the work we were doing really stacked up.

**HATHAWAY**: Oh, so it was kind of an intellectual--?

**ALBER**: Sure. To do a set of experiments, you have to believe that they're the right thing to do. You have to believe in yourself.

**HATHAWAY**: Right, regardless of response for a while, especially [when] it goes against certain kinds of dogma or whatever.

**ALBER**: In the long run, it's got to be independent of recognition. Although it's becoming completely obvious that people tend to work much harder if they're recognized.

**HATHAWAY**: I think that's why in a competitive world this self-confi[dence] or this sense of yourself as being recognized as having the kind of abilities to give that lecture that catches people's ear and to have people say, "Oh, that's person X. She does this kind of work, and she comes from this pedigree," you know?

**ALBER**: Yeah, exactly.

**HATHAWAY**: It's such an important-- That's what people tell me. Actually, I think it's more like ambition is nine-tenths of doing good science. The other tenth is luck. I 'm not saying that's a monolithic view of the world, but a common one: that you've got to "Go for the gold." And because it's the people who are kind of, "Yeah, I like biology, and I'm good at it. But you know, I don't want to work eighty hours a week; I want to play golf some of the time"--well, those people are going to fall by the wayside.

**ALBER**: I would somewhere add talent in there. [laughter] Let's add a little bit of talent. Let's just say that ambition can be substituted by talent, and it's helpful to have more talent. I think people say that about Madonna.

**HATHAWAY**: I think Madonna's the one who puts forth-- Didn't she name an album *Blonde Ambition,* I believe?

**ALBER**: Yeah, well, people say that this is one person who has succeeded on ambition.

**HATHAWAY**: It depends on if you like Madonna or not, right? I guess perhaps you don't, or maybe you can't get by the ambition to see if she has any talent. I don't know myself. I guess that's the other side of the coin. People would cut down a lot on the ambition, and give it only three parts, and give another four or five parts to what you just called talent.

**ALBER**: Maybe this is a more important point than our laughter indicates in the sense that--we talked about this, I think, last time--there are other models: people who have done science and focused on either curiosity or vision about the natural world. And certainly when I look at my mentors, they've all had that to great measure. I haven't really worked with people who can wheel and deal and that's the whole extent of their genius.

**HATHAWAY**: I have come across people--certainly many, many of the Pew scholars I've interviewed--but just in my exposure maybe to other people, through Pew scholars to people who-- They'd make great lawyers, I think, if that's what they'd had a nose for when they were in college, if that's what they found out that they did really spectacularly in. But no, it was mathematics, and that kind of pushed them into science, you know?

**ALBER**: Yeah. There's a lot of that. I think I'm not very good at that. I'm a pretty low-key person who's more focused on the technical issues.

**HATHAWAY**: And maybe some of the more esoteric and intellectual issues behind the technical things, like questions about organic molecules.

**ALBER**: I think one of the things I said about Greg [Gregory A.] Petsko is that he's really bored by doing something twice. He always said it's worth trying to do something that wouldn't have been done if you hadn't done it. It's very hard to do that all the time, but it's certainly something I try to keep my eye out for. I wouldn't necessarily call it esoteric, but different.

**HATHAWAY**: This relates to something that I was going to bring up at another time, but we can bring it up now, and that was your-- I mean, I thought it was an ambivalent kind of discussion on your part. You talked about, "Well, of course, what you have to do is turn out the product, and that's what you are here to do." The rest of the stuff that you think about, and this attitude and approach you're talking about now, is your approach. May get in the way of that-- And you said, "I hope nobody listens to this tape or reads this transcript, because I've just--" And you meant your people in your lab, but of course you're expecting to be turning out products of which I'm sure they're a part of.

**ALBER**: No, I meant the people that fund my work--the Pew [Charitable Trusts] foundation. Although the Pew is not interested in the product, as I understand the foundation.

**HATHAWAY**: I certainly don't think they're looking at these things to evaluate what kind of product they got. We've been told that.

**ALBER**: Lucky you. [laughter]

**HATHAWAY**: I certainly am approaching it from that vein, in telling our interviewees that they can go ahead and say anything they want about the Pew, because the Pew's not going to read it like that--if they read it at all. If "they" be anybody, I guess maybe Ed [Edward H.] O'Neil or something.

Anyway, the way I want to ask the question was, although you see yourself sometimes as this turning out this product thing and getting grants and keeping the lab running and getting some people some decent jobs and training them to be good scientists and think about stuff in a scientific way, and then this kind of other world or other way of working, which you come to have mentors as guides for it, in a sense, as well as your own way of thinking about things--do the two really conflict so much? Without being idealistic and not thinking about the real world, what is the better way? Is there a way to turn this product stuff into some--? Maybe there's a way science was done that you're more familiar with, or you think was in the past, that was less on the product emphasis and more on asking the right questions and pursuing them and getting some answers. Am I being at all clear?

**ALBER**: I think the impression I'm getting from the question is, what's the balance between numerology and numbers of papers and numbers of people and amounts of money versus the more detached approach that may focus on quality, that is more of a--

**HATHAWAY**: That you couldn't do what Barbara McClintock did because, well, you need a lot more equipment and it's more expensive and more people. Just even that level alone--that physical necessity of doing the kinds of things you're interested in doing, never mind that the technology—

**ALBER**: I think with different people there are different optimal strategies. That's true of people in your lab, or heads of labs. Some people really are good managers. They can have big groups. They can keep things organized, and essentially turn out the product. Some people are not good at that, but maybe they have some deeper insights or are more careful, more subtle, and make contributions that are fewer in number but just as important.

For both of these extreme types of people, there's no substitute for getting the result. For a student who you're trying to teach to do careful experiments, if they're not in there trying to do experiments--

**HATHAWAY**: Carefully--

**ALBER**: --carefully-- If they're not in there, at least making mistakes, they're dead. In terms of learning how to do good work, there's no substitute for doing good work. It's fine to say something to someone in the abstract--"You should do controls to rule out alternative models when you do an experiment"--but the person who sort of does that organically is someone who's done it, not someone who's thought about doing it. So I guess I don't really think of this as a theoretical exercise. It's something that people have to go and do, and that's how they learn how to do it. There are certain ways to stimulate people to think and think for themselves and come up with conclusions and read the literature. There are certain elements of how people get to become good, independent scientists, and you can do those things. You can tell people to do those things, or encourage people to do those things, but you can't learn how to do it without doing it.

**HATHAWAY**: And maybe perhaps the other way-- I mean, that's the one extreme of the thinker and the kind of engaged mind, having to also be taught and to learn and experience the fact that, "Okay, you need to turn this into something that other people will be interested in knowing about"--so publishing. And you have to learn about the fact that other people work with you on these things and you can't possibly do this kind of science anymore on your own in your garden with your peas. You have to get along with people, and then you have to find some money because it's expensive. That perhaps the two are kind of working each other out to not maybe the best possible world for doing science, but one of the possible worlds of doing science. In other words, the compromising or whatever that one does--

**ALBER**: Well, balancing different activities, sure.

**HATHAWAY**: And that that's not too bad, right--that if you could just kind of check out to some place like Oregon, and not have to ever worry about money and just think about things, that you might not get much done that way. It might not be as fruitful.

**ALBER**: But different people fit into these situations in different ways. I mean, Oregon is more isolated, and there's less connection to the world. There's less pressure, and there's less having to worry about what people down the street are doing up at the other end of Mass Ave [Massachusetts Avenue].

**HATHAWAY**: You certainly see a new world.

**ALBER**: You just go out there, and you think for yourself. You figure it out, and you think, "This is the way to do it." Maybe you do it slower, and maybe you don't worry about the competition as much. And people who function well in that sort of environment will thrive at a place like Oregon. Whereas even say comparing Harvard [University] and MIT [Massachusetts Institute of Technology], as a graduate student at MIT, the reputation of Harvard was, "Oh, well, they sit around and think all the time." And the style at MIT is you just get in there and work, work, work, work, work. You get so many little bits of data that you don't have to think about it anymore. I mean, it's on your feet and you smell it, and so you know what it is. Any fool could figure it out with all the data that you've already got. Whereas other universities have a motto where you get what might be called the minimum amount of data to draw the maximum amount of conclusion, you know. The styles are different, and people are different. Some people do well in one, and some people do well in the other. I don't think there's a unique solution.

**HATHAWAY**: And you've certainly been around the block in the sense of having done maybe some real pressure-type turn--as well as being able to take the time to sit back. For instance, we were talking off tape about how to approach this review thing [T. Alber, 1989. Mutational effects on protein stability. *Annual Review of Biochemistry* 58:765-98]. That seems to me that's the thinking part that we were talking about, the taking the time. I mean, that must have been as beneficial to you as to anybody else who gets to read the article. You said the hardest thing was figuring out how to put it all together. That must have made you think about a lot of these questions over again in a kind of contemplative way, as opposed to a "This is my little area that I'm doing"-- Sorry. I did not mean "little" to sound like it's-- "This is my part of this work," and this way you get to kind of fit it into the puzzle more. And you certainly seem to do those sorts of things as well as do the product.

**ALBER**: The product. Yeah, absolutely.

**HATHAWAY**: There's a lot of product here that I'm holding.

**ALBER**: You know, just for me personally, I like solitude. Being in Utah or being in Oregon or-- When I was thinking about that review, I was traveling around the wilds of Australia with Julie, out in the middle of nowhere. And there was desert or barrier reef or whatever out there.

**HATHAWAY**: And it helped you to sort things?

**ALBER**: Yeah. I find it stimulates--what?--synthetic work, where a lot of the little details sort of slip away and you're trying to figure out how it all fits together. Or walking down a dirt road with the moon and the dogs running up ahead, and you're thinking about the moon and the night air--random things that cause other thoughts to fit together.

**HATHAWAY**: Just kind of give your mind a chance to start doing that kind of thing, which is maybe pondering it or something. Maybe letting go of a lot of loose facts.

**ALBER**: Loose details.

**HATHAWAY**: I don't know if now is the time to do this, but was coming to [University of California] Berkeley jumping back into a kind of faster pace? Or is this kind of isolated, or in between [University of] Utah and an Oregon and a--?

**ALBER**: Oh, no, not at all. This is a big change, and the position in the lab is very different. My role in the field may be changing. The sorts of scale of things that I'm expected to do is really changed. It's a challenge. It's definitely a challenge. In terms of my own career, I think, or my own life, it was a godsend to be able to go to someplace like Utah, which is interactive and supportive and low-key and genuine, and get the tenure thing out of the way, and get some work done, and things like that. [tape recorder off]

**HATHAWAY**: We're talking about what Utah had to offer to you in a sense, but also then taking up the challenge here. You were leading off on the point of getting the tenure thing out of the way and being able to start some work and maybe start a different kind or a different scale of that work.

**ALBER**: Yeah. A different scale, a different style. Berkeley is different. So we'll see how it

goes.

**HATHAWAY**: You've been here seven months, right?

**ALBER**: Yeah.

**HATHAWAY**: You came back here just before--? Well, actually, maybe almost nine, ten months, almost a year? In October you moved?

**ALBER**: End of October.

**HATHAWAY**: When I was here in January, things just had geared up, and things were kind of in place, but there was still no electricity or something like that.

**ALBER**: The equipment wasn't running. But yeah, things are already going quite well, and students have lots of nice results just in the last few weeks, and so it's very encouraging.

**HATHAWAY**: I was going to say you all seem to be throwing these manuscripts at me left and right. Some of them are from longer planning than just a couple of weeks ago. But obviously, I think one was just kind of put together, right?

**ALBER**: Most of the work is work we did before I moved.

**HATHAWAY**: I thought one was even submitted in June?

**ALBER**: The papers were two submitted in June and one in July.

**HATHAWAY**: I guess I kind of take that as everybody has finally looked at the paper, had their say and that sort of thing, and that to me is kind of like, "Oh, it's ready." Maybe. You kind of think of it, "Gee, we did that work a year and a half ago, you know. It's about time everybody got their approval in and we could send it off." But perhaps things that have happened a couple of weeks ago, as you say, it's going to be another year before they're written up and out.

**ALBER**: No, I'm behind. It's hard to write. It's been hard for me to write in the midst of the move and be caught up on that aspect of things, yeah.

**HATHAWAY**: And we can talk about the most recent stuff at the end, if you want.

**ALBER**: Sure.

**HATHAWAY**: I don't really have anything further. Since you had also brought up this discussion about the way that maybe some people got to do science in another time or another place, and looking at different things, and now what it was--we can kind of follow that through. That's about your style of science, and I consider that something to be kind of important to kind of cover. I find that people whom I've interviewed use the word, and talk about their "style." It is a conscious sort of thing that they interact with when they think about what they are doing. Unless there is something you wanted to continue with? Or to follow that through?

**ALBER**: Well, actually, I thought we might get that information just by, say, talking about the move to Eugene and the work there.

**HATHAWAY**: Right. And you had basically talked about the move, I think, and why you went there, and why you didn't go to Cambridge. So I think where we need to pick up from that is just what happened when you got there: what did you start working on and why, and that sort of thing.

**ALBER**: Yes, so after I built furniture, I went to the coast and things like that. I got to the lab, and I think most of the things I proposed to do for my postdoctoral fellowship were being done by other people in the lab by the time I got there.

One thing that wasn't being done was quite difficult. It was to look at the structure of T4 lysozyme and of mutants at a temperature just below where the protein would unfold to try to see if we could use crystallography to get an image of the protein falling apart. Of course the problem with that is that it's hard to collect x-ray data at high temperature. Also, if the protein falls apart, the crystal of it is also going to fall apart, so you can't collect any data. So it was something that I proposed to do, and something I thought would be fun, but I didn't have much faith that it would be technically possible to do it. So my enthusiasm was low is what I'm getting at.

**HATHAWAY**: Because all the other things you had come up with were being done? Do you mean there was this, "Okay, check that one off" kind of thing?

**ALBER**: Well, no, the things that I wanted to learn next--refinement of structures-- The molecules that I proposed to work on were being worked on by other people in the lab. That left this other project, which I had cer- tainly proposed to do it, but I didn't have much heart for it.

**HATHAWAY**: And as you mentioned, you were in this kind of lull anyway.

**ALBER**: Yeah. So I spent some time just trying to sort out what it was I should do, and started a number of things that all failed. But I would say this work was done in the context of the sense that I was immortal, you know, and didn't have—

**HATHAWAY**: What were some of the--? I take it that they were attempts to try to figure a way to get some sort of image, or get some sort of crystal.

**ALBER**: Yeah, crystals of new proteins mostly, and things like that.

**HATHAWAY**: So you actually tried to do it?

**ALBER**: Oh, yeah.

**HATHAWAY**: Can you--? Do you want to--?

**ALBER**: I don't even remember what they were, to tell you the truth.

**HATHAWAY**: They were really bad?

**ALBER**: No, they didn't work. I've forgotten. I mean, I could dig out my lab notebooks.

**HATHAWAY**: Well, I think at this point maybe we should just-- Please don't throw them away. Or give them to me. No. They'll find their way somewhere someday, I hope, and hopefully be a vital resource to those who want to look at it--

**ALBER**: Anyway, so eventually what happened was that a postdoc in a lab upstairs--Rick [Frederick W.] Dahlquist's lab--named Marilyn [R.] Kehry went to a meeting at Cold Spring Harbor [Laboratory] on site-directed mutagenesis. It was a workshop, really, that was run by Mark [J.] Zoller. He was one of the people with Mike [Michael] Smith, who had invented site-directed mutagenesis. Marilyn came back with essentially a notebook of protocols on how to do this stuff. She and I were friends, and it seemed like an obvious thing to start applying to phage [T4] lysozyme. It fit right in with my experience sequencing triose phosphate isomerase gene. I knew how to handle plasmids and sequence and things like that. I think it was probably the summer of '84.

**HATHAWAY**: You had some sense that people were already using these sort of genetic not necessarily site-directed but mutagenesis studies, if you will, on protein stability questions?

**ALBER**: Well, that was something that Brian Matthews really pioneered, and it was something that was done jointly with George Streisinger. George was a phage geneticist who developed screens for mutants of phage lysozyme in the sixties and had developed a collection of point mutants of lysozyme. George's claim to fame, really, was to use frameshift mutations to show that the genetic code used in vivo was the same as the genetic code that had been worked out in vitro, in the early sixties. The frameshift mutants were mutants of lysozyme. Streisinger had developed a collection of lysozyme mutants that were temperature sensitive, so that indicated there was some defect in the fold--something that held the protein together had been damaged by the mutation. In the second half of the seventies, Brian Matthews's group set about to find out what these mutations were, and to determine the structures of the mutant protein.

**HATHAWAY**: And he knew Streisinger, or this is how he got to know him, because he collaborated with him?

**ALBER**: Well, George was at Oregon. Sorry, I should have made that clear. In fact, one of the best things about the group in Eugene is that there were five different groups working on this one protein. So Streisinger had developed the genetics. Matthews, with Jim [S. James] Remington, had done the crystal structure in the early seventies. Rick Dahlquist had been applying NMR methods to try to study the protein.

**HATHAWAY**: Did you say NMR?

**ALBER**: NMR. Yeah, nuclear magnetic resonance. John [A.] Schellman is one of the leading thermodynamic theorists and experimentalists in the country; he had developed methods to reversibly denature T4 lysozyme. A student, [Margaret] "Peg" Elwell, in his lab developed a lot of the methods for measuring how strong is this protein. If you make a change, does that change

make it stronger or weaker?

**HATHAWAY**: You were using point mutations?

**ALBER**: No. Initially this is just a straight wild-type protein, and it was hard to make. It was a lot of work. They had to infect a large number of liters of *E. coli* cells with the virus, and get the lysate from virally infected cells. The second step in the prep [arat ion] was to dilute the whole thing to sixty liters and then flow it over a column that was the size of a football player's leg, basically.

**HATHAWAY**: Sounds like [Oswald Theodore] Avery and his lab.

**ALBER**: Oh, it's really bad. I mean, by--

**HATHAWAY**: Step after step after step--

**ALBER**: --what we call modern standards, it was really bad. So a typical protein purification would take a month. Once the proteins were purified, the mutations were identified by protein sequencing. Well, not even sequencing actually. What was done was to chop up the protein with the protease, find the piece that purified differently on an ion-exchange column, and then, not even sequence that. The experiment that was done was to determine the composition of the piece. By determining the composition of the piece and knowing the sequence of the protein, they could guess what amino acid sequence change or changes had taken place.

**HATHAWAY**: This is all before the recombinant stuff? I mean, you're still talking--the latest we're moving up to is the seventies?

**ALBER**: Nineteen eighties now, we're talking, okay?

**HATHAWAY**: Oh, and we're still stuck with lysozyme of the T4, because they could do this kind of backward.

**ALBER**: Well, the phage genetics was worked out, so you could make the mutants. And Streisinger had made this beautiful collection of mutants that we eventually, with new methods, characterized and published a comprehensive paper in 1987 [T. Alber et al., 1987. Temperature-

sensitive mutations of bacteriophage T4 lysozyme occur at sites with low mobility and low solvent accessibility in the folded protein. *Biochemistry* 26:3754-58] that ended up being one of the most important parts of the whole postdoc, I think. When I got to Brian's lab in the beginning of '82, there were no what are called pipette men--sort of adjustable pipettes for delivering reproducibly small volumes of liquid. These were standard procedure in molecular biology labs and many protein labs, but Brian's lab was still working with glass pipettes which had to be cleaned after every use, instead of—

**HATHAWAY**: And that was just because they were slow?

**ALBER**: Yeah, it's just a different world, really. So the first thing I did was order pipette men.

**HATHAWAY**: Different world, huh?

**ALBER**: It was a different world, yeah. Anyway, Marilyn got back from the Cold Spring Harbor course, and I thought, "Gee, this is something that nobody else in Matthews 's lab is doing," is to make site-directed mutants.

**HATHAWAY**: She brought this back because she was interested, and she'd gone there particularly to get-- It was a class she went to for the summer?

**ALBER**: Yeah, it was a workshop, a course.

**HATHAWAY**: She also brought it to your attention; she knew you might be interested in it, too?

**ALBER**: Yeah, she was working on chemotaxis with Rick Dahlquist. So we made some vectors for mutagenesis that had the lysozyme gene cloned in a convenient way, and sequenced those, and got people to make oligonucleotides for us to introduce mutations in the lysozyme gene. Back then, the hard thing was getting oligonucleotides. Now you just go and punch it in the machine and it's made.

**HATHAWAY**: Or a lot of times they get delivered, too.

**ALBER**: Or they get delivered pure, yeah. I felt that it was really important to compare the

properties of multiple mutations at a given site. And so, because oligonucleo- tides were dear, we had degenerate mixtures of oligonucleo- tides made, and then we did the mutagenesis, and then sequenced hundreds of clones to get the ones that we wanted. Whereas now, you just make them all separately. So it's a little
bit different style.

**HATHAWAY**: And a lot more work?

**ALBER**: It was a lot more work, yeah.

**HATHAWAY**: But pretty regular kind? You had it down so that it wasn't the kind of work that kept getting screwed up. I mean, it was just a matter of cranking it out?

**ALBER**: No, you had to be very careful. There was no kit for sequencing DNA, for example. You had to make the reagents, and you had to make sure they were perfect, because that really influenced the quality of the sequencing results. That's just one example.

**HATHAWAY**: Your being careful made it pretty consistent?

**ALBER**: Yeah, we had to be careful. So right about that time, one of the neat things is that Brian was on sabbatical in the lab; then he wasn't teaching. But we were starting to produce these site-directed mutants of lysozyme. A postdoc [David C. Muchmore] in Rick Dahlquist's lab had made an expression vector and generously gave it to us to express our mutants.

[END OF TAPE 6, SIDE 1]

**ALBER**: So Matthews really was the person who got in the lab, rolled up his sleeves, and collected data on the first site-directed mutant. In that lab, they developed an efficient method of collecting x-ray data with x-ray film. It's an old technology that they had raised to a new plane. But as a result, I wasn't at all familiar with it, so I didn't know what to do. I mean, I could grow the crystal, but—

**HATHAWAY**: You couldn't take the picture? [laughter]

**ALBER**: I couldn't take the data. So, you know, it was really Brian who said, "Okay, this is happening. Let's figure out how to make this structure determination go well." So he went in and collected the first set of data, and figured out that the process of determining the structures could be streamlined.

**HATHAWAY**: Could you--? I mean, I think of all the technical things I can keep bugging you to go into more detail about. You said, "We basically got it down to a situation where it's like doing an assay, getting the struc[tures]." You know what I mean?

**ALBER**: Yeah.

**HATHAWAY**: That seems to me interesting in and of itself. Was it only something, "I have to go ask Matthews"--that sort of thing?

**ALBER**: No. What do you mean? Why it is an assay, or what happened?

**HATHAWAY**: Why is it so--? Just because the mutations are so close, and you can kind of just-- I guess I'm getting the sense that to crystallize anything and to get a picture of it requires two years of work. I think what you were trying to say was that because these mutants were related in a sense of their production, once you had gotten the structure for one and sort of figured out how to image it and that sort of thing, that the next one was easier and the next one, and pretty soon--

**ALBER**: Yeah, I think a lot of these things are steps that used to be considered difficult. My graduate work, for example. After my graduate work, I used to be introduced as someone--when I would give a talk--who would determine the crystal structure of a protein, determine the crystal structure of a productive ES complex, and sequence the gene. And all of those things were considered hard, and might be the topic of an individual thesis, right? So people go, "Oh, gee, it's possible to do all these things." The postdoc was sort of the same way, determining a crystal structure-- When you got the answer, you normally published a paper. Whereas the attitude we were taking was, "Look, we want to compare ten crystal structures, or twenty crystal structures, and publish one paper about a comparison of all these things." It used to be something that people thought of as, you know, you had to talk to God or something. Or you had to be an expert, and then it would still take months or years or whatever to accomplish. Basically, we got it to a point where a first-year graduate student in a two-month stint in the lab could make a mutation, collect x-ray data, determine the structure, and refine the structure. Whereas before, each of these steps in labs where it hadn't been done before might have been considered a difficult thing to do.

**HATHAWAY**: Is this part of it? This paper where actually it's Sun Dao-Pin that-- You said '87, so I'm picking this one [S. Dao-Pin et al., 1987. Use of site-directed mutagenesis to obtain isomorphous heavy-atom derivatives for protein crystallography: Cysteine-containing mutants of phage T4 lysozyme. *Protein Engineering* 1:115-23].

**ALBER**: No, it's the *Nature* paper [T. Alber et al., 1987. Contributions of hydrogen bonds of Thr157 to the thermodynamic stability of phage T4 lysozyme. *Nature* 330:41-46].

**HATHAWAY**: It is the *Nature* paper, and not a combination of the two? I realize that you're not first author on this.

**ALBER**: No, the other paper [T. Alber and B.W. Matthews, 1987. The use of x-ray crystallography to determine the relationship between the structure and stability of mutants of phage T4 lysozyme. In *Protein Engineering,* eds. D.L. Oxender and C.F. Fox. New York: Alan R. Liss, 289-98] was a study in which we had all the mutants made for other pur-poses. It was a paper where we had cysteines introduced in different parts of the protein, and they were all made for different reasons. But it turns out cysteine is a target of mercury, and that's commonly used to make heavy-atom deriva-tives for structure determination. So it was falling off a log to take these proteins that had already been purified and already been crystallized and add mercury and take a few x-ray photographs and write a paper about which ones worked.

**HATHAWAY**: And to kind of compare this or follow this thing about the isomorphous replacement, whether you could improve upon it or found a more systematic way--?

**ALBER**: The question in that paper was, if you have to make a mutation to make a heavy-atom derivative, where should you put the mutation?

Anyway, so the sort of program in Oregon that developed was, pick sites that have well-defined questions associated with them and make a series of mutations that test each possibility or that you can use to quantify each interaction at that site. So the *Nature* paper was really the first example of that.

There's an ironic story, and that is the first mutation-- Or the reason we focused on that site is that there was a mutation in Streisinger's collection in which threonine 157 had been changed, and in fact they thought it was changed to alanine. The evidence for that was one of these experiments where they purified the protein and took a month and chopped it up and found the piece that was different and got the amino acid composition of the piece but it turned out it wasn't that clear. They thought it was alanine that was different. It turned out that the x-ray diffraction data sort of fit with alanine, but there were always some water molecules in the

model that moved a little bit too close to the methyl group of the alanine-side chain. So it was very uncomfortable. Anyway, we thought it was alanine--so threonine and alanine. We thought, "Well, we want to find out what parts of the threonine group are leading to the change in stability." So we made a bunch of mutations there. What happened was it turned out that because of the way we made the DNA, we ended remaking the threonine-to-alanine change, and showed that its properties were actually different from the original mutation.

So this happened, it turned out, a week before I was scheduled to go give a job talk, of all things, in Seattle, at the Hutch [Fred Hutchinson Cancer Research Center]. You know, it really became important to find out what this mutation really was. So I went back to the original phage stock and crossed out the mutation into a background in which we could actually make and clone the T4 DNA. The problem with phage T4 is that the DNA is modified, so it can't be cut with restriction enzymes. So you have to do some special things to be able to handle the DNA in a conventional way. So we did that. I cloned it out and sequenced it and, sure enough, found that it was really isoleucine that was there in the original phage stock. Fortunately, this didn't at all destroy the experiment that we had done. It didn't take the mutations we'd made and make them irrelevant. In fact, it made them more interesting. The only problem was that I 'd been working essentially nonstop for a week, and I went to this talk to Seattle and I could barely stay awake. It was really awful. I think that was the worst talk I've ever given. God, it was really bad.

**HATHAWAY**: I take it it was still--? It was one of these situations where you get up, you have slides, and you don't read from the text?

**ALBER**: Oh, no, you don't read from the text.

**HATHAWAY**: Actually, I haven't asked anybody this yet, but why? It's just boorish, or it means you're not very bright and you don't know your work? Why does nobody read from a prepared text?

**ALBER**: It's not considered spontaneous, or--

**HATHAWAY**: Because all those slides are mnemonic devices, right? Then it's memorized? Or, well, I'm sure some people put it together differently each time. It's not—

**ALBER**: And at some talks people interrupt as you go along, and ask questions as you go along. It makes the talk less accessible, I think.

**HATHAWAY**: To do--?

**ALBER**: To read it.

**HATHAWAY**: I thought it maybe was kind of a performance thing, too. You know, the best and the brightest--you're good at this, you know it, because you don't need the text.

**ALBER**: I don't know.

**HATHAWAY**: But I come from a world where people read from prepared texts all the time. I wouldn't go near a talk without a prepared text, at least notes to--

**ALBER**: Well, this talk in Seattle was amazing because it turned out there was a blizzard in Seattle that day and the city shut down. I got to the Fred Hutchinson Cancer Research [Center], and nobody could get there. And instead of sending me home and getting me back another week or another month, they said, "Oh, just give your talk."

**HATHAWAY**: To three people.

**ALBER**: Literally, there were six people in this huge room. I really discovered in that talk what you get from the audience. You know, when you look around an audience, you get a lot of energy. When you look and you see they're understanding or they're excited or you've said something that's piqued their interest, you can look at people and that comes right back and really adds to your enthusiasm.

**HATHAWAY**: When you can look out and see [makes snoozing sound]—

**ALBER**: Yeah. If somebody is sleeping, then you know you'd better pick up the pace or try to be more interesting or be more provocative.

**HATHAWAY**: It's an interactive thing, and not a--

**ALBER**: Yeah, whereas when there were six people scattered around this room, and I could barely stay awake because I hadn't slept in a week-- It was terrible. [laughter]

Anyway, so I mean there are better things to come in all this, for sure. I think, the real process that was going on in the lab was trying to put all the pieces together. For example, people in the Matthews lab really hadn't done any cloning and hadn't done much genetics, and so to get that all working and then to get the crystal-lography so that it was streamlined so that people could actually do it in a reasonable amount of time-- Like just even the expression of T4 lysozyme: if it takes you a month to purify the protein, you can't determine twenty structures because you'll never get the materials. Just having an expression vector that made so much of the protein that you could purify it in two days made a huge difference.

**HATHAWAY**: That was just all already understandable to you? In other words, what you kind of brought with you was "Of course, we're going to do it this--" because you'd already sequenced. You had enough of a sense of what was out there to be able to make these changes?

**ALBER**: Well, just the sequencing part is what I had done, and I was aware that other people had expressed proteins at high levels. David Muchmore in Rick Dahlquist's lab had done that with T4 lysozyme for us. God! It wasn't that there was another lab out there, you know, making proteins by the dozen and trying to do physical measurements.

**HATHAWAY**: They were all kind of figuring this out. My question is now: Is all this stuff and this turning structure-making into an assay--if I can use maybe what is a little bit of a simplified--?

**ALBER**: No, that's a perfect-- That's very good. That's fine.

**HATHAWAY**: You picked it. Okay. Is this transferable now to another situation? Can you pick up the next protein and turn it out as quickly?

**ALBER**: Yeah.

**HATHAWAY**: And why aren't people--? I don't get the sense-- And as you said to me, "You know, it's still publishable; if you get a structure, you publish it in *Science* or *Nature."* I mean, you don't just publish it in *Methods in Enzymology*--I guess that's not where you publish it anyway--or *Biochem*[*istry]*. I mean, it's big news. I suppose some of it is. Some of the structures they get-- This actin-myosin complex that was just published in *Science* [I. Rayment et al., 1993. Structure of the actin-myosin complex and its implications for muscle contraction. *Science* 261:58-65]--I guess it was thought to be difficult and hard.

**ALBER**: Oh, it was incredibly hard, yeah.

**HATHAWAY**: That's because it was an interactive kind of--Between two--?

**ALBER**: No, I mean the structures that we were determining, the structures of lysozyme-- There are now over five hundred different mutants, a huge number. When I got to Brian's lab, there were maybe five, and when I left there were maybe fifty, and now there are five hundred. So it's really taken off in that way. It's much easier.

**HATHAWAY**: It really does have something to do with an area being worked well enough?

**ALBER**: No, no. What I 'm going to say is that once you determine one, it becomes much easier to figure out the second one.

**HATHAWAY**: So that first one is still a toughie.

**ALBER**: The first one is still hard, yeah. And this idea that the crystal structures is not an end in itself; it's the beginning, it's an assay, it's a piece of information. It's not an altar, right?
**HATHAWAY**: Sure, right.

**ALBER**: In retrospect, it's something right out of Petsko's lab. He had a postdoc [William Gilbert] that determined the crystal structure of ribonuclease at ten different temperatures, or six different temperatures, over and over again. "It's an assay, stupid." [laughter] I mean, if you read this paper that I gave you that we just submitted to *Science* [P.B. Harbury et al., 1993. A switch between two-, three-, and four-stranded coiled coils in GCN4 leucine zipper mutants. *Science* 262:1401-7], one of the things I like about that paper is that it's a paper about a crystal structure in a way, but not really. In the text of that paper, we don't say anything about how the crystal structure was determined. It's buried in the notes.

**HATHAWAY**: Right. Again, and now that we've discussed this really explicitly, but I was going to ask you-- This is about doing the mutants and getting-- I mean, and now I don't know how many-- I won't guess how many you did, but--

**ALBER**: There is only one [structure solved] in there, okay? But it turns out--

**HATHAWAY**: Oh, I thought you had gotten the results where you had-- Oh, you didn't maybe crystallize them all, but you could extrapolate and say that there has to be a dimer, and then a trimer?

**ALBER**: Yeah, but this is a mutant of the leucine zipper that turns out to be quite different from the leucine zipper. Instead of having two chains, it has four chains.

**HATHAWAY**: Right, and then it has--

**ALBER**: So that's why having one mutant is interesting. The paper itself is a comparison of nine or so different structures.

**HATHAWAY**: The two labs were able to get structural data on this, if you haven't crystallized it all, right?

**ALBER**: Yeah. On the four-stranded structure, we had determined the structure, and that paper presented—

**HATHAWAY**: How many leucine zipper mutants from yeast do you have made, between you guys?

**ALBER**: Well, six or seven now.

**HATHAWAY**: So that's pretty quick. When did the *Science* piece come out, when you did the first--?

**ALBER**: In '91 [E.K. O'Shea et al., 1991. X-ray structure of the GCN4 leucine zipper, a two-stranded, parallel coiled coil. *Science* 254:539-44].

**HATHAWAY**: That's two years.

**ALBER**: Yeah, but see, the thing is the focus of my lab is not mutants of leucine zipper. I mean, I have a grant to work on mutants of leucine zipper, and we're working on mutants of leucine

zipper. But the idea of making point mutations like single amino acid changes and crystals that are essentially exactly the same as the wild type and determining the structures and determining the stabilities and drawing conclusions-- I mean that's exactly what Brian Matthews's lab is doing fantastically well.

**HATHAWAY**: With?

**ALBER**: With T4 lysozyme, right? They've got five hundred structures, and I've got five or seven or whatever in my lab, right? So why bother?

**HATHAWAY**: This is the "Why do it again? Why do it twice?"

**ALBER**: "Why do it twice," exactly. And so there are very specific issues that we're going after with these structures. One of the things that's quite different here is that by accident Pehr [B.] Harbury in Peter [S.] Kim's lab discovered that when you change the interface of the coiled coil, you change the number of strands in it. He made these peptides, crystallized them, and we determined the structure that's described in this latest paper. The shocking thing was that this peptide made a tetramer instead of a dimer. We had no idea that this was going to happen. And then Pehr went back and looked in solution at all his other peptides, and he found dimers, and he found trimers, and he found tetramers, he found mixtures of these different states. I mean, all of a sudden, you know, he had opened up a whole new area, a whole new problem. So we can come to that later, but--

**HATHAWAY**: Yeah, no. I'm just making a parallel in the sense that--not that you are going to go out and repeat point mutations or site-directed mutagenesis on this because, "Well, it worked once." But just that, again, here was a situation where the question about deriving the structures to make things clear had-- That was the point: to go move on, not to publish this thing in *Science* and then go, "Ooh, we did it. We got the structure."

**ALBER**: Well, my feeling is we need the structures to interpret data that's about stabilities. You just need to do it. But we're not going to go out systematically and try to determine five hundred structures and catch up to the Matthews group. It's just essentially redundant information. What are we going to find out that they haven't already found out, or that you couldn't find out by just looking at their data in the database?

**HATHAWAY**: Right. And you think you could do that to any kind of protein, right?

**ALBER**: Yeah, you can do it. People are doing it. You know, now that--

**HATHAWAY**: Okay. Do you think people are going to do it to the leucine zipper also? They are going to do 200 maybe, or 150 to make the point?

**ALBER**: I don't know.

**HATHAWAY**: You're certainly not going to.

**ALBER**: I don't care. [laughter] People are taking other proteins, studying the effects of mutations on stability. Alan [R.] Fersht's group, for example, in Cambridge [University], is working on a protein called barnase. They take techniques that have been developed in other labs and just apply them.

**HATHAWAY**: Do you think that they are going to come up with anomalies, or things that kind of finally--? Is it some notion that the field is still like what happened originally with the myoglobin: "Well, if we got one, now we'll get two, and maybe that will give us this rule. Now, we'll do three; maybe we'll do fifty--"

**ALBER**: Well, you want to find out how general things are. It's important to find out how general things are, but—

**HATHAWAY**: Not on your time?

**ALBER**: That's the way I feel. It's not what I would prefer to focus on if I have a better idea. As long as I have a better idea, I would prefer not to find out how general somebody else's results are. That's one of the questions: Is this "attitude"--right?--is this "attitude" compatible with the style of science that happens at a place like [University of California] Berkeley, where you have to turn things out at a certain rate and the standards are different?

**HATHAWAY**: You've got tenure. Meaning your lab still runs and you get money and you've always got a job in the UC system, unless, I think, you shoot someone in the head or something with a pistol. But I would have actually wanted to-- And maybe this isn't where you want to go, so you can tell me, "No, I won't answer that question now." But I would have suggested that you don't find the generalizing of something you already worked on quite centrally as something you want to do, because there are still more questions about, for instance, protein stability or thermal

stability in proteins that require answering, and you've got some ideas on how to answer them. So you are going to go do those now. I mean, it's not like you're going to just-- Because you've got "attitude." You're one of the first ones because you were involved in the lab that did it, so let's go do something else now.

**ALBER**: Well, part of it is just constitutionally preferring to try something new. The other part of it has to do with funding--funding and credit in science now. There's no way that somebody would fund my lab to work on point mutants of lysozyme. If we have sort of a different idea or a different approach or a whole new class of things we're going to develop, yeah, maybe we could use lysozyme. But I'm not going to be viewed as an original scientist or a creative scientist by continuing to do exactly what's happening in Brian Matthews 's lab.

**HATHAWAY**: Although you admit that what a lot of that was was clearly stuff that your name is on as first author.

**ALBER**: Yeah, that's fine.

**HATHAWAY**: I mean, I understand you didn't take it with you. You didn't. Your projects at Utah certainly were not like just-- There were certainly some things about finishing up where it's the same group of people from Oregon writing.

**ALBER**: Yeah. For instance, the things that we worked on on lysozyme at Utah were some business about the kinetics of protein folding that the group in Oregon is not interested in. They're focused on thermodynamic methods, so doing a survey of kinetics effects was easy to do. Well, it wasn't easy to do. Juli Klemm did a really good job on that, but it was something that was out of the tent, so to speak, the Oregon tent. The second thing was looking at the effects of making cavities in proteins, and trying to bind ligands inside cavities. This was something that we could just never get to work in my lab, that Brian's lab eventually got to work. They're making a lot of hay about this.

**HATHAWAY**: That was also done on T4?

**ALBER**: On T4. Yeah, we tried with T4. We just couldn't get the experiments to work.

**HATHAWAY**: Other things too, or you just always stuck with the T4?

**ALBER**: Well, we also tried with BPTI, bovine pancreatic trypsin inhibitor. It was just a matter of picking the wrong ligands to try to bind. We picked things that were sticky and reactive and hard to handle. Brian's group picked benzene, which is inert, and found that they could stick it into a cavity pretty easily.

**HATHAWAY**: So you dropped that? Because they figured--?

**ALBER**: Oh, yeah, they figured it out, so I don't work on that anymore.

**HATHAWAY**: Was there a suggestion that there was competition, or was it kind of like, "I'm doing it this way, and you're doing that way. Let's just get the answer to this question." Was there collaboration even, sharing of ideas and information?

**ALBER**: No. Well, it was something that I had spoken with Brian about before I left Oregon, and he said, "Yeah, try it." And when we didn't make any progress, and they felt they had a way to do it, they did it.

**HATHAWAY**: So there was no, on either side, any kind of--? Some people have told me of experiences of great difficulty, or a lot of negotiation going into "Which project am I taking away from your lab?" that they have with their mentor. Other people, it's just so obvious what they're going to take away, and nobody cares. I was just curious as to whether there was sort of a negotiation.

**ALBER**: Oh, yeah. We talked about it, and this is one of the things we talked about. I just couldn't get it to work. You have an idea. You don't like pee on the post, and nobody can-- That's my attitude. Ideas are cheap. I mean, some people have one idea, and if it's stolen and they get scooped, their career is over. When I get to that point, I might as well hang it up, anyway.

**HATHAWAY**: Unless you'd like to develop a sense of what you did in more detail-- I mean, not what didn't work, but you said, "Juli Klemm did a really good job on that." Do you just want to pick up this thread of your research in your own lab now? Is there a whole bunch more you need to discuss about Oregon in the sense of work done there? The other way to pick it up was this--

**ALBER**: We can go back and forth.

**HATHAWAY**: --review [T. Alber, 1989. Mutational effects on protein stability. *Annual Review of Biochemistry* 58:765-98]. Because that to me is where all these ideas-- You say, "Ideas are cheap." It's the execution of them. It seems that what you're suggesting about the review is there's a million ideas that need to be--

**ALBER**: Tested.

**HATHAWAY**: Yeah. It's almost a map of what you think you could possibly do--and maybe a hundred other labs, right?-- over the next five or ten years. I don't know how you want to- -

**ALBER**: Yeah, okay. So--

**HATHAWAY**: I didn't mean to cut short your actual postdoc work.

**ALBER**: Oh, no. It's boring. What to say? Do you want to talk about the review?

**HATHAWAY**: I have a slew of questions about the review, if you want. I want to ask about this Juli Klemm thing, and Utah, setting-up-a-lab stuff.

**ALBER**: We'll come to that. So Oregon. I would say one thing about Oregon that we haven't touched on at all is sort of how to organize science in general. Oregon happens to be a very cooperative, communal kind of place. There's a common kitchen; people share equipment; people get along, people work together; people don't get along, people work together.

**HATHAWAY**: Are you talking about all these labs working together? It sounds like a huge sort of--?

**ALBER**: It's not huge, but it is a group of people from different departments called the Institute of Molecular Biology, and it was sort of the opposite of MIT in that sense. At MIT people sort of had their own empires. They had their own everything: their own centrifuges--

**HATHAWAY**: Their own kitchens--

**ALBER**: Well, there was an autoclave that people shared, but-- People call these things empires, and you would go—

**HATHAWAY**: We call them fiefdoms in the humanities.

**ALBER**: --from one part of the building to another, and there would be a different king--not very many queens--in every little part of the building. Whereas the model in Eugene was much more cooperative, much more efficient use of equipment. [tape recorder off] I think as a result, too, there was a lot more interchange of ideas. What can I say? I think that's a better way to organize.

**HATHAWAY**: And this is a kind of conscious model on the part of the [IMB]? Is that what it's called? Institute of Molecular Biology?

**ALBER**: Institute of Molecular Biology. The people that started it started it that way.

**HATHAWAY**: Who? Like Matthews?

**ALBER**: Brian wasn't one of the original people. Aaron Novick, Streisinger, Frank [Franklin W.] Stahl were some of the original people--Sid [Sidney] Bernhardt. But you know, this gets back to the issue of there are different places that have different styles and different people do well in different environments. I can imagine people who would just go nuts if they had to share their equipment and sign up and wait and not have it already there and waiting for immediate use.

**HATHAWAY**: Right. Even if they only use it one month of the year. That's inefficient--to have to wait. Whereas perhaps it's inefficient to have twenty-five of them, all used one month of the year.

**ALBER**: So anyway, it's a very stimulating sort of place because there was a lot of scientific interaction.

**HATHAWAY**: Was that maybe formalized with larger group meetings?

**ALBER**: Yeah, sure, we had joint group meetings. Like any place, we had seminars. That was

actually something that I got involved in. With two other postdocs, I helped run the seminar series for a couple of years in Eugene. That was really fun.

**HATHAWAY**: Who were they?

**ALBER**: Molly Schmidt and David [J.] Grunwald.

**HATHAWAY**: So not people you were necessarily collaborating with? It was a big enough situation--

**ALBER**: No, not at all. They were postdocs in other labs.

**HATHAWAY**: It sounds like maybe there were ten PIs [principal investigators]?

**ALBER**: I'd have to count. Maybe a dozen, something like that, ten or a dozen. It wasn't huge at all. In fact, one of the neat things about moving to Utah is that by comparison it was huge--ninety or something, instead of ten or fifteen.

**HATHAWAY**: Do you mean PIs in molecular biology/biochem?

**ALBER**: Right, right. Energy level is way up.

**HATHAWAY**: Energy level? [laughter] There wasn't a year of lull, right?

**ALBER**: You wanted to talk about the review?

**HATHAWAY**: Yeah, but we can pick that up tomorrow, if that's going to be a better situation for you.

**ALBER**: I think we can talk about it. During my last year there, virtually all I did was write. So I was writing up, catching up.

**HATHAWAY**: A lot of papers with '87 and '88, right?

**ALBER**: Yeah. Petsko had suggested to the editors of *Annual Review of Biochemistry* that they ask me to write a review on protein stability, and specifically, what have we learned from mutations? At the time, you know, I was feeling basically that all we had to do to understand protein stability was make enough mutations at carefully chosen sites where you could isolate different effects, do careful characterizations and comparisons, and basically we would understand how to then analyze a structure and quantitatively determine what specific interactions were contributing to stabilizing that structure. That was an article of faith, essentially.

**HATHAWAY**: And that's what maybe kept you going through all of this?

**ALBER**: Yeah. You just make enough mutations. This is a new method, right? We've never had this kind of information before, and we just have to collect enough of it, find enough correlations, for example, between destabilization and dynamics calculations or something. And then plot it out.

**HATHAWAY**: And then you'll get some mathematical formulas out of it, and you can just plug it all in from now on, or something like--?

**ALBER**: Right, exactly. You take the T4 lysozyme mutations, and then analyze them and then apply them generally.

**HATHAWAY**: They just had to do one mutation, right, and then get the x and the y.

**ALBER**: Exactly. And so that was the underlying attitude that I took to that review.The other major thing I wanted to point out in the review was that the field's view of protein stability was derived mostly from studies of much simpler model systems--so guanidinium acetate to study ion pairs.

**HATHAWAY**: And that was kind of like the model of the electrical ion or charge role in stability or instability?

**ALBER**: Exactly, yeah. N-methyl-acetamide to study hydrogen bonds and solid-transfer experiments to study the hydrophobic effect. What I wanted to say in this review is, "Look, we

think of protein stability because of all these studies of model systems where people use really simple compounds to isolate interactions and measure how strong they are. By the way, now you can do that with a protein. And let's see how the results with proteins compare with the results from these model systems." And the obvious thing is that they don't compare. The basic assumption of a model system is that every interaction of that type contributes that amount, and you just count the number of interactions and then multiply by the scale or amount of contribution and you get-- But what we found in modifying proteins was that with different hydrogen bonds, when you interrupted them or disrupted them with mutations, you got different effects on the stability and the structure of the protein. That immediately sort of blows away the basic premise of using model systems. I sort of wanted to say that without being hostile to all this classic work, but just to talk about what are the differences.

I would say that the most important finding in my graduate work really was this study that was published in *Biochemistry* in '87, where we finally streamlined the methods of cloning out T4 DNA, phage DNA [T. Alber et al., 1987. Temperature-sensitive mutations of bacteriophage T4 lysozyme occur at sites with low mobility and low solvent accessibility in the folded protein. *Biochemistry* 26:3754-58] . Julie [A.] Nye, who was to become my wife--

**HATHAWAY**: Now, this is the--

**ALBER**: I'm slipping this in here. [laughter] She was an undergraduate who was assigned this sort of--

**HATHAWAY**: An undergraduate, you said?

**ALBER**: Yeah, she was an undergraduate. She was assigned this sort of tedious, back-burner project of characterizing all these mutations in Streisinger's collection. To do that, we just got really serious about all the phage crosses and standardized everything and got the vectors set up so that you could do a single restriction digest and clone the gene. We had the primers made so you could sequence a whole gene all at once. [tape recorder off]

**HATHAWAY**: And you were talking about this is a project being set to your future wife, but that made you get on the horse. You got to do the sequence and figure out everything, for all your mutations.

**ALBER**: Okay. She sequenced enough mutations that it became clear that there was a pattern in their location. The pattern was that these destabilizing mutations exclusively occurred at places in the protein that were either buried or rigid in the structure. That meant you could think about any protein crystal structure in terms of "Well, the important stuff is buried and rigid, and the

stuff that's not important for the structure is outside or floppy." And it was really a simplifying concept that was absolutely generally applicable and really opposed this view of proteins as just being a collection of different interactions that all made the same contributions. It was saying a hydrogen bond inside is different from a hydrogen bond outside. Either this had to do with the fact that interactions on the inside were, by definition, exchanged when the protein folded--that is, in the folded protein that partners were always different because they were other protein atoms, and the ones on the outside still could interact with solvent in the folded structure, and those interactions with solvent might be similar in the unfolded structure.

**HATHAWAY**: Or different, it didn't--

**ALBER**: But at least equivalent, or that there was something special about atoms that were constrained by the framework to interact, held in a favorable position. So that result--that rigid parts were important--fit very well with this idea that model systems aren't the whole story, and also--

**HATHAWAY**: Or that there's another model, maybe?

**ALBER**: Well, it also suggested how--

**HATHAWAY**: Okay, that wasn't modeled that same way-- Okay, I'm sorry.

**ALBER**: Yeah, it suggested why some interactions are different from others.

**HATHAWAY**: Perhaps model building as it had been done was kind of two-dimensional--and I'm not talking about structure or anything, I'm just saying in a sense complexity--and here was something three-dimensional, because it took into consideration a third variable or something like that.

**ALBER**: Well, if you really look at the data on model systems thoroughly, the conclusion that models lack something, the assumption that all interactions are the same that is inherent in models--it's not applicable, even to models. It's there in the data on model systems. For example, different solvent transfer experiments for measuring hydrophobicity come up with different scales. And so instead of saying that scales don't apply to proteins, because we don't know what kind of environment side chains are being transferred into, the debate was, and still is, "Which scale is appropriate?" [tape recorder off]

Another example is the field of hydrogen bonds. So studies on N-methyl-acetamide were done in the sixties and interpreted in such a way that suggested that hydrogen bonds don't contribute to protein stability. On the other hand, when we did experiments with proteins and eliminated hydrogen bonding groups, we changed stability, so there was some kind of contradiction there. But also, if you just looked at the data on other model systems-- So [J. A.] Schellman's work in the fifties on urea suggested that, in fact, hydrogen bonds might contribute to the stability of the urea dimer, even in water. And Bill [William P.] Jencks wrote a review of different hydrogen bonding systems that suggested that the more constrained hydrogen bonding groups are to interact favorably, the more likely--

**HATHAWAY**: And that was ignored then? It was kind of like in the past, when something funny came up with this model system about hydrogen bonding's participation being minimal—

**ALBER**: Yeah--

**HATHAWAY**: --it had been left by the wayside, because it didn't fit into the construction of the model.

**ALBER**: It didn't fit with what was in the textbooks and what everybody thought and what everybody was taught. And then if you really challenged people, they'd say, "Oh, well, the model systems are first order. You're talking about second-order perturbations," or these special technical words.

**HATHAWAY**: You're talking about proteins folding. [laughter] Whether it's a kick in the butt, or a kick direct to the head, right?

**ALBER**: So, anyway, the review was really about the issue of how do model systems relate to protein folding, and part of the inspiration for it was this result that rigid, buried parts are important. Also, [Thomas E.] Creighton had written a paper in 1984 suggesting how different interactions of a given type might make different contributions. [T.E. Creighton et al., 1984. Kinetic role of a meta-stable native-like two-disulphide species in the folding transition of bovine pancreatic trypsin inhibitor. *Journal of Molecular Biology* 179:497-526].

**HATHAWAY**: This is the thing that he called the cooperativity thing?

**ALBER**: Yeah, exactly. Effect of concentration.

**HATHAWAY**: I have a slew of questions, but I guess your review article is a great starting-off point for anybody who ever wishes to start making a whole history out of this area of biology. You've got some references in here that may end up falling by the wayside. I certainly found that there's a story, that people's names keep showing up here and there and everywhere. Mix and change just the footnotes-- If you follow the footnotes, you could start constructing a kind of a stage.

[END OF TAPE 6, SIDE 2]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **29 July 1993**

**HATHAWAY**: We were in the beginning of talking about the review that you wrote in '89 [T. Alber, 1989. Mutational effects on protein stability. *Annual Review of Biochemistry* 58:765-98]. And again, I don't want to cover it, as we'll just rehash on tape what anybody can read. But I wanted to try to get more at-- Maybe get into some of the competing ideas almost that are expressed by these sorts of different models. That's what you were in the middle of discussing, was your criticism of all these different models.

**ALBER**: Yeah, well, I think the thrust of the review was really that work on simple chemical model systems didn't explain the results that we were getting studying mutations of [bacteriophage] T4 lysozyme, and certainly other proteins worked on by other people. The genesis of that really came from the idea that to write a worthwhile review you have to have something to say. There are a couple of reviews in the field that are like that, and they're what you would call the classic reviews in the field. So certainly [Walter] Kauzmann's '59 review [W. Kauzmann, 1959. Some factors in the interpretation of protein denaturation. *Advances in Protein Chemistry* 14:1-61]--

**HATHAWAY**: I think you cite almost all of them, right?

**ALBER**: Right.

**HATHAWAY**: Is there something by maybe [Peter L.] Privalov [P.L. Privalov, 1979. Stability of proteins: Small globular proteins. *Advances in Protein Chemistry* 33:167-241]? Is that the name? Russian? One or two, even.

**ALBER**: Yeah, absolutely. And [C.] Nick Pace's review from '75 [C.N. Pace, 1975. The stability of globular proteins. *CRC Critical Reviews in Biochemistry* 3 :1-43]. I guess I looked at those papers and tried to figure out why is it that people still read them, and how did they fit into what had happened before. Not that I could write a review that will be cited in the same way, but the issue in general is, what makes a good review? There are a lot of reviews that are basically lists of papers that have been published on a topic, and those really aren't very useful

because they don't have any sort of intellectual organization. They are often not very critical. So that was also a challenge for me, was to write a review that actually was critical without actually being critical of the people that did all the work that I was, in a sense, discounting.

So, you know, I had worked with a couple of people who had very different styles in terms of criticism. [Gregory A.] Petsko is inflammatory, and has a hair trigger about saying what he thinks about other people's work, or being blunt.

**HATHAWAY**: In print as well as--? More so probably—

**ALBER**: More so, yeah, than most people. [Brian W.] Matthews, on the other hand-- [tape recorder off]

**HATHAWAY**: You were evaluating Matthews's criticism.

**ALBER**: Yeah, so Matthews-- He's less critical. He's conciliatory in public. He's generally encouraging, well liked by just about everybody in the field. Anyway, so I felt that there was some basically middle ground where I could be critical without being insulting.

**HATHAWAY**: And in many cases, I thought also, there was a sense that, yes, there was something to be gained almost from-- I mean, like you totally discount [Thomas E.] Creighton's notion of cooperativity--that's my opinion--in the sense of it having any relation to reality: in other words, a map that you could do one-to-one. At the same time, the whole idea of discussing protein stability in this sort of non-mechanistic way you find to be helpful, at least as even a sounding board, if you know what I mean by that.

**ALBER**: Well, I'm not sure I understand the question, but I would say, yeah, I took the parts of Creighton's ideas that seemed useful, and then pointed out aspects of—

**HATHAWAY**: That's what I - -

**ALBER**: --the work that just didn't fit with the data, that aren't accounted for, or that aren't consistent.

**HATHAWAY**: So again, maybe his view or his model, which is kind of a non-model--an amechanistic or unmechanistic model--you don't like, or you don't find useful. But certainly

some of the ideas behind wanting to construct something like that you found very helpful.

**ALBER**: Yeah. In fact, I think his ideas really form the intellectual basis of the review. And so that was the issue really. How to present it? How to figure out what's really new? His ideas are or were what's really new at the time, and people still don't generally accept them. They're hard to understand; they're hard to test experimentally. And yet they still account for the great majority of the data.

So, I think in considering the review, the process first of all was to figure out what to say, and then to figure out what topics to cover. Once I had a set of topics, it was actually pretty easy in the sense that I literally just got manila folders with the topic on it, and went to the literature--a lot of which I was already familiar with--and just took all the papers that I had, and papers that I could find, and put them in all these folders. And then I could break the thing down and deal with each of the topics, which are basically headings in the review, one at a time.

I would say that Brian Matthews was very cordial about having me stay in the lab and work on this. You know, literally I'd just come to the lab and mostly write all day.

**HATHAWAY**: You were still there, right? I mean, what can he--? Not allow you to come into your own office?

**ALBER**: Well, it was sort of a funny thing. There was a game of chicken going on with people at [University of] Utah. The problem is, of course, you take a position somewhere, and to do any work, you need a lab. So the usual thing--and what happened in Utah and what's happened here--is that the university agrees to renovate the lab. So you come up with some plans and you get some kind of preliminary schedule. Then you make plans on when to move and when to get there. And of course, as soon as you get there, your leverage goes down in terms of getting things done. Basically, the usual thing happened, which was the lab wasn't finished. So basically, to keep their feet to the fire, I just said--

**HATHAWAY**: You left again?

**ALBER**: --"I'm not going to show up until"--

**HATHAWAY**: So you came to see how things were? You just asked on the phone?

**ALBER**: Well, I just visited. I asked on the phone, "How is it going?" And "It's not done, it's not done." "Well, I don't see any point in coming."

**HATHAWAY**: And you kind of knew you were going to have to do this because of other people's experiences, or you just--?

**ALBER**: No.

**HATHAWAY**: It was a whole evolutionary thing where you finally realized, "God, this is how it goes."

**ALBER**: There's no point in showing up if I can't do any work there, so I stayed. Julie [A. Nye], who I was living with--or actually, I wasn't living with in Oregon--my companion, as they say.

**HATHAWAY**: My "partner," my "life partner"?

**ALBER**: Anyway, she had agreed to take a technical position in a lab in Utah, and in fact she didn't have any excuse. So she left and moved to Salt Lake [City], and I was still in Eugene. [laughter]

**HATHAWAY**: Because she had a job there, right? She had to move.

**ALBER**: Yeah. She had a job. She had to show up, exactly. I had a job, but I was like--

**HATHAWAY**: Not showing up--

**ALBER**: --playing this game. So apparently there were bets on whether I would really show up or not.

**HATHAWAY**: At Utah? They thought maybe you just were having a change of heart?

**ALBER**: Yeah, essentially.

**HATHAWAY**: Really? When it was clear--? There was no—what do you call those things?--

bench? No desk or tables or chairs or computers in your lab, and that sort of thing?

**ALBER**: That's right. So it was fun. In the event, the other funny part of it is that I had set up a cross-country ski trip to Yellowstone [National Park] with friends from Boulder. It was set up for, I think, the second week of February. I had expected to be in Utah in September, so I thought, "Oh, gee, this is not going to be a problem." Well, I show up a week before this trip, and then, of course, it was planned, and I decided, "What the hell?"

**HATHAWAY**: How long was the trip?

**ALBER**: It was a week. But I was there a week, and I was gone. [laughter] It wasn't a great way to make a first impression, I tell you.

**HATHAWAY**: But there was this issue of--? I got the impression from-- Each institution that nominates a person for the Pew, the head cheese has to explain how the process works. So a letter of theirs is included in the application--as a matter of fact, also from the chair of the department or of the division or whatever it is that you are in. There are two letters from people at Utah explaining why you're the nominee, and all that sort of thing. I get the impression that you were part of, or you were the-- A situation of beefing up a department, of building something solid in structural biology or just in the whole biomedical research thing. There must have been some sort of sense on your part, too. They must have talked to you about "We're doing this. We're planning on developing that."

**ALBER**: Oh, absolutely, yeah.

**HATHAWAY**: And since we're on it, we could get back to the review. We don't have to cover it right here, but since we are on the issue, we might as well kind of--

**ALBER**: Well, I mean, the review-- You can read the review.

**HATHAWAY**: All right. I still have a few questions about it, but we can go on with the--

**ALBER**: There's nothing in the review. [laughter]

**HATHAWAY**: There are all sorts of things in the review. But I guess maybe from a different

kind of-- I'm thinking about it as-- I want to ask my questions about the review. We'll get back to Utah. I can't remember if I talked to you about this on tape or I talked to Hillary [C. M.] Nelson or I've just been talking to myself in my sleep about it. If you recall that we spent twenty minutes on this already, shut me up. You can do my job for a second and I'll try to pretend that I understand protein stability and I'll do your job.

I get the sense that a lot of emphasis has been put on the highly conserved, you know, twenty-five base-pair sequence of whatever, where the protein folds. That "This is what's important, and this is what we have to figure out, this is what we need models of." You call it the floppy part. All this other stuff you could retake the heck out of it, and it will still come out, it will still look like this protein; it will still fold and unfold, pretty much. Sometimes it's even more stable, right? Which is another question I have later. Why does the possibility of the fact of the floppy stuff, and in its floppiness--? Not just from a kind of theoretical view of, "Oh, natural selection demands diversity and flexibility." Why can't that be seen as having a fundamental role in the folding and unfolding process? Because it ' s this huge kind of border area between areas that are going to be more rigid and more stable. In other words, is there another way to turn this around, or turn the question upside down?

**ALBER**: Well, I think the attitude comes directly out of the experiments, and that is that the regions that are floppy tolerate changes. They can be replaced at will, in general, and still get function. Tony [Anthony R.] Poteete has done an unbelievably tedious but interesting experiment with T4 lysozyme, where he set up a system where he could mutate every position one at a time, and put in one of thirteen different amino acids.

**HATHAWAY**: At each position?

**ALBER**: At each position. And check for function.

**HATHAWAY**: And this is on the outside, or on the floppy areas around?

**ALBER**: The whole thing. Starting at--

**HATHAWAY**: The beginning? How many--?

**ALBER**: Yeah, it's actually starting at residue 2 and going to 164.

**HATHAWAY**: I bet you're glad you're working on the short ones- -procaryotics.

**ALBER**: Right. So he did all this work and made these mutations, called amber mutations, that normally stop the protein. But in certain strains of bacteria, the amber codon, or the stop signal, is read as an amino acid. So that amino acid gets inserted at some frequency, okay? So then you produce the protein that has that amino acid where you used to have the stop codon. And then to make another mutant, you just take the same DNA and put it into a bacterial strain that puts in a different amino acid instead of stopping, okay? So it's a relatively quick way to make many mutations at every site in the protein. All you have to do is engineer one mutation at each site and that's stopped.

**HATHAWAY**: And then you can just run it as one long experiment, right?

**ALBER**: Right. You get this huge table.

**HATHAWAY**: You said tedious.

**ALBER**: Right, horrible. I wouldn't want to have done that. So the result is that there is only one position in T4 lysozyme that has to be what it is.

**HATHAWAY**: To get the protein to fold and unfold?

**ALBER**: No, to get it to work, not to get it to fold.

**HATHAWAY**: Just to make sure that I understand, what [is the] difference we're talking about, then, between it working and folding?

**ALBER**: Enzymatic activity.

**HATHAWAY**: Okay.

**ALBER**: Right? It has to fold to function. That's not to say that every substitution at every position works, but there's only one position that can only be one amino acid--the one that's found in the normal protein. That is an amino acid that is the heart of the catalytic mechanism of the reaction.

**HATHAWAY**: And to you, that's further indication that really this floppy stuff is just floppy stuff. It has its function and its purpose, but it's really of very little interest in solving this rather difficult question about protein stability.

**ALBER**: No, I wouldn't actually go that far. Well, in terms of protein stability, yeah, the floppy stuff is the floppy stuff, as far as I'm concerned. There's one sort of caveat that--actually, the person that has done the best work in this is Bob [Robert T.] Sauer at MIT [Massachusetts Institute of Technology]--comes from the notion that the stabilizing contribution comes because an amino acid changes its environment in the folded structure relative to the unfolded structure. The unfolded structure is by all measures very floppy.

**HATHAWAY**: The whole thing becomes floppy, right?

**ALBER**: Yeah, like boiling spaghetti or something. Even so, on average each amino acid might find itself inside of this bowl of spaghetti some fraction of the time. So that sort of led to the idea "Well, are there amino acids in proteins that are outside?" In fact, they're so far stuck out there on the outside that they're exposed to solvent more when the protein is folded than when it's completely unfolded, even though in the unfolded chain residues are highly explosive. It might be covered up more when the thing is unfolded. So that's an example of something that's outside that may be important. And even if it's outside, it still might have a role. Things that are floppy and outside would tend to get covered up occasionally, and so couldn't serve this other type of role. Floppiness-- It's important in the sense that the chain has to lose it to fold, okay? So it's a critical determinant of stability. Its major role is in the unfolded chain: How floppy is the unfolded chain? In fact, that's sort of one of the major questions that we're asking in the lab right now is how much floppiness is lost when a chain folds and how much energy does that take. So I don't think of floppiness as unimportant. But basically, what we showed was that interactions in floppy areas apparently don't count. They apparently don't contribute as much to the stabilizing, to the structure.

**HATHAWAY**: Now, his name is Tony what?

**ALBER**: Poteete, at U. Mass [University of Massachusetts], Amherst.

**HATHAWAY**: So he's not of the Matthews clan?

**ALBER**: Actually, after he'd gone halfway through this experiment, he went to Oregon and did

a sabbatical.

**HATHAWAY**: He's a convert or a supplicant or whatever the religious image is of the person who makes the pilgrimage. I guess I didn't want to say, "Oh, you should be looking at the floppy stuff, and kind of put the other stuff in the background." I was just curious: Is it maybe more frightening to think of the floppy stuff as needing to be investigated with the same sort of rigor, because it's going to be even less willing to be subjected to mathematical rules or to a model? If your description of it is spaghetti in boiling water, you've got a real mess on your hands.

**ALBER**: In fact, our work now on the floppiness of the unfolded chain-- It's actually more mathematical than any of the work.

**HATHAWAY**: Like Fourier analysis. You just forget it's spaghetti in boiling water, but you kind of look for point-- I mean, you don't even have to kind of think of it almost as stuff in stuff, and distinguishable, right? But just as a grid. Well, I think of my very simple understanding of Fourier fields or whatever they are called and that sort of thing as being much more easily mathematized. But then again, as you point out here in the review, there is a lot lost. What a biologist wants is not nice elegant mathematics, perhaps, but--?

**ALBER**: Well, one of the people who's done the most careful work lately on sort of mathematical models of the unfolded chain, and the implications of those models, is Ken [A.] Dill, who was a Pew scholar. So you might have interviewed him?

**HATHAWAY**: I think he was interviewed by the Beckman [Center for the History of Chemistry]. I think I actually briefly looked at his interview.

**ALBER**: So his work actually extends predictions that go back to the forties about the randomness of the unfolded chain. We've actually done measurements for the first time to test those mathematical models.

**HATHAWAY**: Are they kind of close? I mean, do you think the testing will correct it in a worthwhile way, or you think it will--? Maybe it's too early to tell.

**ALBER**: Well, I would say it's not too early to tell. The bottom line in terms of the results so far is very exciting--that the models are basically correct, that there is a significant energy contribution to lose randomness. But the results also show what might be called second-order effects, and I sort of scoffed at second-order effects on the last tape. The results seem to indicate

the different parts of a polypeptide chain have different degrees of randomness. One of the simplest predictions of the mathematical theory is that the amount of randomness that's lost is a function of the life of the chain. And that's it. What we've shown is that in general that's true, but in detail there are deviations. So it's not a simple linear relationship. We don't really know yet whether that has to do with differences in the compositions of the chains that we examined in the experiment or whether there's actually structure in the unfolded chain, or the unfolded state, that makes certain collisions more or less probable than random. That's in essence where our next experiments in that system are going, is to rule out these models for where the prediction of this chain theory, or polymer theory, is breaking down. You know, that's been a really fun set of experiments, and in fact is what we did with the Pew money instead of doing the cavity work that I originally proposed.

**HATHAWAY**: And we'll just get in a plug for the Pew, right? In a sense, that was perhaps a boon because you didn't have to resubmit--call up the Pew and say, "Oh, what I originally proposed didn't work. Now will you approve this?" The money was there to be used, and you needed to change direction.

**ALBER**: Well, also to be used for something creative.

**HATHAWAY**: Right, and that's certainly creative. I guess one reason I'm asking a lot of questions around this area of models and the use of mathematics in your work is not only because it's always something you're always looking for and pushing yourself, it's also because of all the different areas of biology. It seems that the structure-function look at proteins is one of the few areas where that's a serious endeavor, more like polymer chemistry and other disciplines. I mean, Ken Dill, I believe, has his Ph.D. in physics, right? From UCSD [University of California, San Diego]. Or a joint degree in physics and chemistry, and not in biology. I forget where he is now.

**ALBER**: UCSF [University of California, San Francisco].

**HATHAWAY**: In a typical biological--

**ALBER**: Pharmaceutical chemistry, yeah.

**HATHAWAY**: And perhaps protein design, I suppose? No.

**ALBER**: They don't do experiments.

**HATHAWAY**: They don't do experiments. They think?

**ALBER**: Computer models.

**HATHAWAY**: Don't get me wrong. I understand a lot of the materials and whatnot and computers are used in a lot of other areas of biology, but people who do protein transport are not looking to mathematize the secretory pathway. They're looking to create it in vitro and reconstitute it and then stick it back in vivo and get this-- They're still doing very much what I guess I would call the experimentalist approach, just simple gathering of facts.

**ALBER**: Yeah. But that's a much more complicated system. And so the idea is that can proteins be simplified enough so that they can be described in terms of mathematical rules, or algorithms, and whether those algorithms have anything to do with the physical world or not. I mean, sort of the standard approach is to say, "Let's write an algorithm that recapitulates the physical world." But it may end up being that proteins are too complicated for that and we'll end up writing an algorithm that just predicts how the physical world is going to behave.

**HATHAWAY**: Which is in a sense maybe what a lot of physics has finally kind of decided it needs to do. I mean, I think that a lot of the perspective of quantum-- The quantum representations of the world are guesses at possible outcomes of the behavior of the physical world, not a picture of any part of the physical world. It's an averaging over, a trying to account for all the different events, or effects on a particular event, that can happen.

**ALBER**: Well, to get back to your question about floppiness, and the emphasis of that in the review-- Floppiness, you know, it's something that Greg Petsko works on. It's a recurring theme in his career. It was certainly the floppiness in triose phosphate isomerase that got me interested in folding at all, or to the point where, I think, I wanted to work on folding as a problem. Folding is certainly a process where the chain loses floppiness. I didn't really intend to discount it in the review, in that sense, as saying it's not important. I think what I was saying is that if it's left in the folded structure, then it didn't really change very much when the protein folded. And so it doesn't have much to do with structure.

**HATHAWAY**: No. I wasn't suggesting or asking--not even having my own opinion really, or my own thoughts on the subject--"Aren't you missing the real treasure trove to be found? It's all in the floppiness, not in the--"

**ALBER**: Well, a lot of the function is in the floppiness. That's a matter of--what?--faith. There are parts of that statement that are completely obvious. I mean, it's trivial to say, "Function requires floppiness, and evolution requires floppiness, and blah, blah, blah." But to actually do an experiment to show how a change in floppiness or flexibility alters the function, that's very hard.

**HATHAWAY**: Isn't that the same sort of situation you ran into with this unpublished paper that actually helped you and Peter [S.] Kim become friends as well as intellectual soul mates or whatever, and that this other reviewer said, "Oh, yeah, it's obvious," and kind of like, "Okay"? It's so trivial as to be obvious, and yet you said, "No, it's really hard. It's so obvious, yeah, but how can we recapitulate it or make it happen in an experiment? Or even just demonstrate that, indeed, what we hold as dogma, so obvious and there, can be shown in a step-by-step way to be indeed what--"

**ALBER**: Yeah, it's easy to have an idea about that aspect of protein molecules or DNA molecules, but it's hard to test those ideas.

**HATHAWAY**: I guess another reason the area of floppiness kind of struck me or held my curiosity was the mention in the review that still this floppiness is not some sort of ideal random situation. Indeed, the floppiness has probably a way of being, if you will, that falls within certain parameters. So that it was obviously something that had handles, which one could start doing this kind of work on. It wasn't some sort of—

**ALBER**: That's an active area in the field now: defining what structure is there in the unfolded chain.

**HATHAWAY**: And it does. It seems like really hard—

**ALBER**: Yeah, it's hard. It's also antidogmatic in the sense that, until the eighties really, people considered the unfolded chain to be random. And there are lots of experiments that support that view, that the proteins become random when they unfold.

**HATHAWAY**: You cite some work, at least--maybe it's theoretical work; I thought it was experimental--that indeed it wasn't completely random, right?

**ALBER**: Oh, yeah, but that's quite recent.

**HATHAWAY**: Okay. You know, I can't remember, who was that? I know you're working on it now, too. Was it your own work?

**ALBER**: No. Some of the first was from Buzz [Robert L.] Baldwin's lab, although it wasn't interpreted that way. Someone who's sort of made a crusade or a career out of this is David Shortle--to look for nonrandomness.

**HATHAWAY**: So as you say, this is a whole kind of-- These kinds of questions that I'm asking, "Oh, gee, why am I getting--?" Since '89, let's say, since the review, that's really become an area that's received more attention, or that was, at the time of the review, starting to become a--

**ALBER**: I think intellectually, from a historical point of view, it was an important question that had to do with a question of where is the information for the fold. The idea is that people could purify proteins from living cells and denature them and then renature them and get activity back. But the criticism of that work was a proposal, or a contention, that maybe there was something, some kernel of the structure, that didn't get destroyed when the protein was unfolded, and that kernel was sort of established biologically. It was established during the process of synthesis, or during the lifetime of the protein in the cell. There's some cellular factor or function that imparted this kernel of structure that was needed for the thing to fold, and it just wasn't destroyed in the unfolding steps. So it wasn't really until ribonuclease was synthesized chemically with no cellular participation, and then where a chemically synthesized material was refolded and reconstituted--that was really the nail in the coffin of the question, "Is there some kind of biologically required step for folding?"

**HATHAWAY**: It's something that I'm really fascinated by. Is there still some sense of, if you will, the biology police, of a notion that there is something about organic systems that is undefinable, or not reducible to a mechanical kind of analysis and description? You know, it's almost like the cooperativity of Creighton's-- At least it's a holistic kind of attempt, or attempt to challenge the hopes and the dreams of those who would like to be able to reduce this all. And we use the word "reducing" in the notion of reductionism as not a pejorative--unless you are a holist, of course--notion but as something that science is, and science in Western culture certainly has been, working out for a couple of centuries, at least.

**ALBER**: Well, I don't think there is anything that molecular biology--as a mainstream, as a social activity, cultural activity--would say is not reducible. That's a different thing from saying, "Is there anything about living things that's historical?" So you can see that in sort of maternal-effect mutations--

**HATHAWAY**: I hadn't thought about taking it and splitting it up that way. You can still--

**ALBER**: --in lots of different organisms, there's something that's imparted in the egg. It requires a history for that organism to grow. Probably, at this point, you would find a lot of skepticism about the sort of growth of dinosaurs, for example, that you saw in *Jurassic Park*--that if you have the DNA, you could make an organism.

**HATHAWAY**: Right. You'd probably need a little bit more than—

**ALBER**: Right, that there is something-- You'd need the egg, you know.

**HATHAWAY**: At least, right? If not the egg and the sperm, as well--

**ALBER**: Well, you need sperm or God--

**HATHAWAY**: Poor Aristotle's homunculi theories out the window.

**ALBER**: No, I mean, I think everything is reducible, but that doesn't necessarily mean you can put Humpty Dumpty back together.

**HATHAWAY**: And I guess I wasn't even so much as getting it from that view of-- I think maybe this talk that Sydney Brenner gave at the Pew [Scholars Program in the Biomedical Sciences] meeting in March [1993] in Hawaii has got some-- I mean, he's doing it for shock value, but I mean he's also got a point. Molecular biology and then biology since we cracked the genetic code isn't anything more than about being [Dr.] Frankenstein. Anybody who tells you differently--we're "out there to stop disease, and blah, blah, blah"--he says, "It's baloney. We're here to be able to reconstruct life in a laboratory situation. And that's what we're going for." He was trying to wake up a very, very tired audience who spent the day listening to papers. It was now after dinner, and they were really tired and jet-lagged, but I think he was also making an important point. I was getting more at the suggestion that-- Does somebody like Creighton maybe kind of say, "Let's drop the mechanistic and the reductionistic approach for a while, because maybe we're missing something"? "We've got all these trees we want to put together, and we may be missing what the forest really looks like," or something like that? Whether that was an issue you dealt with, or something you just think is--?

**ALBER**: Well, I don't think of his work that way at all. I think he's proposing a mechanism for cooperativity. It's not that he's not being mechanistic. He's talking about how interactions might change each other if they occurred together. So to me, that's really a mechanistic idea. It's hard to test, but nonetheless there is some experimental support for it.

**HATHAWAY**: I guess one last thing, and I won't go on to a whole lot of it. One thing that has occurred to me is-- Let's take our ideal biochemist. This biochemist thinks that a biochemical approach or a chemical, a "put this in and see what comes out at the end" approach, is better than a structural-functional or a structural approach, and that's perhaps why they are doing it. That's the approach they like. And they are much less worried about rules and models and generalities. They're looking at their stuff that they've got as a chemical, right, or as a compound of chemicals, and they want to see what happens to it. And they run it through their in vitro system, or they do it in vivo again, finally, and label it and check it out. And the ideal biochemist, who's a little over-secure in her or his field, would say, "Ah, the structural-functionalists. They are just asking questions that are going to take-- They'll never answer them," and that sort of thing. "What they want to do in biology and to biological systems is just too far off in the future, or not important about curing disease or delivery of drugs or whatever." You obviously would probably have a difference of opinion with them, because you're doing structural-functional studies. Do you see the payoff coming in your lifetime? Or is this you're just doing one little bit of work along the way of a whole series of work that maybe begins back with certain chemists, like what's-his-name?

**ALBER**: Oh, yeah, him: what's-his-name. [laughter]

**HATHAWAY**: Stop. Is it Hooke? What's his name? Hooke, right? [Joseph] Priestly.

**ALBER**: No, I don't even need to get into this debate with your ideal biochemist. I mean, it's silly. The payoff is already happening, as you say, the social payoff. I think that's what you mean by the payoff. The payoff is happening to produce products, and people are being paid off in terms of getting rich. I mean, yeah, it's a difficult problem. Protein stability is a difficult problem, that's sort of what you're saying. I guess when I went to Oregon and started applying this new combination of approaches that other people had worked out--all the individual methods--I thought, "We're going to solve this problem." Of course now, you know, I'm much more pessimistic about it in terms of "How solvable is this problem?" Is there going to be a theory that will explain the stability of proteins, a mathematical theory? I'm very pessimistic about that.

**HATHAWAY**: You mean while you're still around doing it and working on it, or two centuries from now?

**ALBER**: Well, certainly in my lifetime. But I think of the finding that the thermodynamics of protein denaturation is really complicated. That, you know, is a basic advance that happened, say, starting in the early seventies. But it's a big concept--the notion of sequence homologies implying structural homologies. That's a big idea in structural biology, and that's something that's developed despite our inadequacies--the idea that proteins tolerate mutations, that what's important is inside, that the volume of a cavity that you leave after you've made a mutation affects the outcome of the mutations. These are ideas that can apply to any protein, any mutation, to any structure, really, that anybody determines about in any biological process. So I would say we are getting much more sophisticated about looking at structures and seeing what's important. What can we do in terms of practical applications? People are getting much bolder about modifying proteins to change their intrinsic activities to be useful, in the sense of salable.

**HATHAWAY**: I can see protein engineering as a discipline within an engineering department in the next ten years or something, almost.

**ALBER**: Yeah, I mean making proteins more stable for industrial catalysts, or changing their specificity so you start with different starting products or you end up with different final products. These are really active areas that people are doing. And you could say, "Well, you know, it’s monkeys typing on typewriters, and you may get Shakespeare." But yeah, you may get Shakespeare. What's happened in the last decade is that there are a lot more people typing, because people have realized that proteins can be manipulated.

**HATHAWAY**: When you say "monkeys," do you mean just any old dodo head is doing this kind of work now?

**ALBER**: Sometimes, yeah. It's certainly not anybody with a coherent theory of what's going to happen.

**HATHAWAY**: And they aren't even necessarily supposed to do, right? It's the old notion that they build medieval cathedrals without any even clues as to what's the theory behind why they stay up. And sometimes they didn't, they fell down, right? They had little manuals on how to build a cathedral, but they couldn't tell the person who's building it "This is why it's standing." Especially of course the dome structures that they were making in such huge--with almost no support. That's actually interesting.

**ALBER**: There are huge corporations now designing, modifying, getting out new proteins, formulating proteins as drugs—

**HATHAWAY**: So much for intelligent drug design, as opposed to hit-or-miss drug design?

**ALBER**: Well, no. I mean, what people call intelligent drug design is not completely successful right now, but that's what people are working on. Even the sort of most staid, most conservative corporations are designing drugs rationally, rather than just screening libraries of compounds now. People want to know what is the target, what is the structure, how might a potential drug fit into that structure. So the whole culture of how you make a drug is changing.

[END OF TAPE 7, SIDE 1]

**HATHAWAY**: I do recall something when I was first starting off reading-- I think it was some sort of review or editorial-type piece in *Cell* about doing this with antibiotics: "We don't need the rabbits anymore. We can do this all synthetically. Now we can just change the one thing, so we can do a whole series of antibiotics on one sort of thing with just the minor changes. We can have them ready to generate enough whenever we need it. And we can have library after library, or stock after stock of all these-- It doesn't matter. We'll just synthesize it and make it. This is all just down the road." And the person set forth kind of the three or four general rules about making these-- I can't remember who it was; I think it was somebody at Scripps [Research Institute]. Like I say, this was like two weeks into realizing I was in big trouble with having to learn--

**ALBER**: They were saying that you didn't need design or that design would be helpful? I missed the--

**HATHAWAY**: In what this guy did?

**ALBER**: Yeah.

**HATHAWAY**: He was saying that this was not just about drugs, but antibiotics even. It was completely going to be removed from the requi-- Even, if you will--he certainly didn't use the word--nonintelligent way of getting the bunny and doing the process kind of manually. It was just a matter of punching-- Well, perhaps your image is accurate: just a bunch of monkeys on typewriters: "Okay, we'll synthesize this one." He was talking about randomness in the sense of you just plug in finally and change it, and somebody thinks, "Oh, this will work." It seemed rather hit-or-miss to me, but it almost at the same time was amazing to me that they were at this point, if you will, or he was convinced they were at this point of simply-- I guess the idea was "Somebody's sick; okay, we need an antibiotic. So we'll just analyze the virus and then we'll

punch in the numbers into the computer and we'll get enough of this antibiotic and it should fight this virus."

**ALBER**: Yeah, I mean, on a social level, this is a key point. People argue, for example, that the reason that you need biological diversity in the world, say "Save the rain forest," is that there are compounds out there that could be useful drugs.

**HATHAWAY**: Or the synthesis of those compounds. We need to know what they're like first naturally or something.

**ALBER**: So that's one sort of benefit. In addition to sort of ecological arguments, there is this sort of self—

**HATHAWAY**: Sure, taxol I guess being the epitome because of its scarcity.

**ALBER**: It's also very complicated. I mean, taxol is an example where I think the effort now is to clone the genes for all the proteins that are involved in biosynthesis of taxol.

**HATHAWAY**: And hasn't some lab actually got some taxol precursor synthesized, or something that came close, or, my God, whatever.

**ALBER**: I don't know. The idea that is sort of taking hold is "Well, maybe we don't need all this because we can just eventually just design what we need, and synthesize--"

**HATHAWAY**: Oh, I see, it could be the opposite side of that.

**ALBER**: I would say that randomness has a huge benefit if you can screen lots of things rapidly. Then you find out things you didn't know. I mean, that certainly, I could say, motivates lots of my work. Certainly it's obvious in my postdoc, where what we started with was a collection of random mutations in a protein. It all made the protein less strong. And so, without any preconceptions, we went and looked and found "Ah, so this is what makes a protein hold together." But if we had preconceptions, and used exclusively site-directed mutagenesis to change one thing after another, we might have missed the pattern. We certainly would have taken a lot longer to get to this issue of what's important. The site-directed mutagenesis was really there just to ask specific questions about very specific sites, and really not to ask the general question what stabilizes proteins.

**HATHAWAY**: Sure, but as you say, that's instructive into that question, right? The more general question of what stabilizes proteins is a more specific look at a particular protein, and getting a look at it in a kind of directed way.

**ALBER**: So I think if you get the false impression that you know too much, then you'll miss learning what's new. It will be interesting to see what happens when corporations decide that all they need is the structure and they'll be able to find new drugs. It may be that that means that they'll completely miss compounds that don't actually act through the mechanism that they had thought about ahead of time.

**HATHAWAY**: If you are going to completely rely on randomness, you're going to have to do an awful lot of missing before you hit, right?

**ALBER**: Well, that's true. If you look at drug discovery, it's ten thousand misses and a hit.

**HATHAWAY**: Do you think nature is that way, too? Or do you give it some sort of teleological or Leibnizian advantages? In other words, that a protein folds a certain way, or not completely as stable as you can make it in the lab, because it knows, if you will, that it may need to be more flexible and less stable. In other words, entropy is kind of playing an intelligent role in a situation, or natural selection is the best possible situation because it's random. In other words, it doesn't care whether the humanoid is bipedal or moves on all fours. It just so happens that the random events—

**ALBER**: Well, again, the randomness doesn't eliminate history because there hasn't been time, and there will not be time, to try all possibilities of arrangements of amino acids even in a protein, let alone ways to make the world. Maybe to answer your question more specifically, I think in the review I wrote a little bit about that, that either there's no selection for the most stable proteins or there is an active selection against them. So the active selection against them is of the type that you mentioned--that molecules have to be flexible to function. They have to be flexible to evolve. They have to be flexible to be degraded inside the cell when you don't want them to hang around or when they are not useful. A completely rigid protein, yes, it would be completely stable. That obviously isn't the most functional state.

**HATHAWAY**: And of course, we've moved into totally murky areas. Like I say, "Does one want to attach a teleology to all this? Can we almost escape using teleological language to describe what we're describing?" I realize we're not Ernst Mayer and [Edward Osborne] Wilson sitting at Harvard [University] Museum of Comparative Zoology, writing their polemical books

about these issues.

**ALBER**: But no, these things do have implications for even practical design issues.

**HATHAWAY**: And what gets funded in a sense, I suppose. If you convince the congresspeople and whatnot, or the people who have the ear of the people who represent the taxpayer-- It's a very layered situation, I realize. Yeah, I know, I think they do. These issues always have some sort of more immediate effect than people want to think about. And also I find it just interesting to ask you guys about these things, "What do you think?" It's an indirect way of asking you "What do you think about God?" or something, I suppose. I don't mean that in a trivial or silly way. This is how we kind of make our own world have some structure, if you will, and some stability, is to have certain beliefs and ideas, and we base them on what we know. So I guess I'm in a way kind of sneakily trying to get at some of that too from you.

**ALBER**: Well, I guess I would add maybe a darker side of this, which is what is happening in science now, in the sense of the demand that work be immediately practical. It's very different from Barbara McClintock, or Max [F.] Perutz, who just wanted to know what a protein looked like, or what is the genetics of maize.

**HATHAWAY**: And what was the atmosphere in which-- With Barbara McClintock, perhaps that's clear: the atmosphere, the situation, the circumstances in which she found herself. I think they were rare, yes, and unique almost. But again, they're sort of odd. Where as far as maybe with the Max Perutz situation, it's a little more difficult to-- Here is somebody who held a teaching job and a research job for thirty-four years without-- He published left and right--a very productive, prolific career. But the answer, the result, as we might want to term it now, the applicability of his work, took thirty-four years to find out. And then kind of the answer was "No, it doesn't answer all these questions."

**ALBER**: Yeah, so I mean in that sense it was disappoint-ing. But I think I'm also saying that there isn't much scholarship left--

**HATHAWAY**: Like that--

**ALBER**: --in the world. The funding agencies want to cure cancer. It's not that they want to know about x, you know.

**HATHAWAY**: Max Perutz would have had a hard time--his attitude, and the way he worked

and operated--today; he might not even get a Pew scholarship, right?

**ALBER**: Yeah. It's not to say that there wasn't directed research before. Work on coiled coils was funded by the Wool Board, because keratin has a coiled coil in it, you know, and things like that. They wanted to know the properties of wool.

**HATHAWAY**: And a lot of people came to Perutz and sent him samples of this stuff because they wanted some answers about stuff. And certainly he was helping people or collaborating with people who had very practical ends in mind.

**ALBER**: It's interesting. The universities have much more become vocational schools: premedical, pre-something—

**HATHAWAY**: You know, I've actually-- I was shocked at first, and I think this came through in one of my earlier interviews. It took me a whole long time-- And even, I look at people at UCSD or-- Well, there is a medical school there. But [University of California] Berkeley had "You can't be in medical school here. You can't be; there is no medical school here." So if you're doing academic biology at Berkeley, you're doing it devoid of that professional aspect, the vocational aspect, supposedly. And yet it took me a long time to realize, of all the fields, it's the biologists who are not, for instance, teaching anymore. They're simply not having contact with undergraduates. And I've had people tell me, "Why should I? I was trained to run a lab, not teach a class of twenty-year-olds the basics of biology."

**ALBER**: I don't think you'll find that in this department.

**HATHAWAY**: No. I mean, you have to teach, right? You are, I assume. That's maybe something we should cover at least briefly, is some sense of what your teaching duties are, and who you do teach. Because you're not teaching those two lectures in the oncology section to the med students as your teaching duties, because they don't exist here.

**ALBER**: Well, I was in a med school in Utah, but I made a tacit deal with the department chairman that if they ever asked me to teach the med students, I'd quit.

**HATHAWAY**: So you taught undergrads at Utah?

**ALBER**: Undergrads and graduate students, yeah.

**HATHAWAY**: In a kind of traditional--?

**ALBER**: Undergraduate biochemistry. Protein chemistry for graduate students.

**HATHAWAY**: Okay. So the protein chemistry was for straight-out Ph.D. chemistry students who were in the chemistry department, and not in the biochemistry department or physiological chemistry?

**ALBER**: Well, we had an unusual situation where five departments had a joint graduate program. So it was people from all over campus.

**HATHAWAY**: Including maybe some people in the medical school, but getting a Ph.D.?

**ALBER**: Oh, yeah, yeah.

**HATHAWAY**: Their affiliation was first and foremost with the medical school.

**ALBER**: Well, actually the initial association was with this interdisciplinary program, and it was only after they completed the core curriculum that the students would choose the department.

**HATHAWAY**: Oh, okay. That is unique, right?

**ALBER**: But the faculty came from all these different departments, and the students would have access to all the departments that the contributing faculty came from.

**HATHAWAY**: And the biochem[istry] course for undergrads was the biochem course for biochem or chemistry majors--the premeds.

**ALBER**: Yeah, it was jointly offered by the chemistry and biology departments.

**HATHAWAY**: And it was the--? Usually it's either the organic chem or inorganic chem that is the killer class. But biochem is used sometimes too as the second gate, if you will, the second gated ion channel, right, to let the students through or not. Is that how you--? Was it a tough course that you taught?

**ALBER**: I taught a tough course, yeah.

**HATHAWAY**: Because you were asked to make it tough? Or because you see that as a good place for anybody, potentially an M.D. or Ph.D. student, to kind of cut their teeth on work? Or just because you like a serious group of students and you want the other twenty to please turn around and go out the door when they realize how tough it's going to be? Or you like seeing somebody kind of come in unformed and leave with a real--?

**ALBER**: No, it was just that I wanted to teach at a level which I find useful. It wasn't that I just sort of ignored the people that were having problems. I mean, I would definitely spend time and give a lot of attention to people who were having difficulty, but I don't think it's useful to water material down to make it so accessible that you can understand biochemistry without any work. I mean, not to say that you should deliberately make it hard or boring--

**HATHAWAY**: I wasn't meaning to make it sound in any way like that.

**ALBER**: Yeah, I think there are subtleties to this that shouldn't be ignored.

**HATHAWAY**: And require some hard work.

**ALBER**: And require some thought, yeah. Questions like "Here's the story. How do people know the story? What's missing from the story?" People find that hard.

**HATHAWAY**: "Can you take a critical look at the story, and do you have anything to add, or criticize about it even, and some critical thinking?" [tape recorder off] I don't know what the quality or level of the students is at the University of Utah. I mean, my own experience at a place like UCLA is probably pretty indicative though, right? It's a large public institution, so you get really everything--

**ALBER**: Public state university.

**HATHAWAY**: --from the most brilliant to the least brilliant.

**ALBER**: Yeah, really, actually some wonderful students. Enthusiastic--

**HATHAWAY**: Serious? I mean, they are kind of like you were when you were an undergrad chem major at--

**ALBER**: [University of California] Santa Cruz--

**HATHAWAY**: --and looking for the good stuff, if you will.

**ALBER**: Yeah, you know, thoughtful. I had good undergrad-uates in my lab, for example. Many of them came from my course.

**HATHAWAY**: You're talking plural--more than one at a time?

**ALBER**: Oh, yeah.

**HATHAWAY**: Because a lot of people view that as a responsibility they'd like to take on because-- Actually, I don't know if I can think of one of you [Pew scholars interviewees] who didn't find themselves in a lab early on, and that has a lot to do with why you're doing what you're doing today. [tape recorder off]

I was going to go on and ask about people in your lab, if people had seen what they were getting was much more than what they were giving to a lab. Even washing glass-- You know what I mean? That was what the culture of science, at least in this country, was doing to perpetuate itself, was bringing somebody at an undergraduate level without any experience and exposing them to something because they were interested in it. And this was the way one kept the science going was through this exposure. I'm wondering: Do you take the same kind of view, that introducing undergraduates into your lab was more of a thing for them to be exposed to science in the hopes that they would go on to become good scientists than the fact that they were even skilled labor and technicians who were turning out really high-quality--or fast or something like that--work for almost no pay? Because certainly that seems the typical thing: you don't get paid during the year, you get credit; during the summer, you get paid, oh, about three bucks an hour. It works both ways, right? They do a little bit of sacrificing, too. And you did it a lot. I mean, it's something that sounds like--

**ALBER**: I had really good undergrads: Juli [D.] Klemm and Eric Bertelsen, Nick [Dominic] Benvegnu. Boy!

**HATHAWAY**: So in other words, you're almost talking about these people are what your lab was in the beginning? When you were starting up, they're so important.

**ALBER**: Yeah, they made important contributions. Juli worked on three projects in my lab.

**HATHAWAY**: She was the first author on papers, wasn't she?

**ALBER**: You know, all of them worked. Actually, she worked on four projects, and three of them worked.

**HATHAWAY**: Now, you said that one that she worked really hard on-- We already went through the one that, quote, "didn't work." You didn't ascribe any kind of problems to the person?

**ALBER**: To her? No. Yeah, she's the first author on a biochemistry paper [J.D. Klemm et al., 1991. Correlation between mutational destabilization of phage T4 lysozyme and increased unfolding rates. *Biochemistry* 30:589-94]. She's a second author on the leucine zipper paper [E.K. O'Shea et al., 1991. X-ray structure of the GCN4 leucine zipper, a two-stranded, parallel coiled coil. *Science* 254:539-44] , and some of her work is still unpublished, but it certainly--

**HATHAWAY**: And it was all done at an undergraduate level. She didn't continue on as a grad student in the department or anything like that?

**ALBER**: I think she stayed for the summer and fall after she finished.

**HATHAWAY**: And now she is--?

**ALBER**: She's a grad student at MIT.

**HATHAWAY**: Oh, and she was-- You even mentioned the class still goes on. The Logic and Methods [in Molecular Biology] class that you and Charlie [Charles S.] and Hillary [C. M.] Nelson-- And even David [J.] Julius at least had some notion of it. I mean, as an undergrad I guess they wouldn't let him in, but he knew it went on.

**ALBER**: But what the lab gets out of it is a certain freshness and a certain vitality and energy and life--asking the basic questions again, connecting them to Kafka or whatever it is.

**HATHAWAY**: You require all your undergraduates to have a good grounding in modern European lit, right?

**ALBER**: Well, no, but they haven't gone through this incredible narrowing process that when you start graduate school-- I described to you that even compared to my postdoc, my graduate time was much more creative.

**HATHAWAY**: Really?

**ALBER**: Oh, yeah. We played music, and my housemates played music and wrote poetry and made things. One of my housemates was a painter, etc. And then, you know, I started postdoc. I'm playing less music; I didn't write any poetry. I mean, it goes on and on. And my friends are just doing less and less that's just sort of raw creativity or craft or something, and just more and more that's related to the job.

**HATHAWAY**: You have expressed already, I think on tape, and certainly off tape, some ambivalence about where you've come--and here you are at Berkeley--and some of the responsibilities that come with it. You've also kind of expressed the opposite ambivalence. You used to be really shy and hated giving talks and papers and having to be that kind of public-persona-type thing. Now that you do it, you realize that of course, if you can get up and give a good talk about the work that your lab does, that's important. People are engaged in that, motivated by that to ask you questions, to get you-- I mean, that's what science is about, in a sense, or how it gets communicated in further. The ambivalence runs both ways, right? "What a sacrifice I've made, in the sense of I've narrowed my life. But at the same time, what a good amount of interesting science I've been able to accomplish within the requirement of being narrowly focused." I guess maybe this is a good time to ask about-- I mean, to a certain extent it's a sacrifice, right? I don't mean "Okay, you could be an M.D. or work for a biotech firm and make lots of money, more than you're making now." I don't mean that kind of sacrifice. I meant like maybe playing music, or still playing musical instruments, or having hiked a lot more and camped a lot more in places you'd like to go hiking and camping. It's a pretty recent thing where you-- I suppose moving from Salt Lake to Berkeley is kind of going from one foot in the water

to putting both feet in the--

**ALBER**: No, not at all. It's the whole feel that doesn't relate to whether you're at Salt Lake or whether you're at Berkeley.

**HATHAWAY**: I don't mean to put Salt Lake-- You're right; it's a medical, it's a big-time--

**ALBER**: Yeah, it's a serious research institution.

**HATHAWAY**: I'm sorry. I didn't mean to imply otherwise.

**ALBER**: People are going crazy at how much you have to focus and how dogged you have to be and how hard the work is, with uncertain funding and not much recognition sometimes, you know.

**HATHAWAY**: Beyond the smaller circle of kind of colleagues in the same field, or that sort of thing?

**ALBER**: Yeah. Or just what is it that you give up to do it? The standards are of accomplishment. Certainly you get more done by being dogged and being persistent and putting in the hours. Definitely, you get more done. There are people obviously willing to do this. So then you have a choice as an individual. Do you do what it takes to be at the head of the field or not? When funding is very uncertain, if you slip a little bit, does that mean you're out of the box completely? How hard do people really have to work? You know, when I look at my colleagues--assistant professors, junior faculty, associate professors even--just the sheer number of hours and the culture of-- In some places--thankfully not Utah--people who have children are under suspicion. Their commitment to the field is under suspicion: "You're having a child, this is going to take a lot of time."

**HATHAWAY**: You certainly aren't going to take the time off to-- I can't imagine some father saying, "Oh, by the way, I'm taking a sabbatical, and not to go do a sabbatical in so-and-so's lab but to sit at home and vacuum and raise a child."

**ALBER**: Well, I don't know. People maybe don't do that so much anymore. I would say we're still suffering from a model in which male faculty took advantage of their wives, and wives raised the kids.

**HATHAWAY**: Or they work in their labs as research assistants.

**ALBER**: Yeah, exactly.

**HATHAWAY**: I mean, as a kind of historical interest.

**ALBER**: It's a historical thing. Science in this country is still fighting it.

**HATHAWAY**: I still get the sense that in England they don't-- They still take teatime, right? I may be exaggerating. You were there.

**ALBER**: They do. They did, yeah.

**HATHAWAY**: They work fifty hours a week, and not eighty. Sure, they come in on Saturday afternoon, but just to-- It's still more humane. It seems very much an American thing. A conversation I had with some Pew scholar--it's on tape-- And the notion of you have to do eighty hours a week and you have to never stop, because you won't be a good scientist and you won't get funded. I suggested it was the peer review system, because, of course, the people who are getting funded, who are sitting on review boards, who were on top of their field, were also the ones who are workaholics and working eighty hours a week. And of course the system would perpetuate itself; it wasn't because it was the only way it could be done. It was because people who are at the top of the heap are working that hard and are willing to perpetuate it. And they thought this was wrong. They just thought this is the only way science gets done--that the English sit around thinking too much anyway, and their work's not as good. They may have some great ideas here and there, but the work is just not good. And I was wondering if you kind of had the--? You've kind of drawn a picture that's like that.

**ALBER**: There are exceptions to that, obviously, but I certainly feel that way.

**HATHAWAY**: How many hours do you put in a week here, now that you're kind of settled here at Berkeley with tenure?

**ALBER**: No comment. [laughter] I mean, I could say that, before I left Salt Lake, I was working till midnight virtually every night, or beyond.

**HATHAWAY**: Seven--? Five days--? We're talking five days a week, that kind of midnight work? And then you were working on the weekends maybe less?

**ALBER**: No, I usually worked every day. I either worked or didn't work. You know, like I'd go skiing or I'd go for a hike or I'd go out of town. But if I was in town, I didn't sit home and read a novel on a weekend.

**HATHAWAY**: And your wife [Julie A. Nye] is still speaking to you?

**ALBER**: Well, yeah.

**HATHAWAY**: She appreciates--

**ALBER**: This is a problem. This is the balancing act, you know. We had times that were pretty bad. I don't mean bad in terms of the relationship, just hard to get through.

**HATHAWAY**: Right, where you were just working too much?

**ALBER**: Where I was just working too much, yeah. We solved it by doing things together and going places and skiing and whatever.

**HATHAWAY**: It's kind of like the joke about quality time. In other words, you just had to schedule situations where the work or the lab was just completely out of the way.

**ALBER**: Yeah. Just ignore it.

**HATHAWAY**: Hiding at home, or it didn't work like that? It had to be, "Next Thursday evening we'll go out to the movies or go dance," or whatever it is one does when one has some time.

**ALBER**: Well, also Julie made lots of friends in Salt Lake, and so that took some pressure off.

**HATHAWAY**: She's not waiting at home with three kids? I didn't mean to imply that she works an eight-hour day, goes home, and twiddles her thumbs until you get home.

**ALBER**: She's also very conscientious. So she worked pretty hard--so that helped--in the lab that she worked in. Then she had lots of friends. I'm not saying that we didn't spend any time together, but there were times when it got out of hand, that's for sure.

**HATHAWAY**: And also there's perhaps this notion on her part, and your part, of an understanding about the mechanics of running a lab. Whereas your mother might go, "Tsk, tsk, tsk. You shouldn't be doing that, Sonny. It's not good for the--" You and Julie have the situation worked out pretty well; some of these pressures are dealt with in an adequate fashion. Are you working less here?

**ALBER**: Definitely. [laughter]

**HATHAWAY**: That's not just because things aren't in full swing or something? That's just because it's now time that you can--?

**ALBER**: Why am I working less?

**HATHAWAY**: Some kid keeps coming by, some guy--

**ALBER**: With a tape recorder, yeah. Why am I working less? There's definitely more people in the lab, so they can do more of the work. In Salt Lake, I was doing experiments and calculations--

**HATHAWAY**: You were at the bench a lot?

**ALBER**: --and running the computer system and maintaining the x-ray equipment, and basically lots of different things.

**HATHAWAY**: Because there were less people?

**ALBER**: Yeah, less people.

**HATHAWAY**: In other words, some work attracted people that maybe would have been with you in Salt Lake now, who are now with you here? Or just because there were just a whole bunch of people in Berkeley, at the university, let's say?

**ALBER**: Some of both.

**HATHAWAY**: In the program?

**ALBER**: It's definitely easier to attract people to come to Berkeley.

**HATHAWAY**: I would assume that. So that maybe has had that influence, too. Although just being at a place like Berkeley, you may have more students just looking around for something like this lab.

**ALBER**: Right, yeah.

**HATHAWAY**: So as you've expanded, have you really kind of left off--? Do you get your hands wet?

**ALBER**: I had a sabbatical visitor for the last six months who left in June. He and I did some things together.

**HATHAWAY**: Who was this?

**ALBER**: Bob [C. Robert] Matthews. And you know, I show students or postdocs specific techniques or things like that.

**HATHAWAY**: By giving a lot of that up, and I'm not suggesting that it's not a good--

**ALBER**: Well, I definitely don't have a project that I'm working on.

**HATHAWAY**: There was an article in *Science* that also included Charlie Zuker, about were these labs getting out of hand, like Leroy [E.] Hood. It's called a stupid title: "Labstyles of the Well Funded" [M. Barinaga, 1991. Labstyles of the famous and well funded. *Science* 252:1776-78].

**ALBER**: Lab styles, yeah.

**HATHAWAY**: I don't know if you ever saw that?

**ALBER**: I saw that, yeah.

**HATHAWAY**: Of course, I was impressed by the German. I think he was the only non-American interviewed for the piece. He said, "Who cares if I'm not working at the bench anymore? Do you think that they're paying me this salary to use my hands, instead of my mind?" or something like that. "They hired me because I manage people well, and I have some good ideas," or something like that. He was highly insulted that people might suggest that a large lab precluded him from diddling around in the lab. I don't have an opinion either way, that you're supposed to always be a hands-on researching scientist. But I'm wondering if you have your own kind of sense of that's a loss or it's a good equilibrium you've reached or the lab's getting too big or too small?

**ALBER**: Oh, no. It's not too big. But definitely you lose something when you get away from the bench. You lose a lot of things. You lose an intuition for what really might be happening next. You lose access to the data in a way that you can actually look at the subtleties, and look at the results more critically or something, carefully.

**HATHAWAY**: Just as it doesn't matter who it is--the best graduate student, the best postdoc--they can't be your eyes for you or your hands completely? They can't, right? Is there something that's replaced? In other words, some advantages that are gotten--perspective or that sort of thing--in putting a little bit more distance between you and direct--?

**ALBER**: Well, you can try lots of things. You can follow a lot more ideas. You can have other people who chase down, follow up specific things that are actually important that you would never be able to do by yourself. You have to work with people.

**HATHAWAY**: Sure. No, you can't be Mendel, you know. That's a nice idea, but it just doesn't

work--or even like Barbara McClintock. Really, I mean, that's an idealized and romantic notion that just can't happen anymore, I don't think, because of the equipment, right? You can't even maintain all this equipment yourself. You just can't do that Barbara McClintock-style experiment without certain kinds of equipment anymore.

Do you think that--? I mean, theoretical physicists, even kind of experimental physicists, you know, they can work alone. Other people who use their minds in a creative way--artists, movie critics, novelists; you talked about getting your writing done in Australia, right?--can be alone and get their work done. Do you like the fact that you almost by default have to work with other people, even if it is kind of lonely sometimes when you're here at three A.M. by yourself? Especially the grad student phase, right? Do you like that part of it?

**ALBER**: Actually, with graduate students in the lab, you know, it's much more lonely around here at eight A.M. compared to three A.M. You can always find someone here at three A.M.

**HATHAWAY**: Right, but nobody's here at eight A.M. You're  really in at eight A.M. yourself?

**ALBER**: Me? No. Forget it.

**HATHAWAY**: Nobody's here at eight A.M.

**ALBER**: Well, you know, when I teach I have a more coherent schedule.

**HATHAWAY**: The cooperation and collaboration is, you think, good--? You are, as you said, at least you are of the opinion that you are- - I don't want to use the word extrovert/introvert, but maybe I will. You think of yourself more as an introvert than an extrovert in a world where I guess a lot of people are extroverts, or forced to be. But do you like--?

**ALBER**: Oh, yeah, it's fantastic.

**HATHAWAY**: I'm facing the fact that my work-- Of course this can't get done without other people; it is based on cooperation.

**ALBER**: Oh, sure, it's really exciting.

**HATHAWAY**: I can do that. I used to do dusty old books and stuff. Everybody I wanted to talk to was dead. It just occurred to me that there's something that affects people's attitudes and the work they might do when they are in a situation or dealing with others: compromise. There must be an awful lot of compromise. I don't mean intellectually--how things get done and what pace and that sort of thing.

What classes are you teaching here?

**ALBER**: Protein chemistry, and a new course that's called Introduction to Structural Biology, for undergraduates.

**HATHAWAY**: Once you get through some basic biology, this is an elective they can take.

**ALBER**: Yeah, it follows biochemistry.

**HATHAWAY**: So it's a requirement for some majors then?

**ALBER**: Not in the first year. We are just going to try it this spring and see what happens.

**HATHAWAY**: Do you expect to get junior-level--?

**ALBER**: Juniors and seniors.

**HATHAWAY**: How many are in a class?

**ALBER**: Well, we're limiting it to forty-five because it has a computer lab, but what I was told is there would be several hundred that may be interested.

**HATHAWAY**: "If you're willing to put in ten hours of work in my lab." Is it something you came up with? How did this--? Obviously, I can imagine the bureaucratics of getting it approved, but I'm more interested in the genesis of it intellectually.

**ALBER**: Structural biology is a new focus in the department here. Several new faculty have been hired in the last two or three years: Hillary Nelson, Susan Marqusee—

**HATHAWAY**: Who was the newest hire, right?

**ALBER**: Well, actually, I'm the newest. Tracy [M.] Handel is coming in June, so she was just hired this year.

**HATHAWAY**: And where is she--? Can you give a little bit of the pedigree or something? Or if you don't know?

**ALBER**: Tracy did her graduate work at Caltech [California Institute of Technology] and did her postdoc with Bill [William F.] DeGrado at Du Pont [Merck Pharmaceuticals] and is now at Du Pont. She has a group there.

**HATHAWAY**: So she's coming in at tenure level?

**ALBER**: She's been promoted. No, she's coming in as an assistant professor. Susan was with Buzz Baldwin as a graduate student, Bob Sauer as a postdoc, so Stanford, MIT. Hillary was with Bob Sauer and Aaron Klug.

**HATHAWAY**: And she came at the assistant level, too?

**ALBER**: Yeah.

**HATHAWAY**: And Susan also?

**ALBER**: Yeah. [tape recorder off]

**HATHAWAY**: This is a real plan they have?

**ALBER**: Oh, absolutely.

**HATHAWAY**: Is it kind of step-by-step, or it was all planned? Have you now participated in

the plan, once you got here?

**ALBER**: In terms of resources, Tracy is the last person on board. We don't have any other faculty positions to offer. Her work is on NMR [nuclear magnetic resonance] of mostly proteins, so structure of proteins in solution.

**HATHAWAY**: And Susan Marqusee?

**ALBER**: Protein folding. And Hillary would be protein-DNA interactions.

**HATHAWAY**: So that kind of covers the area of structural protein.

**ALBER**: Yeah. I mean, we're missing a computational person, but it's hard to find the right sort of person.

**HATHAWAY**: They seem to be kind of like the cowboys now, the cowgirls of the--right? They kind of hire themselves out for projects sort of thing?

**ALBER**: Yeah, maybe so.

**HATHAWAY**: I've come across indirectly a few of them, by other interviews. They really are jockeys. They come in and solve the problem, and they have been at sixteen different places in the past three years.

**ALBER**: I see.

**HATHAWAY**: They get great consulting fees. [laughter] That's why you aren't finding them; they can do the consulting-fee route.

**ALBER**: But no, this is an attempt to strengthen struc-tural approaches on campus. Berkeley's been strong in biochemistry--

**HATHAWAY**: Since the--?

**ALBER**: Since the dawn of time, apparently. And you know, this is a new area of biochemistry. It's a growing area of the field, and so they raised the money to set up all these people.

**HATHAWAY**: And this is internal? This is university funds, I take it, and not--?

**ALBER**: No, it's all external. Not all, but virtually all external--Markey foundation [Lucille P. Markey Charitable Trust], [William M.] Keck Foundation.

**HATHAWAY**: The Markey foundation funded them? I know things like the Pew [Charitable Trusts] gives money to the Rockefeller [University], in a kind of general sense, right? Maybe for specific projects, but they're not given to labs.

**ALBER**: Oh, no, this is for a specific proposal to set up structural biology. It was probably two or three of the faculty here in the department.

**HATHAWAY**: Do you know who they were?

**ALBER**: [Daniel E.] Koshland [Jr.], [Jeremy W.] Thorner, [Robert M.] Glaeser. I mean, I wrote a Markey grant with Marty [Martin] Rechsteiner at Oregon for a structural biology center that was funded the year I left, actually.

**HATHAWAY**: Funded in the sense with an FTE [full-time equivalent], an academic teaching kind of thing? Or you were asking for funding for space and equipment and that sort of thing?

**ALBER**: Equipment. We asked for $8 million and got $2.5 million.

**HATHAWAY**: That's not bad, right?

**ALBER**: Oh, it's fantastic. Yeah, I mean, Berkeley got $8 million from the Markey foundation.

**HATHAWAY**: For this whole--? And this included the cost of the renovation?

**ALBER**: Yeah, the renovations and the equipment. It's all spent, basically. We're trying to raise more now, because we would like to get more equipment.

**HATHAWAY**: More equipment, not more-- And you feel that the four-- These are four new positions, right? They didn't end up losing a biochemist, or a--?

**ALBER**: Yeah, they did. The positions have to come from the university.

**HATHAWAY**: And they wouldn't allow more to be created. They docked this whole division, I take-- Molecular and Cell Biology, but the whole thing is called--? And then there are three?

**ALBER**: It's not really worth going through the organization.

**HATHAWAY**: But worth mentioning, making it explicit because all this structural stuff--

**ALBER**: It was endorsed by the whole department, in that sense, yeah.

**HATHAWAY**: Including these guys-- I mean, this whole department is-- What's it called then?

**ALBER**: [Department of] Molecular and Cell Biology.

**HATHAWAY**: That's got the three groups with the three chairs in it--three very powerful people, it seems like. I don't know how it works. I think we used the word "fiefdom."

**ALBER**: This is something actually that we tried to do in Utah.

**HATHAWAY**: The faculty groups?

**ALBER**: No, the department that I moved to had sort of gone downhill. What was done was to get co-chairpeople from within the university to take on the task of rebuilding the department, and specifically to emphasize structural biochemistry or physical biochemistry or at least biochemistry on campus. So there were six open slots, and two chairmen, and they had money

to recruit people. Part of the reason that I went to Salt Lake was the fact that, you know, who in their lifetime gets to be on the ground floor of a department? You can have a big influence. I could help hire the other five people. In principle, in the ideal world, you would get your friends and colleagues who you most want to work with to come and be in the department. So it was to me an exciting opportunity to help organize a place. The history of the Institute of Molecular Biology [at the University of Oregon] in Eugene was that way.

[END OF TAPE 7, SIDE 2]

**ALBER**: So what happened in Salt Lake [City at the University of Utah] is that we did continue to hire people. And we hired wonderful faculty after I got there to the [University of Utah] Department of Biochemistry. By and large, though, most of them were not physically oriented, they were biochemically oriented. Wonderful colleagues-- Brenda [L.] Bass is another Pew scholar who was hired.

**HATHAWAY**: And she's from [University of] Colorado, right?

**ALBER**: Colorado.

**HATHAWAY**: From Tom [Thomas R.] Cech's- -

**ALBER**: Tom Cech, and Hal [Harold] Weintraub at the Hutch [Fred Hutchinson Cancer Research Center] in Seattle. But, you know, she's a really wonderful scientist, a great person to be in the department with. So the people that were hired in Utah--really great.

**HATHAWAY**: But you were kind of disappointed in their emphases?

**ALBER**: Well, it wasn't that I was disappointed. It's that we had made offers to a number of more physical people, computational people, NMR [nuclear magnetic resonance] spectroscopists over the first few years after I arrived. Basically the people that we would have loved to have in the department were the types of people that had many, many, many offers.

**HATHAWAY**: And they just wouldn't come?

**ALBER**: Yeah. So we ended up making offers to people that went elsewhere. That was

definitely a frustration.

**HATHAWAY**: Were structural people just really also in such demand that--

**ALBER**: Oh, absolutely.

**HATHAWAY**: --you were finally hitting a level of people you just didn't--? In other words, the really, really-- Whereas in biochem[istry] perhaps--like Brenda Bass; she was top--there were so many people looking for top jobs, and less of a market, [so] that you more easily get someone like her to agree to come to a starting-up place or a revitalized sort of place.

**ALBER**: Yeah. Well, also it takes a special kind of person to move to Salt Lake. People don't grow up wanting to go to the University of Utah in general.

**HATHAWAY**: No, but maybe after the experience of enough places like MIT [Massachusetts Institute of Technology] and your other-- You didn't take a whole lot of convincing, right? It looked like a pretty--?

**ALBER**: It was really actually exciting. It's a very vital research community, and people just can't stop talking about science. Politics are low. It's supportive. I think it's a really great atmosphere. It just sort of lacks the prestige or--

**HATHAWAY**: True.

**ALBER**: --the sort of respectability, in part because of the Mormons, that many other places have.

**HATHAWAY**: Now, is their influence as heavy at the University of Utah as it is at Brigham Young [University]?

**ALBER**: Oh, not at all, absolutely. It's a secular university.

**HATHAWAY**: That's a doubtful word in the state of Utah. Maybe I shouldn't expose my prejudices.

**ALBER**: That's exactly the problem is that there are all these prejudices out there, and it is hard to recruit people at any level to go there.

**HATHAWAY**: But it was truly secular. Because I've had colleagues who have had experiences, like at Weber State [University], that are quite different--

**ALBER**: That's different.

**HATHAWAY**: --secular university or not.

**ALBER**: No, it's not. But the University of Utah is, at least in chemistry and biochemistry. Perfectly fine, very eccentric, eclectic set of people who are just lively as hell, and it's fun to be there, do nice work.

**HATHAWAY**: Do you get the sense that you have the same opportunities here [University of California, Berkeley] of seeing the program develop?

**ALBER**: Oh, yeah, it's very exciting. That was the thing that-- It's a little bit different because I'm coming in at virtually the tail end of the recruiting. I was number three.

**HATHAWAY**: There is only one person after you?

**ALBER**: Right. So in that sense, it's different. But this group has been put together very rapidly.

**HATHAWAY**: And do you think by people with the same sort of outlook you might have? I don't mean in doing science and how one does science, but in the sense of building, of making-- Here you can concentrate that-- I mean, four people kind of en masse. You really have, it seems to me, on one side a big gamble, right? It could just not be. But on the other hand, it seems like such a great opportunity. Is it expected you'll collaborate? Is there a sense that you'll just feed off each other's work, that you're all at a level where things are going to take off, and so it will just be a matter of being a center where a lot of people interested in structural issues will just kind of be here?

**ALBER**: I think that's starting to happen. We share a lot of equipment. Students benefit from the presence of being in the labs. There are collaborations going on. [Susan] Marqusee and I have joint group meetings. Yeah, it's a good atmosphere. I think the students come and they see how good it is, and that makes them want to get into the field. So our labs were very popular among the entering class this year.

**HATHAWAY**: The rotation students?

**ALBER**: Yeah, exactly. So that was very encouraging.

**HATHAWAY**: You're saying to people, "Well, maybe next rotation period." Right? In other words, you have more people asking you to come in to do rotations here than you can handle?

**ALBER**: Absolutely.

**HATHAWAY**: That's a nice--

**ALBER**: Oh, it's very nice.

**HATHAWAY**: I don't mean that you go "I've got power; I'm turning people away." But it's just that you get to--

**ALBER**: Yeah, it's exciting.

**HATHAWAY**: --ensure some high-quality students and that sort of thing, and a chance to mold people about--

**ALBER**: Because they are sort of this critical mass, we can have a journal club or a seminar series that's more focused in structure, and the students find it more of a compelling discipline. Instead of having two students in five years, I can basically count on having a student each year.

**HATHAWAY**: Of which again--if they are clamoring to get in, if everybody in the department knows that, "Oh, I have to either be put on a wait list, or there's a chance I might not get into that lab. I need to have some interest in the first place"--your hit-rate must go up. More of the

people turn out to be productive and interested and have something to offer.

Is it worth talking about the fact that three out the four of you are women? I mean, that's pretty high.

**ALBER**: Oh, yeah, that's definitely worth talking about.

**HATHAWAY**: Even today, I wouldn't have expected the odds to come out like that. It would have been three guys and one woman, or maybe two and two.

**ALBER**: Yeah. The pressure's on. Absolutely.

**HATHAWAY**: You thought the pressure was on to actually make sure that maybe even they got--

**ALBER**: Oh, it's got to work.

**HATHAWAY**: There has to be, in other words-- And there was certainly--

**ALBER**: People are going to look at this from the outside and go, "Uh-oh!"

**HATHAWAY**: "They were forced to hire them."

**ALBER**: "Look at all these women."

**HATHAWAY**: But indeed, perhaps it was--

**ALBER**: No, I mean, this is going to work, and then people are going to go, "Why aren't we doing this?" But if it doesn't work, then--

**HATHAWAY**: So while you were certainly looking for women because nowadays one has an obligation to, it wasn't just that. The four people who are here are not here because three of them are women. "Boy, structural biologist X, you know, he looked just as good as one of the women

who was hired, but let's hire a woman." It was just that these women are really the best.

**ALBER**: I don't really know the process for Hillary [C. M. Nelson] and Susan and me. With Tracy [M. Handel], it was pretty straightforward that she was--

**HATHAWAY**: The best fit, even.

**ALBER**: Yeah, she was the best fit. And so it's going to be interesting.

**HATHAWAY**: Are there a lot of women already in the faculty here? I know Elizabeth [H.] Blackburn's here.

**ALBER**: She's moved.

**HATHAWAY**: Okay, never mind. How many other women?

**ALBER**: I don't know; I haven't done the sums, but not enough. Berkeley does not have a good reputation. Our department does not have a good reputation with respect to hiring and promoting women.

**HATHAWAY**: I have interviewed the woman who's the first chair of a hard sciences department in the entire UC [University of California] system [Margaret Kivelson]. She became chair in 1984. And that's the entire system. That's pretty sad. Maybe I shouldn't show my colors so much, but for a public institution versus a--

**ALBER**: Yeah, you've hit on something that's important in the sense of-- Yeah, I'm in this department. We have all these women hired. We get more minority graduate students because the student body here is diverse. We get many more minority undergraduates. In Salt Lake it was impossible to recruit minorities, and the undergraduate population was mostly white. That's because those are the people who live in Utah, and minorities don't want to come to Utah anyway because of all the racism. That makes a lot of sense.

**HATHAWAY**: But this is Berkeley.

**ALBER**: This is Berkeley. So you have this opportunity, because it's Berkeley, to accomplish something in the world that's different and that's got to be accomplished. I mean, there isn't any screwing around.

**HATHAWAY**: Do you think that these issues about just simple representation of a population--? But do you think that people with different cultural experiences, be they in this culture, but again from an African American point of view or Latino or people who share-- I'm thinking a lot of Asian students in California whose homes are still very much from another culture, or they are actually foreign-born and here now, so they have a double culture, if you will. Do you think they do science differently? Do you think they're going to not just change the face of science in the sense of there will be less white men and more representative sampling of the population at large? Do you think that they come to science with different questions to ask or different ways or different styles?

**ALBER**: Well, I think you can look at science in foreign countries and just answer that in the affirmative.

**HATHAWAY**: The idea that the British sit around thinking and don't do any--

**ALBER**: Yeah, sure. But look at issues of *Nature:* "Science in 'blank,'" "Science in Nigeria," "Science in Japan," "Science in Sweden." That means that it's done differently by these different people; otherwise there wouldn't be any reason to write about it.

**HATHAWAY**: Even among *Nature*'s editors, who have their heads in the sand sometimes, I think, about some things, but especially this is women's issue. Actually, this may-- Because I've discussed it with a few others. The NSF [National Science Foundation] recently instated a policy where they will not fund meetings if women are not featured in the lineup of speakers, and *Nature* came out with an editorial condemning this. It was basically the same as giving special preference to minorities. Especially they cited the case of black Americans getting into Ivy League schools where they were always perceived then as having been given an extra thing. You know, they weren't really as smart as-- It just perpetuated notions of inequality. The editorial condemned what the NSF was doing, and of course went on to say that it didn't matter anyway. Less white men were going into science, anyway. Eventually it will work out anyway, why bother doing this? Is this something that strikes you as a common attitude among colleagues? That by giving preference, like the NSF requiring that you find a woman as capable as any of the men to give a talk at a meeting, that everybody is going to be looking at that woman, the one woman at the meeting with five featured speakers: "There she is. Oh, she got this invitation because she's a woman, not because she's a good scientist." Do you get that sense that people think that way?

**ALBER**: Sure, people think that way.

**HATHAWAY**: In other words, do you think the outsiders are going to look at this program at Berkeley and say, "Oh, one of those multi-culti universities. That's why they hired three women out of four in this new group with these [Lucille P.] Markey [Charitable Trust] funds"? Do you think that's still pretty common?

**ALBER**: Boy, I don't know why people are going to think we hired women, or women were hired here. People who think that way, you just wait for them to die. [laughter]

**HATHAWAY**: It does change, don't you think? Don't you think your generation has a different attitude than previous ones about, for instance, women?

**ALBER**: That's a pretty broad generalization. There are people catching up all over the place, of all ages. Irene [T.] Weber and I ran a Gordon Conference last summer.

**HATHAWAY**: I don't recognize the name at all.

**ALBER**: It was on diffraction methods, so that's the crystallography, basically. We had a really large number of women speakers and women attendees. The meeting got very high ratings--

**HATHAWAY**: From the attendants.

**ALBER**: --from the people that attended, yeah. Frankly, the way that it worked out, we simply picked topics-- And we were certainly careful to try to find women who were doing the leading work, but frankly we would have had to actively exclude women to have a meeting that was that male-dominated. Although in the event it turned out that there were more women at this meeting giving talks.

**HATHAWAY**: More women than men, you mean, were featured?

**ALBER**: No, more than usual. More than two years ago.

**HATHAWAY**: And it wasn't fishing around for them, right? It was simply a matter of actually maybe the opposite.

**ALBER**: Absolutely. Yeah, all we had to do was not exclude them. It turned out to be a really nice meeting.

**HATHAWAY**: It's an interesting-- The statistics.

**ALBER**: I mean, I could give you another horror story with respect to that. As you know, the Gordon Conferences are set up where the chairpeople write grants and raise money from the government, from private companies. The Gordon Conference puts in a small fraction: the cost of the meeting.

**HATHAWAY**: The cachet.

**ALBER**: Right. We raised enough money to deal with child care, no problem. But the director of the Gordon Conference wouldn't permit the money to be used for that.

**HATHAWAY**: They would have a say over that, even if it was mainly outside funds? Once they approve the meeting?

**ALBER**: Oh, right, absolutely. Yeah, they felt that this was a liability problem.

**HATHAWAY**: So they had use for the funds-- They're ultimately responsible.

**ALBER**: Yeah, they have to approve every use of the funds, so we couldn't use money for child care. That came down from on high. The Gordon Conferences have a policy that children under ten or something are not allowed in meeting halls and dining halls and wherever it is.

**HATHAWAY**: People must be using this opportunity also for a vacation in the Berkshires or something.

**ALBER**: No, these meetings are not vacation.

**HATHAWAY**: I meant, okay, your spouse is off in one of the meetings--

**ALBER**: Well, the problem that we have is there are some couples in the field where one or both are really leaders in the field, and are doing excellent work, and you just can't get them to come to the meeting. And they can't come to the meeting because they can't get child care.

**HATHAWAY**: How was that handled? You just let it happen? I mean, there was no way to really fight it. It happened later. And people actually didn't come, or you provided child care yourself?

**ALBER**: One person didn't come for the meeting. She just came for her talk. Two other couples, they both came and traded off child care with each other, so they had to skip some of the sessions, and couldn't eat meals with any of the people. So we had a table set up sort of on the lawn out in front of the cafeteria, and people would join them for lunch so that they would be included in informal scientific discussions. We simply, as the chairpeople, allowed them to bring their children to the poster sessions and things like that. But the director of the site was obviously violating the rules to allow this to happen. So what we did is we had a petition available for people to sign--and virtually everybody at the meeting signed it--that, number one, we should be able to use money for child care; number two, the director of the site shouldn't face any disciplinary action, shouldn't be fired.

**HATHAWAY**: "We made him do it."

**ALBER**: Yeah, exactly. Because he let these people have their kids on site.

**HATHAWAY**: Do you know if the policy has been changed?

**ALBER**: No, it hasn't. We sent the petitions to the director [Alexander M.] Cruickshank of the Gordon Conferences, and he didn't respond, doesn't return calls.

**HATHAWAY**: Do you worry that perhaps the next time you want to chair a Gordon Conference, you--?

**ALBER**: No, he's retiring.

**HATHAWAY**: Okay, and Gordon himself just recently passed away, right? I think I remember reading that old Gordon died or something. But maybe policy will change then. That's interesting, though, to see. That's an indicative kind of—

**ALBER**: These are major international meetings, and people's careers get made by the fact that somebody in their study section heard the talk or saw the poster. And they get in the meeting, and they get funded, and they go do work. This is not a trivial thing.

**HATHAWAY**: As you say, this is not an issue of being politically correct, and you and--?

**ALBER**: Irene Weber.

**HATHAWAY**: --Professor Weber didn't just sit there saying, "Oh, let's be politically correct and make sure there's child care." You knew there were situations of course where people couldn't come and participate if they didn't have child care.

**ALBER**: These are our friends.

**HATHAWAY**: And why should they have to come up with the extra money and expense of providing child care if other people don't have to? Well, with the world changing, those more kind of practical situations maybe-- I think of state institutions that try to perhaps deal with this a little more upfront than other institutions, not necessarily all the time. Child care at UCLA-- there's a wait list of approximately four years, so of course your child doesn't need care anymore. [laughter] What does one do? Say "Oh, I'll have a child in three years, I'll put my name down now." And of course Harvard [University] has changed its tenure policy. As of 1990, both men and women on tenure track can have the tenure process delayed for up to eighteen months for the chance to raise two children, so you can get an extra year and a half.

**ALBER**: Well, it doesn't matter at Harvard, anyway. Who cares? [laughter]

**HATHAWAY**: I actually read about indeed a woman who had just had a child who's a Pew scholar giving an interview saying, "But it doesn't matter. It's a great policy." She actually took advantage of it. She said, "So it did have that--" You know, she got the time off.

**ALBER**: Connie Holm, probably.

**HATHAWAY**: Yeah, and she said, "But it doesn't matter, nobody's been tenured on tenure track here since 1958." She said so. But she certainly felt the policy was a tilt in the right direction, I guess, in her interview. [laughter] That she was there at the point to see at least a place like Harvard--the old boy school, if there ever was one in everybody's mind--understand that she may have a different clock to follow than her male colleagues when it came to coming down for tenure.

I know of another Pew scholar woman who just had a child. And three weeks later, she is back full-time in the lab because, she said to me, "People don't wait--the rest of the lab. The experiments don't stop because I have a child," that sort of thing. And wow, you know, it just doesn't accommodate a situation like that. Which you may feel as well comes on the male side as a parentless half of a couple? I don't know. Maybe you just don't want to-- The issue hasn't come up; I'm not digging around for it.

**ALBER**: Oh God, no. That's the great thing about having tenure. I can retire and raise the kids.

**HATHAWAY**: Okay, so you're going to have kids now that you got tenure.

**ALBER**: It's a joke. Connie Holm and Larry [Lawrence S.] Goldstein are moving to San Diego. So Harvard has this policy, but they--

**HATHAWAY**: Yeah, I don't know when she was up--

**ALBER**: --will be gone.

**HATHAWAY**: If she got tenure, that's great. She would be the first one since 19-- In any department.

**ALBER**: Yeah.

**HATHAWAY**: Nobody gets tenure. You go do something else, and then they'll invite you back in ten years once you've been-- With tenure, right?

**ALBER**: Yeah, I guess that's how they do it.

[END OF TAPE 8, SIDE 1]

[END OF INTERVIEW]

**INTERVIEWEE:** **Thomas C. Alber**

**INTERVIEWER:** **Neil D. Hathaway**

**LOCATION:** **University of California, Berkeley**

**DATE:** **15 December 1993**

**HATHAWAY**: I did have one follow-up question that I did want to get you to talk a little bit more about. Some of the material you've given me today ties in there. On the last tape, you were talking about-- The jumping-off point was the review [T. Alber, 1989. Mutational effects on protein stability. *Annual Review of Biochemistry* 58:765-98] and Ken [A.] Dill's work. I think you were talking about the prospect of, and your feelings about, being able to find a simpler regularity in the issue of the stability of proteins. That it would be more easily mathematized, and it wasn't turning out that way, it seemed.

**ALBER**: Absolutely, yeah.

**HATHAWAY**: And I would say there's also just been a real increase in all this sort of stuff in the literature, including your own lab, but just more of it in the general journals, like *Science* and *Nature*, related to protein stability, or instability perhaps. I was wondering if you could expand upon that a little bit more now that you've seen some of this stuff come to fruition, and maybe flesh it out a little bit more?

**ALBER**: Well, I think when we started working on this sort of area in the mid-eighties, really the idea that you could make very small changes on proteins and see how they change structure and stability, it just hadn't been done. And so when I was in [Brian W.] Matthews's lab, we started to do that. We published papers in journals like *Nature* and *Science*. These are papers that really aren't publishable today, in a funny way. It's just that there's so much data like this, as you say, that it's very hard to add another rock to the pile, basically. The goal now is to start to organize some of this material. And so it's funny. I review papers now that are the same old thing we were doing ten years ago, and it's incredibly boring. It's not work that I would do anymore.

**HATHAWAY**: Could you name a title just so we have the one paper that you did in Matthews's lab that-- I mean, I've got them all. [laughter]

**ALBER**: Like the first paper on hydrogen bonds [T. Alber et al., 1987. Contributions of

hydrogen bonds of Thr157 to the thermodynamic stability of phage T4 lysozyme. *Nature* 330 :41-46] looked at a bunch of crystal structures, and we correlated a feature in the folded structure with this stability of a protein. To tell you the truth, that's more than most people do now. Mostly they make some mutations, and then they do a few simple measurements and crank out another paper.

**HATHAWAY**: So who's publishing--? I mean, if it's coming at you left and right, and you're being asked to review it, this kind of stuff is getting published, and in *Science* and *Nature?*

**ALBER**: Well, it depends how new the issues are. No, there are still plenty of papers in *Science* and *Nature.* I guess even if they're in *Science* and *Nature* I tend to be quite skeptical these days. It's just that there's so much of the same approach, or the same limited methodolo-gies applied to another wrinkle.

**HATHAWAY**: So it's all the same in the kind of general picture that's being drawn. In other words, they're just putting another layer over the thing, which is that proteins can take quite a bit of--

**ALBER**: Abuse--

**HATHAWAY**: --abuse before they give up their structure-function relationship, or something like that.

**ALBER**: Sure. But, you know, to get--

**HATHAWAY**: That would seem to me as kind of quantifiable. The more you get similarity or-

**ALBER**: Let me put it another way. In the *Nature* paper, in 1987, we measured a factor or a parameter called $T_m$, which is the temperature at which the protein melts. We also determined some crystal structures to correlate $T_m$ with structural features. It's pretty clear now that $T_m$ doesn't have enough information in it to really do experiments that give you information about the components or the interactions that are really operating. But at the time it's what we could do. And certainly people still do that now.

**HATHAWAY**: But yet it has, as you say, little value if it's reiterating, in another protein or another system, what you said and what this lab said and--

**ALBER**: Well, I'm not that cynical. I think just—

**HATHAWAY**: You mentioned that somebody needs to kind of start synthesizing all this stuff and--

**ALBER**: People do. I mean, people are trying. I would say that in the mid-eighties this was a field that had new ideas, and new methods and ways to test old ideas. It was really exciting. What you say is there's a flood of work like this now, and so in that sense it continues to be hot and at the forefront. My own read now is that it's a field that has fewer ideas, and people are sort of tripping over themselves a bit. Some real new analytical methods or new experimental methods are what's really needed.

**HATHAWAY**: Do you see it? You must be hunting for them. The questions still interest you, obviously.

**ALBER**: Oh, absolutely.

**HATHAWAY**: Could you tell us maybe what some of them are, or maybe what you're starting to think of using? [What] the next brilliant postdoc in your lab has already suggested to you, or something like that?

**ALBER**: Well, I think Brian Matthews's lab actually has, as of a little over a year ago, a new way to sort out the issue of the energetic costs of voids in proteins--that is, spaces rather than stuff. What happens when there's an empty space?

**HATHAWAY**: Right. Which means that it's not filling it with its-- So that it's doing something else, i.e., it's folded, right?

**ALBER**: It's folded but it leaves a cavity, it leaves a hole. That's something that every interaction is offset by: what are in the holes and things like that. We are just starting to get data that we can use to sort of--

**HATHAWAY**: "We" meaning your particular--?

**ALBER**: My lab is starting to get some data that can bear on that issue of what is the intrinsic contribution of an interaction. How much does it cost to have the defects? And separate those two ideas: intrinsic contributions versus local contributions. The problem is basically that as people try to assess how much a given type of interaction is worth in a protein, every interaction is worth something different.

**HATHAWAY**: Do you mean if you see the same protein fold happen over and over again, it may be different at different times depending on the--?

**ALBER**: No, what I mean is if you ask, "What is a hydrogen bond worth?" That was the question that we asked in that paper in '87. We had an answer, but if you looked at another hydrogen bond in another protein, you'd get a different answer. Or if you look at what's hydrophobic interaction worth? Again, the experiments have gotten pretty systematic, which is the exciting thing in the field, or one exciting thing in the field now, is that you can do things very carefully. But the answers don't often coincide. This Matthews work that I alluded to was really an idea or an approach that could be used to synthesize data from a whole bunch of different labs. People didn't really realize that the reason that their numbers look so different is that they weren't taking the cavities into account, or the holes into account.

**HATHAWAY**: So in other words, he can go back and now perhaps correct a lot of what looked like conflicting data or conflicting results.

**ALBER**: Well, that's been done with a broad brush, and now people are trying to do it in detail. It turns out to be a fair amount of work. It's tough. That's what I'm saying is, now we have some data that we can use and really check those ideas.

**HATHAWAY**: Is this a new technology sort of thing, or just somebody in his lab came up with a bright idea? Perhaps him?

**ALBER**: Just a new idea. I don't know the genesis of it. So that's one thing.

**HATHAWAY**: And then that's the stuff that he's been publishing recently in *Science,* or this is still not seeing completely the light of day?

**ALBER**: No, it's out. The main paper has the first author of Eriksson. It was early in '92. And then he wrote a review in *Annual Review of Biochemistry* this year. He pointed out that there are

two new things in the field. One is this thing that he did with Liz [A. Elisabeth] Eriksson as the first author. Then they've done a large-scale test of the question of which positions in proteins matter for structure. The results of that are described in the review. It's completely consistent with the *Biochemistry* paper that I wrote in '87 when I was in his lab [T. Alber et al., 1987. Temperature-sensitive mutations of bacteriophage T4 lysozyme occur at sites with low mobility and low solvent accessibility in the folded protein. *Biochemistry* 26:3754-58] . We sort of found the tip of the iceberg, and then they just totally nailed it. The story is the same.

**HATHAWAY**: And just again for me, just in one sentence, the story is?

**ALBER**: That the inside is important and rigid parts are important.

**HATHAWAY**: And the floppy stuff is, as you very kindly and very carefully--and actually I think it's really neat stuff--discussed-- You're not discounting the floppy stuff but talking about its importance as-- You used the bowl of spaghetti as the analogy, and I thought it was very helpful.

**ALBER**: So then I think there are a couple of other things. A guy called Michael [H.] Hecht at Princeton [University] came up with just a fabulous idea that is going to change the field of protein design, I think. Basically, what his work I think will lead to is the idea that you could design a protein structure without having to specify the sequence that folds into that structure. That's sort of a wild thing, because people have always been beavering away thinking, "Okay, what is it--phenylalanine or leucine--that's going to work at this site?" That's been the big question.

**HATHAWAY**: So you got a template, in other words.

**ALBER**: What Hecht did was, number one, realize that you can make a template from a structure. Number two, you could make enough genes on a gene synthesizer using some tricks that he developed so that you could make $10^9$ or $10^8$ sequences that all fit the template. The bias in the field was that maybe only one of these would fold and you wouldn't be able to find it. Well, what he has shown is that a huge fraction of them fold. He hasn't shown what they fold into, but it's really neat, neat work because you really don't have to be smart anymore to design a protein structure.

**HATHAWAY**: I could go into his lab and kind of--

**ALBER**: Absolutely. I think, basically, you can pick your favorite template and go in there and make whatever structure you want. Now it's work to find it, but I don't think it's going to be as hard as it was six months ago, let me put it that way.

I don't know, I think that-- Not in the class of the work of those two people, but this paper that we just submitted to *Nature* is really an attempt to get at a new approach to ask an old question [T. Zhang et al., 1994. Eutrophic effects of disulphide bonds on protein stability. *Nature Structural Biology* 1:434-38] . This is a question that Ken Dill's been working on for over ten years from a theoretical point of view, but his predecessors go back to the mid-forties where there are calculations about how much energy it takes to make the bowl of spaghetti sit still, basically. We've come up with a new method to experimentally answer that question relatively directly. You're not going to like this, but what we find is that the amount of energy depends on the sequence, and that's the same old story: it depends. How much is it worth? It depends. And so in that sense, it's sort of depressing. But on the other hand, now we believe in the importance of sequence-dependent effects. There's a whole raft of experiments that we have thought up that will allow us to pin down what those are and how much they count and which things are important and stuff like that.

I can't remember what your original question was, but in terms of what's going on in the field-- You were saying there's a lot going on. Well, another direction in which there's a lot going on-- Just as in the early eighties people started to be able to clone genes, now it's relatively easy to express gene products and purify a lot of what you're interested in. So just as in the early eighties just the genes that are out there were the object of the hunt, now it's sort of getting down to mechanistic questions. So biophysical approaches and structural studies are getting to be much easier and much more popular, and sort of much more to the point. The applications in terms of drug development, for example, are so obvious that even huge drug companies are getting into this, and therefore the money going into this direction of science--it's going way up. And you know, there are new journals starting--

**HATHAWAY**: New positions in chemistry departments.

**ALBER**: Right, you know, just in the last two or three months a couple of new journals started in the field of structural biology.

**HATHAWAY**: The *Nature* one [*Structural Biology]*.

**ALBER**: The *Nature* split-off one, yeah, exactly. Like you say, things are changing and it's because problems that were inaccessible before are now accessible.

**HATHAWAY**: You seem to temper--and I don't mean this tempering like a damper tempering--

the idea with the example of the answer to the question is "It's sequence dependent," so you're back to the same situation you were painting where people were carefully building: "Which amino acid do I put on next to build my protein?" I was wondering, do you see a situation, rather than my kind of citing a specific thing-- Well, I will then. I guess it's easier for me. This little newspiece in *Science* on these PNAs, peptide nucleic acids, that bind even better than any kind of DNA that nature's been able to produce and that sort of thing. Yet they say, "Well, we don't really know what that might mean if something can bind much more tightly--what the side effects or the downside of something that's better in the sense of DNA may do if we start using it for drug design and whatnot. But do you envision a situation in which the way you ask questions about these things changes? Do you follow me?

**ALBER**: I don't get the correlation or the connection between that and the PNAs. Certainly the way that we ask questions is changing, and that's the whole point. If you ask questions the same way people were doing it twenty or thirty years ago, you wouldn't be actually getting qualitatively new information. Maybe that's what I was saying. My response to your previous question is that many of the papers that I read now are so much of the same thing, asking the questions in the same way. It's not compelling. It's sort of old work. The issue of PNA-- You have to read all these things with a big grain of salt. Something like that seems still to have the problem of delivery of the material inside a cell: targeting, side effects. There's something about the *Science* popular press that is geared up to take minute--

**HATHAWAY**: To get suckers like me to go "Ahh."

**ALBER**: Well, no. It's not bad. It's really to take minute progress. You know, genuine progress is a new area, it's exciting, and there is a simple idea involved: that these are not degradable, and they have different properties of rigidity, and things like that. I mean, that's all true. There's nothing untrue in that. It's just, how important is it in the long run for the culture? Maybe it's going to end up being important. But it is certainly not that way now.

**HATHAWAY**: The little funny part of this article is the quote, "We thought nature or God or whatever had made the best kind of form. Here we've got something that actually binds better, and is more--" I understand that's tongue-in-cheek, don't get me wrong, but I guess I see-- You said you didn't see the connection in what I was trying to say before with your notion that "Oh, before everybody was worried about exactly what the sequence was. Then we realized we just needed a template. Now we go back and we study that template even. We find it's sequence dependent in a broader way or something like that. We have a template, but we're still back to the same old point." I was getting at a situation where our notion of "better," or our notion of "what is it doing"-- Like this protein-DNA interaction thing where there's just the structure-function studies of proteins and how they fold. And you going and talking further about its flexibility, or the fact that part of its built-in qualities maybe it's not going to do it the best way, or--

**ALBER**: Oh, sure, yeah.

**HATHAWAY**: --that it's always going to have a way out. Is it indicative of some sort of change, or the need to recognize that we need to approach some of our work a different way? Our idea of "best" is not necessarily nature's idea of "best."

**ALBER**: Well, these are different goals that you're talking about: "best" means "tightest binding" versus "Does it work in the cell?" We have a situation like that that we're exploiting in the lab now. We've been working on this motif called the coiled coil, an incredibly sort of simple protein structure that turns out to be present in a huge number of different circuits or structures or proteins in the cell. It does a lot of things, the coiled coil. It turns out that when you take your favorite coiled coil out of the cell, it will fall apart at a temperature that ranges from 40 degrees, you know, really cold if you get it out of a lobster that lives in the bottom of the ocean, to really warm. By really warm--most of them are falling apart by the time they're up to 65 degrees or so. We've found that you can make really short coiled coils that don't fall apart at 100 degrees c[entigrade]. So that implies immediately that the real coiled coils themselves are just loaded with defects. It would be like you had DNA and there were lots of mismatches in it and so it wasn't held together as well as possible.

**HATHAWAY**: It still replicated and made a new cell, and that sort of thing. It worked.

**ALBER**: But in fact, it's got to fall apart. That idea is it's got to fall apart to function. Just recognizing that there are these defects in coiled coils has led to a direction in my lab now where we're trying to sort out how to complement the defects. In other words, what are the best pairs? If you had an alanine on one side, what's the best pair on the other side--best in terms of making it the strongest?

**HATHAWAY**: Just so you can start comparing?

**ALBER**: So that, number one, allows you to identify where the defects are. Number two, it's leading to the direction that we can complement those and basically make-- on a peptide synthesizer or a synthetic gene--a little piece of protein that will bind very specifically and very strongly to any coiled coil that we want in the cell. Now, is it in the HIV [human immunodeficiency virus] code or is it in the muscle or is it in the tumor suppressor protein, or whatever?

**HATHAWAY**: Because they're so ubiquitous, these cells.

**ALBER**: Right, but the sequences are all different. They all have different defects. So by learning how to complement those in terms of the issue of stability-- The cell could care less about maximizing stability. But if we know how to do it, then we can essentially make probes. It's sort of like making antibodies. You can make it inside the cell if you want, or you can make it on the peptide synthesizer instead of injecting it in a rabbit.

**HATHAWAY**: You're talking about using that for yet further investigation of these questions about like protein folding, or why this sequence might be the one that's determined in this particular situation to get the protein folded?

**ALBER**: Yeah, well, I don't know--

**HATHAWAY**: Or you're talking about its applications in--?

**ALBER**: There are these sort of pure science kind of questions of what are the rules for specificity and the tightest folding and things like that. But then there are also lots of practical applications in terms of diagnosing diseases, or working on genetic circuits. I don't know if you've heard of a technique called antisense RNA: this is sort of antisense proteins where you could express a peptide in a cell and that peptide would go and knock out the protein that it binds to.

**HATHAWAY**: Am I thinking of it correctly to think that antisense RNA is a neat tool, and you can mess around with all these different RNA things with it, but that when you have it at the level of a protein, you kind of like just exponentially-- Because proteins are more diversified than RNA sequences. In other words, the potential use of mixing and matching proteins and whatnot is exponentially more than mixing and matching DNA and RNA and recombinant sort of technologies, right? Or is it just really the same?

**ALBER**: With antisense proteins, first of all, the way that we envision this now is the first application would be to the coiled coils, because that's what we know about. But in principle, if you knew how to complement surfaces, you might be able to do it for any protein. The idea is with a coiled coil probe, or a coiled coil peptide, you can go and disrupt a very specific interaction. It's not that you get rid of the whole protein from the cell; that's what antisense RNA does. It's that let's say a protein forms a dimer through a coiled coil-- What happens if you get rid of the dimer and now you've got the protein floating around as a monomer?

**HATHAWAY**: Like that one paper as well, where you found the four versions of the coiled coil [P.B. Harbury et al., 1993. A switch between two-, three-, and four-stranded coiled coils in GCN4 leucine zipper mutants. *Science* 262:1401-7] . That's your proof or your demonstration that this is a defect-full situation, or one that's flexible in a very fundamental way.

**ALBER**: Well, that paper shows that you can get very stable coiled coils. And then the next step that we've sort of taken is, "Oh yeah, well, that means that natural ones aren't,"
as you say, "'the best,' in terms of stability."

**HATHAWAY**: But that may be the best, or the ideal; that's what nature is about. I know we're getting on to--

**ALBER**: I was at a meeting in September [EMBO workshop, Coiled Coils, Collagent Co-Proteins, September 5-11, 1993, Alpbach, Austria] and I heard about a possible coiled coil that is proposed to be very similar to the one that we just published in *Science.* This is a four-stranded rope that is incredibly stable. It turns out that people working on archaebacteria from the bottom of the ocean, from these hot vents, have found that the surface of the bacterium has a sort of four-stranded stalk structure that sort of opens up like an umbrella, and then the tips of the stalks are bonded to each other. And they make this incredibly heat-resistant net that's on the outside.

**HATHAWAY**: They've been around a long time, too, evolu-tionarily, right? We're talking about as old as they get.

**ALBER**: Yeah, that's true. But, you know, it's not going to cure any diseases to know that archaebacteria have this structure, but--

**HATHAWAY**: It may say something about selection or evolution over time toward--

**ALBER**: What I'm really saying is here's a bacterium that lives at 100 degrees C, and it uses a structure or may use a structure that we found by accident that also is stable to 100 degrees C. And we had no idea when we went into this. So what's best for archaebacterium isn't necessarily best for you and me, but at least this particular structure has the versatility to be either strong or weak, and that's expressed or seen in nature.

**HATHAWAY**: I guess maybe in the back of my mind through all this is the old scare notion of "Don't screw with Mother Nature." The more it seems stronger now, because again we look at

improving and nature seems to keep telling us to our face that "Well, improving doesn't necessarily mean improving at all." That it is more dangerous, perhaps-- I don't mean we're going to release some sort of--by doing some sort of therapy with designed proteins--terrible side effect that's going to wipe out the human population in one month, and this is done five years down the road. I don't mean any kind of scare thing like that, but just more do we know or do people who work on this know what they are exploiting, let's say, when they exploit their knowledge of protein design?

**ALBER**: No. But that's what you do toxicity testing for. I mean, really: Would you say penicillin is an improve-ment or not? I would say it's an improvement. You learn more; you have more power. You have more approaches. It doesn't mean that they're all going to work. It doesn't mean that they're all going to be safe. But that's politics. You keep—

**HATHAWAY**: Nuclear power, I guess, is one other example of—

**ALBER**: But then that's not a reason to not do it and say "Nature knows best, and let's stick to the nuts and berries."

**HATHAWAY**: You mean like, "Oh, okay, we'll stop now that we know we may be getting in over our heads," sort of thing? No, I guess I meant, is it a warning, or is it a signpost to take a different approach, or to--? No, not for you. I guess I'm not saying the reductionistic--

**ALBER**: I'm not really into changing society right now. [laughter]

**HATHAWAY**: No, just academic biology. I guess this is all due to a reductionist approach to these questions and issues—

**ALBER**: I mean, intellectually--

**HATHAWAY**: --that seems to keep paying off.

**ALBER**: That's sort of post hoc justification: it works, so it must be good. I don't buy that.

**HATHAWAY**: We get this great discovery out of it, we should keep doing it, right?

**ALBER**: Yeah, I don't see it that way. But let me just give you an intellectual example. The field of biochem-istry has felt that the real problem of biology is how you get binding: how you get two things to recognize each other--two or more things--and how you make that strong.

**HATHAWAY**: We're not talking about just organic situations right now, or are we?

**ALBER**: Yeah, in cells, you know, and all these things like DNA. It doesn't function in isolation. It functions because it's read out. It has information in it because there's machinery to read it out. Maybe rocks have information in them, but we don't have any machinery to read it out. Getting really crazy here. The point I'm trying to make is people have been sort of obsessed with this idea of tight binding. I mean, there are a few people in the field that say, "Hey, the problem really isn't tight binding. The problem is perfect binding, getting it weak enough so that the thing works." So, yeah, you're right. It has to be specific, it has to be selective. But it's easy to get things so they're too tight, and that's what is really clear from this paper that we just wrote.

**HATHAWAY**: Now, this is the one you just gave, right? The one you submitted--

**ALBER**: Yeah, the *Science* paper. I mean, it wasn't discovered in the *Science* paper. The *Science* paper is one of the billion examples of this, okay? And the paper that I talked about from my graduate work that was never published--the real problem in that paper was, how do you get weak binding? How to make it so the things fall apart. That's a different sort of problem that is not generally worried about or considered.

**HATHAWAY**: I think we talked about this before, but just to maybe reiterate: I guess I got the sense in talking to you before that this was the other side. The question from the other side of the coin, or the complementary question of how do we get tight binding or perfect binding, was-- You're just asking the same question, but from the exact opposite sort of-- Maybe the example was of the floppy stuff, right: that it's important, but not important in the same way that one looks at the stable stuff. It's important in exactly the opposite way. So yes, of course you need to understand it, and yes, there are worthwhile questions and things to ask about it, and to perhaps even try to think of developing ways of asking those questions.

**ALBER**: Exactly. One of the toughest things is to not only figure out what the question is but to figure out a way to address it. It's much harder to come up with a new method or way to put together old methods.

**HATHAWAY**: Is that how you function? Is that really what you're doing, though? Do you see yourself, and perhaps the other things that you admire and like when you see out there--that you really are always working on the harder one of the two? You're not so much just redoing--that method worked before, we'll do it again--but--

**ALBER**: It's really boring. So like the three things I just mentioned, you know: the Matthews stuff was a new method of analysis; the Hecht stuff was a new method; the paper that we just submitted is a new method. It's a new way to look at an old problem, and it gets back to this issue that you mentioned of there's a lot of work in this area of structural biology now. And the real question is what's novel, or what's qualitatively different about one paper versus another. It's like going to a department store. There are some things that are rare and there are some things that aren't. And it's just loaded with junk.

**HATHAWAY**: Or maybe one time you go it's on sale, which makes it worth buying at that point. Maybe that's how sometimes the reiteration of work--

**ALBER**: That's science. "It's on sale. You can do it, so you might as well."

**HATHAWAY**: Well, or maybe the time that somebody does relatively the same thing but it's a different system. They find out some totally bizarre thing that really does open up the world a little bit more. I think of the mice they found with the totally reversed insides because of something they were doing. They weren't even looking for that, but they found it-- Somewhere in Texas, right? It's got a term for it, where the heart is on the other side. This is all weird stuff, and they weren't even looking for it.

**ALBER**: But what I'm talking about are things that come like maybe not every day or-- Like Brian Matthews's lab has published--what?--fifty papers or something on the effects of mutations on structure and stability, or maybe it's a hundred, who knows? It seems like a thousand.

**HATHAWAY**: And you published some of them.

**ALBER**: Well, there's a joke now that one structure is called a mini-Matthews, and Matthews himself is actually getting close to having a whole Matthews come out of his lab.

**HATHAWAY**: Does he find this humorous?

**ALBER**: Yeah, he finds it funny. [tape recorder off] The point I was trying to make is that you do a lot of experiments that aren't synthetic. You know, they're just the next thing. They're doable. They're what's on sale, so to speak. You do them as well as you can, and you say smart things about them, and you think about them and try to get the last bit of new information about this thing that you just watched happen or this measurement that you just made. And you basically have to do that so that every once in while you come up with this new way of looking at things.

**HATHAWAY**: That's the day-to-day, or the mundane, that gets the work done and leads somehow to--

**ALBER**: Well, it's not even mundane, you know. If it was really mundane-- No, I think there's a distinction to be drawn. It ' s not mundane in the sense that you're sitting around moping that you're doing this boring stuff.

**HATHAWAY**: No, I mean it in its totally neutral, and perhaps original, use: it means daily, or of this world--the regular stuff of the lab, in this case.

**ALBER**: Yeah. But it doesn't make those experiments easier to do.

**HATHAWAY**: Do you mean the fiftieth time--

**ALBER**: It doesn't make the craft any easier. You still have to be careful with your hands, and you have to not make mistakes. When you look at the results, you have to think just as hard.

**HATHAWAY**: I don't mean mundane in a pejorative way at all. I should be more careful of my choice of words, because most people do think of it as having a negative connotation almost all the time, whereas I think more of it as just the daily routine.

**ALBER**: Well, it's people really doing the best that they can; it's what they can think of doing, so that's what they do.

**HATHAWAY**: Having talked about that-- I don't know if you really wanted to pursue this much, but certainly just talking to you today, I went and took a little while in the library while you went and dealt with something that's just happened with one of your postdocs, I'm not sure.

Lots of papers have just been submitted or just been published. What I'm saying is, when I first started interviewing you ten months ago, things were in a different kind of flux: you had no computers up, things weren't-- So it's been quite, I guess, a kind of a year of--

**ALBER**: It's been exciting.

**HATHAWAY**: --from kind of being anxious to being—

**ALBER**: Happy--

**HATHAWAY**: --high. Happy? Okay. [laughter] Sorry. I thought you were maybe high, but happy--generally satisfied and content with your lot in life.

**ALBER**: I wouldn't go that far! [laughter]

**HATHAWAY**: Okay. I'll quit putting words in your mouth. I got the sense in just talking off tape that this is a different world than you were in a year ago. Since we took a year to do this, why don't you, if you would, give us some sort of sense of why it's not the same boat you were in a year ago?

**ALBER**: Well, the lab is up and running. People have lots of new results, and we're writing new papers. And, you know, I actually like the experiments that people are doing, and I like the people in my lab.

[END OF TAPE 9, SIDE 1]

**ALBER**: So you were saying, "What's different?" The lab is going very well. I guess I'm feeling more comfortable. I certainly still feel like the new kid on the block. But just little things: I made my first joke in the faculty meeting, and people laughed. I guess I'm feeling less under the microscope, and I can just go do my work and live my life and pick and choose. Berkeley, of course, has great charms. Initially it's all very new, or it's even strange, and then you sort of get used to it. So there are things that I like, favorite places that feel like home now. Just physically, moving is very disrup-tive. Sort of getting over that--

**HATHAWAY**: You've managed to bounce back without a whole lot of ado. It seems that you--

**ALBER**: Oh, yeah, it's been a piece of cake, Neil.

**HATHAWAY**: If you can't hear the tone of his voice on the transcript-- [laughter] Ten months [ago], when I first met you, you were probably like, "Why are these people here now?" It's nice to see it-- I don't know, it makes me feel like I participated in it.

Quickly, when you say faculty meeting--just to get the facts down because [University of California] Berkeley has such a weird setup--do you mean the entire MCB [Department of Molecular and Cell Biology] faculty or you meant your wing of it?

**ALBER**: Our wing of it.

**HATHAWAY**: Do they ever get together, the entire--?

**ALBER**: I don't know. [laughter]

**HATHAWAY**: Just a few of the hoi polloi perhaps, right?

**ALBER**: Not that I worry about.

**HATHAWAY**: Not that they're telling you about yet. You were talking off tape a little bit about--as you get more people in your lab, and as you find yourself in a perhaps more centrally located place like Berkeley, as opposed to Salt Lake [City]--just some of the adjustments that one makes. I was wondering if you wanted to talk about some of those adjustments on tape.

**ALBER**: Well, my group is already bigger than it was at Salt Lake [University of Utah]. It means I have to be more organized. I work less in the lab. I write more.

**HATHAWAY**: Are you doing any bench work?

**ALBER**: Yeah, mostly computing things. There's a lot more bureaucracy here, which I still find crushing. You've had some experiences with this that you told me about.

**HATHAWAY**: Uh- huh.

**ALBER**: It is easier to get people to come to the lab, and so I guess in retrospect I realize I didn't design enough desks for the size of group that I could envision having. But I don't know. I'm being very cautious in the sense that I like to have the group run fairly smoothly. At this point what is limiting that is how organized I am and how I budget my time. You know, I find myself too easily distracted and too unwilling or unable to say no to things.

**HATHAWAY**: So I guess if I could get your sense of what you mean by more organized, which I guess on the face of it sounds kind of vague. More organized? That means what? You didn't keep a date book and now you do? I think what you mean is that you just concentrate on the management part, right? That you do say no to everything on the outside, or you say it more often, and concentrate on those things that you feel you need to do and nobody else can do?

**ALBER**: Well, I mean, organization means a lot of things, from just keeping this messy office neater to budgeting time. I think budgeting time is the main thing--to really focus on all the things I have to do, instead of just the one thing that's in front of my nose and get that done and then all of a sudden I 'm swamped with ten other things. I can't afford that. So by budgeting time I also mean delegating a lot of that to other people--things that I would normally do. Asking people to be more responsible. If I ask a graduate student to have results by a certain time-- And I rarely do that, but at this point I'm doing that more and more.

**HATHAWAY**: Or if they're not going to have results by a certain time, they'd better let you know in advance, or something along those lines?

**ALBER**: Yeah. Or I had to get some information out of some protein sequences, and it was a project that one of the students was doing. So I really had to say, "Look, I need this information by a certain time." Normally, I would have just sat down and analyzed it myself, but it wasn't something I needed to do. Instead I went to the person--

**HATHAWAY**: That person certainly had the capability.

**ALBER**: She has the capability; it's in her project; she would be interested.

**HATHAWAY**: And she did it, right?

**ALBER**: Well, she made some mistakes. Then I realized I have to- -

**HATHAWAY**: Do part of it.

**ALBER**: --even plan in the mistakes now. I have to say I need it a week before I really need it, so that we can go over it. It's just all these little things, you know, delegating and--

**HATHAWAY**: Have you got a situation going now, or are you in the process of having one of the lab techs or one of the postdocs in charge of the lab? That kind of delegation?

**ALBER**: Oh, sure. Everybody has lab jobs and things they take care of.

**HATHAWAY**: But that one of them is the head?

**ALBER**: No.

**HATHAWAY**: That's you still. I mean, I've interviewed some people where the ordering, the day-to-day mainten-ance, any kind of issue about space and use of equipment goes to a lab manager and not to the PI [principal investigator].

**ALBER**: Well, I'm sure a lot of that happens, and there are natural leaders in the lab. But I don't stand up in group meeting and say, "So-and-so is the person you should go to first."

**HATHAWAY**: Does this recognition of needing more organiza-tion, needing more attention to planning ahead all the things that are going to happen, instead of dealing with them as they come up--is that more of a challenge? Is that something you take on willingly?

**ALBER**: Oh, absolutely. Sure. I mean, I don't have a choice. Even as large as my group is now, I don't have a choice of running it the same way I did in Salt Lake. Unfortunately, a lot of that is just because the bureaucracy at the University of California is so much more time-consuming that there aren't that many hours in the day.

**HATHAWAY**: It's well in place.

**ALBER**: It's entrenched.

**HATHAWAY**: It's five miles thick. It doesn't move very easily.

**ALBER**: Yeah, it's the crust. It's geological. So you know, I've stumbled around with that. That's been a big problem, and the move is just-- In some ways just people not doing their jobs. But I don't have the energy or the interest in taking that on. I have to figure out how to manipulate it or use it or suffer through it. I don't have any illusions about changing the university.

**HATHAWAY**: And this, you mean again, is this bureaucratic-- Could you--? And I don't mean this in a "I don't like the UC bureaucracy either--" This is the pejorative, mundane part, I realize, but anything that really is an impediment, or something that you need to now get not to be an impediment, that looms pretty large that you see as an issue of academic scientists and is therefore important--

**ALBER**: Do you mean what are some of the examples? Hiring takes weeks. Ordering takes months if your thing doesn't get lost. Just getting a room for a seminar is impossible. What else? I was thinking about a lot of things a few seconds ago and they just popped out of my head.

**HATHAWAY**: And you don't have a staff-- I mean there really isn't interdepartmentally, or you haven't written it into a grant, and there's not somebody then who is going to be the one who pounds the requisition through step by step and makes sure that it gets through, so that the eight weeks that it does take--it's only going to take eight weeks.

**ALBER**: People don't have that attitude. You would think that the people that do that job would have that attitude, but they don't really care.

**HATHAWAY**: And that's a departmental sort of thing, I guess?

**ALBER**: Well, it's departmental. It's universitywide. "Don’t step on my turf; I can take it. It's my job to get these orders out, so don't tell me how to do it." Getting lines for my computers has taken a year. And fortunately, we strung our own lines when we first showed up in the building. To do that, we used up all the connections. So we needed, at that point, more connections than have been built into the building. It's taken a whole year.

**HATHAWAY**: For them to come in, bring the lines in, and then drill the hole in the wall or whatever it takes?

**ALBER**: To string the cable.

**HATHAWAY**: And a whole year to actually do it, or a whole year for them to finally show up and do it in however long it takes?

**ALBER**: To finally show up to do it. I mean, it's absurd. Something that would have taken a week, ten days, in Salt Lake. You go down to the computer center, and you give the manager a six-pack. You say, "Look, we're getting this computer delivered, and- -"

**HATHAWAY**: "We can't plug it in."

**ALBER**: "--we can't plug it in. Don't you think that's really horrible?" He goes, "Oh, yeah, no problem." And then he'd call the very efficient carpentry staff. They come wearing their brown uniforms, and they just do it.

Another example: We had equipment delivered, and we had to put it on the sixth floor of the building. The elevator only goes to the fifth floor. So I said, "Great. We'll just get the students in the lab and take it upstairs." And the head of the building goes, "Oh, you can't do that because if someone gets hurt, we'll get sued." So we had to hire a moving company to come and move a piece of equipment up one flight of stairs. These are things that waste time. They waste an incredible amount of time.

**HATHAWAY**: You just feel the circumvention of that--like had your students moved it up--would have, in a situation like here, just not-- That would not have flown. You would have gotten the--

**ALBER**: They wouldn't let us do it.

**HATHAWAY**: They would have prevented you, or you would have been called up on it?

**ALBER**: Oh, well, that I don't care. I assure you I've been dressed down.

**HATHAWAY**: At every institution you've-- [laughter]

**ALBER**: I would hope so.

**HATHAWAY**: It is frustrating when you think of that, especially if it's impeding your actual doing of what you think they're paying you to do.

**ALBER**: Yeah. I mean, I can give you some other examples which are sort of strange. One of my students was mugged. She lives near campus. She wasn't hurt, great. But as a result, she didn't work at night for months. You know, we've got to come up with some solution of having taxi money or something so that she can get home.

**HATHAWAY**: Escort service?

**ALBER**: The escort service stops three blocks from her house.

**HATHAWAY**: And they won't walk her the three other blocks?

**ALBER**: No. We're talking about adjustments, you know, what's different.

**HATHAWAY**: And you say the one time in your life where you had to deal with it, it seemed easier. Of course, beforehand this wasn't your headache, right? You were a postdoc.

**ALBER**: Boy! I'm really glad I didn't come here and start my lab. [laughter]

**HATHAWAY**: Again, to a certain extent, we're just kind of talking about this as a conversational thing, but I think these are the things-- You made the decision to stick with this lab-running thing and being a PI. It involves you having to deal with these things. I'm not saying you sat and really, really scratched your head and thought about it for a month: "Maybe I should just retire or something." But you have to make the decisions to go along--

**ALBER**: No, no, no. There's something going on in science that I don't really-- Well, I

understand it, but I don't really understand it. And that is that I know a lot of people who are really smart, who do great work, who are genuinely burned out or depressed. And it comes--

**HATHAWAY**: About how they do their work?

**ALBER**: Yeah. This comment of mine is coming from your question or query about retiring. So that's not something that's as light as you thought. The problem is that people do nice work and it's still really hard to get money. It's hard to be recognized. It's hard to get good people. You have these crushing bureaucracies that you end up dealing with, that you were never trained to deal with. You're trained to do experiments at the bench, not figure out how to circumvent the regulations at the computer center or the turf battles that you go through or problems with people in the lab who aren't doing what they're supposed to do. If you combine how hard it is to really think everything up and actually get things to work with how hard it is to fund the work, it's leading to a great deal of unhappiness and a sort of a malaise, I think, in the field now. And maybe you don't see that.

**HATHAWAY**: I guess I would tell you about prior experience. Actually, it's probably the most commonly talked-about thing outside of publishing in *Cell,* or getting published in *Cell.*

**ALBER**: Well--

**HATHAWAY**: But that's part of the same thing, I think, too, that I've actually come across. And it, I find, is kind of depressing.

**ALBER**: It's very depressing. I mean, even let's say you're publishing in *Cell*-- I recently was a consultant at the Helen Hay Whitney Foundation meeting, which they have annually. One of the board members rode back to the airport with me in a van. He's in his seventies. He was saying that the young people in his place, "It's amazing these days. They do the strangest things. They actually celebrate when papers get published in *Cell* and *Science.* You know, when they get a grant, they have a party. I mean, we used to just-- Of course, you send in the grant; you send in the paper; it gets published." The guy's like "Why are these people--?"

**HATHAWAY**: Is he not aware of that because he's retired and he's not doing any more--?

**ALBER**: No, he's not retired, but--

**HATHAWAY**: Is he totally insulated from that?

**ALBER**: He's not even totally insulated from it. So then of course I say, "What do you mean? Blah, blah, blah." He knew it's there, but he still--

**HATHAWAY**: He doesn't want to hear it, maybe?

**ALBER**: He doesn't want to hear it, and he doesn't want to do it.

**HATHAWAY**: Or deal with it.

**ALBER**: Yeah, he doesn't want to deal with it. His papers still get published.

**HATHAWAY**: Because that's the second thing I've heard, and because people will say this. They'll say, "You know what? It stinks the way the NIH [National Institutes of Health] doesn't work anymore. Bozos from U[niversity of] Iowa"--excuse me U. Iowa, they are great scientists there, I'm sure, but I'm just picking--

**ALBER**: "The University of Utah, those assholes."

**HATHAWAY**: "--are doing all the reviewing. The real top-notch people in the field aren't going anymore. Why? And now they're only funding 8 percent in my section. Eight percent. What does that mean? They're not funding twenty-five to fifty good proposals; they're funding like fifteen. You can't do science in that atmosphere." And I say, "What are you going to do about it? What do you think you and your colleagues should do about it? It's a peer review sort of system, so maybe you have a say?" Their responses are, "We're too young. We're in the crush and the crunch of this. We're just trying to get our next grant written, and hopefully it will get accepted or partially funded. I don't have the time. And, you know, I don't have the influence to do that." Yet you're describing a seventy-year-old man who is the person who is at that point to do that. He's almost doing this denial thing with you about you're doing strange things, instead of that's what the reality is now: a grant is worth celebrating.

**ALBER**: Well, I mean, even this Pew [Scholars Program in the Biomedical Sciences] money--They had this idea that it was going be sort of gravy.

**HATHAWAY**: Well, I've done enough interviewing now with [class of] 1990 people to know that in some cases it's not gravy. It's going to get them through maybe two years of no funding. I mean, that's going to be it.

**ALBER**: Exactly. This is it. It's more than one.

**HATHAWAY**: Oh, yeah, and I've only interviewed five or six—

**ALBER**: They talk about this group as some select group, and blah, blah, blah. I mean, if this is a select group, imagine what it's like out there--

**HATHAWAY**: In the trenches.

**ALBER**: Well, everybody's in the trenches. But if you didn't have the $50,000 a year-- I mean, it's just horrible. Retire? Well, who knows?

**HATHAWAY**: I guess another way of asking the question more positively is I have witnessed--by talking to people, by just reading around from news and gossipy stuff, to doing a nonstatistical study of where the acknowledgments say the money is coming from--that things are changing. The funding gap that's being left by the federal government, by NIH, by NSF [National Science Foundation] is actually maybe being filled up by private institutions--nonprofit ones like the Pew, but also pharmaceutical companies--

**ALBER**: The army.

**HATHAWAY**: --the Tobacco Research Institute, or whatever it's called. Perhaps there is kind of a reshuffling and a restructuring of the funding for research in this country, and maybe it's not all dismal, dark stuff, but that it's still going to change the way science gets done, because it will be Sandoz [Pharmaceuticals] that's giving you the money.

**ALBER**: Well, clearly one of the differences from the old days, if you were seventy years old, is the amount of time it takes to get a grant is so unbelievable. You get it, and you just don't look back. Your life changes. The things that you have to do every day change dramatically when you get that letter that says you are funded. When you get your second grant-- Even people who are doing incredibly well worry about that renewal incredibly much.

**HATHAWAY**: So you're including yourself in this--?

**ALBER**: God, yeah. I mean, who isn't concerned in these days about--no matter how well they do--will their renewal fly?

**HATHAWAY**: And you're on the second go-around, right?

**ALBER**: First.

**HATHAWAY**: Oh, so you're up--? Your first renewal is--?

**ALBER**: It's in a couple of years.

**HATHAWAY**: Okay, I thought you were-- So you had a--I mean, we've probably discussed this--five-year grant, and then it's up for renewal. In another fiscal year, you've got to go on. So you've got to submit your stuff this fall coming up?

**ALBER**: Two more years.

**HATHAWAY**: Oh, okay. You're telling me you're worried.

**ALBER**: Who isn't worried? I'm very happy with the work, but who isn't worried?

**HATHAWAY**: Do you see a place like Berkeley filling in the cracks, if you get nothing?

**ALBER**: No. Zero, zero.

**HATHAWAY**: What do they do? Just say, "Good-bye"?

**ALBER**: This place is so broke. [laughter] You're at UCLA. What do you see at UCLA? All this extra money?

**HATHAWAY**: Well, the UC [University of California] system has cut its funding by 30 percent in five years.

**ALBER**: So, yeah, I mean, there's some money there. We're trying to raise money that can do the sorts of things we're talking about. That sort of money is what set up my lab when I moved here.

**HATHAWAY**: What's--?

**ALBER**: It was just a grant from the Markey foundation [Lucille P. Markey Charitable Trust].

**HATHAWAY**: A one-shot deal sort of to start up this structural thing that--?

**ALBER**: So Dan [Daniel E.] Koshland [Jr.] is trying to get more, but they've always said, "No, it's a one-shot deal," and so we don't know.

**HATHAWAY**: I've noticed the Pew is doing stuff like that, too. They've done it at Rockefeller [University] for the cell biology section. You see these occasional, "Thanks for giving this grant to the Rockefeller Foundation from the Pew." If the Rockefeller is looking for that kind of money—

**ALBER**: Oh, that's good news. I'll write them. [laughter]

**HATHAWAY**: You think of the Rockefeller endowment as a pretty solid sort of thing, but if they're looking for money, I guess everybody is. Do you think this is just structural change, and you're hitting it at a bad time? Let's say you and your cohort, you and your age group. So the seventy-year-old had the gravy train. Maybe things are tough now, but science will still get done--basic academic research. Even if you read about what happened to the [superconducting] super collider, the Hubbell telescope, and science taking a drubbing maybe even in the popular press--that still, it's going to come back, it's going to always be there on the American scene. Or do you--?

**ALBER**: Oh, yeah. I don't think it's gone from the American scene. But we're talking about the question of what it's like to do it. It won't be gone from the American scene because it's very

practical.

**HATHAWAY**: Of course your work kind of straddles that area too--as being eminently applicable at some point, not necessarily by you, but being very much so of that sort that it would be of great interest to a lot of different private interests as well as--

**ALBER**: I don't think I really have any answers to the problems.

**HATHAWAY**: You don't see a solution?

**ALBER**: There are some changes which always happen. Fields change. Like you were talking about new technolo-gies or new approaches. When new approaches come on, people that end up doing the old approaches are going to lose their funding because they're not finding out anything new.

**HATHAWAY**: They're going to stop having people coming into the lab, and they're just going to go into the other lab.

**ALBER**: And then that's going to make a cohort of people who are unhappy: "There must be something structurally wrong with the system." But some of the changes are-- It's very hard to get papers published. It's very hard to get funded. People these days rarely do things without competition, whereas-- To take the seventy-year-old example--what you did in those days was you started working on a problem—

**HATHAWAY**: You wrote your three pages, sent it to the NIH, and your friend Bob looked at it-

**ALBER**: Well, no, it's not that. It's that it was much less crowded. You were telling me about this person that you interviewed, David [J.] Julius, who worked for four years to clone a gene, and when he was finished, somebody else had cloned the same gene.

**HATHAWAY**: Well, not quite. They finally ended up having to exchange some information so they could both get it.

**ALBER**: Yeah, but it's not the same. In crystallography, it used to be that if you crystallized a

protein, then people would leave you alone and let you go solve [the structure of] that protein, but now it's very different. You don't even tell anybody, "Oh, I crystallized such-and-such" because that tells them, "Oh, it's possible." So if it is very interesting, then they'll go try to do it too. People who are postdocs now, or graduate students now--they will not have had the experience of working without competition, even on important problems. When I was a graduate student, I felt I could work on important problems and not worry about getting run over.

**HATHAWAY**: Heck, even as an undergraduate you got to work on an important-enough little project that somebody-- That you were the one who kind of put it together.

**ALBER**: No, Greg [Gregory A. Petsko] was the one who put it together.

**HATHAWAY**: I meant the actual physical putting together, because you went there and did it, and came back or whatever.

**ALBER**: He did it, too. Well, he did it; I helped.

**HATHAWAY**: But I mean would an undergraduate be helping somebody like Greg Petsko? I mean, I know he was young at the time, but today would you take your undergraduate bottle washer with you on that--? You know what I mean? I am thinking that kind of experience is harder to come by nowadays, at a young or impressionable age or whatever, unless, of course, you really shine. Maybe this is a depressing note to leave things on, maybe not. It's not totally depressing. You certainly have made this decision, and certainly think it's the right one to kind of continue on with this situation the way it is anyway, and at a UC. When you showed up here in January, even then--the decision had been made earlier--things weren't quite so dismal looking as they have been this year. This year has been-- And it's only at UC. Other universities are restructuring and looking for money elsewhere and maybe tightening their belt here and letting some faculty go in that department. They did a study. There's not another state-run institution across the country that's done more than a 10-percent cut over five years. The UC is hemorrhaging. So we're kind of looking in at the worst possible view: the economy, the whole state, that sort of thing. Do you think you made the right--?

**ALBER**: Oh, absolutely. We've had new ideas; my lab is running. My work is going fine. And certainly in the move, I've really had to ask myself what is it I really want to do and try to sort out-- I've gone from having so few people in the lab and so little time that all I could do is the next experiment to really being able to think about "Well, where am I going? What's interesting? What's not interesting? What is it I want to accomplish?" So it's a change, you know, and I like that. It's a good experience. It's very healthy. I'm learning a lot. I would say the UC system is in

trouble. And from what I hear, it's only going to get worse, actually. And I'd say there are problems in science that people are—I don't know, what's the right word?--too competitive.

**HATHAWAY**: I think you hit it. They're depressed.

**ALBER**: People are depressed for whatever reason. It's not just that people are complaining. There are some real problems. But in terms of the move--

**HATHAWAY**: Even as you say, moving to the kind of the site of the real-- Well, again, the way that academia is moving, and certainly the UC was at the forefront of it, and perhaps maybe that's why it's suffering the worst sort of--

**ALBER**: Well--

**HATHAWAY**: --change, as these institutions kind of face it.

**ALBER**: I have somewhat of a different perspective. But it's not informed, is the problem. You know, this shrinkage at UC hasn't affected me personally that much, because I've had a million bucks to go set up my lab and do research that came from the Markey foundation. This is great, okay? I've taught more than I would have had the system not gone through the shrinkage.

**HATHAWAY**: In other words, you all had to pick up more teaching to make the faculty-to-student ratio stay the same?

**ALBER**: Yeah. And I will end up teaching more. It's a difference from what I was led to expect, if you will, but the course seemed to go okay. So that was actually a pretty good experience. I liked the students.

**HATHAWAY**: They just tack on a teaching assignment to you--a whole course?

**ALBER**: No, it's a piece of a course that I wouldn't have otherwise done.

**HATHAWAY**: Again, for factual purposes, what was the class?

**ALBER**: Physical Biochemistry. So it was in my field. It was a graduate course, about fifty students.

**HATHAWAY**: This is a kind of a hands-on lab course?

**ALBER**: No, it's not a lab. It's a lecture. I did a third of it--ten lectures, eleven lectures.

**HATHAWAY**: In three and a half, four weeks? Or you switched off?

**ALBER**: Well, actually, it was spread out over the whole semester. Yeah, we switched off. And it went well. That's all fine.

**HATHAWAY**: And it was done all straight out of the biochem department--just MCB--and not out of chemistry at all?

**ALBER**: Yeah. But the University of California-- They're cutting departments. The physics department is cut in half. They want to cut the art department.

**HATHAWAY**: They're shutting schools down at UCLA--[the Graduate School of] Library [and Information Science], [the School of] Social [Welfare], [the Graduate School of] Architecture [and Urban Planning].

**ALBER**: It just seems to me that part of this is coming from the cost of running the system the way it runs. The cost of inefficiently ordering, for example. The cost of having as many safety--

**HATHAWAY**: Checks and balances?

**ALBER**: Checks, yeah. The cost of building labs so that every single one of them is wheelchair accessible, so that someone with a wheelchair can work in the lab maybe someday. It would be worth to me, for example, taking 10 percent of the money that would be spent on that and making a fund to retrofit labs so that people with wheelchairs can be accessible--just do it.

**HATHAWAY**: On an ad hoc sort of basis.

**ALBER**: Yeah, have it totally free, because it would save a huge amount of money.

**HATHAWAY**: Or that money could be invested and the interest could be used.

**ALBER**: I mean, this is just a wild, top-of-the-head idea, but the sort of legalistic culture here and the culture of people not working to produce a product to make the system run. They want to know what their rights are, and "fuck you" if you tell them not to do something that they have a right to do. If you tell them to do a better job-- Well, you don't have a right to do that: you're harassing them or something. I just think that there is a cost. The things that are being saved compared to the things that are being cut don't make sense to me. You know, it's not anything I worry about. Here I am barely able to run my own group and get my own papers out and teach my own classes and find out where to buy stuff for my house and which store to shop in--all of these new things. But I find it strange to see--

**HATHAWAY**: Well, actually, I think you have described somewhat of an effect it's had on you. I would say that although you don't personally know what's going on with the people who thought they had a nice-running art program here perhaps--I know nothing about the art department--but watching it get slashed in half, realizing that's going to kill it because that's too much to cut it-- I mean, you're cutting out the guts and heart of it. But, you know, you hear about it. Somehow I think that does probably add to your sense of-- People are kind of depressed in the world of biology right now in this country. I think that perhaps it has its intended effect. I suppose there are bureaucrats here in the UC system who also know the art department's being cut in half and have a completely different response to that, right? It's not from the sense of "It's not good to cut any program in half; that's going to kill it," as opposed to the notion of—

**ALBER**: Well, the budget for our building's been cut by 30 percent in the last couple of years, so people are depressed. You can do less. So what do you do? Well, you go out and try to raise more money from other sources. That's what we're doing.

**HATHAWAY**: I think it's been very hard to ask people at UCLA to take a pay cut, which they are doing this year--5 percent—

**ALBER**: Oh, yeah. We took a pay cut.

**HATHAWAY**: --after no pay raises for two years, and then with that say, "Do a better job. Be

more efficient. Save money for us. Make the system work." "Okay, but you're asking me to take a pay cut--"

**ALBER**: I don't think those things are connected. I mean, maybe I'm very naive.

**HATHAWAY**: No? In other words, you can take the 5 percent pay cut, and you're still going to work hard to make it--?

**ALBER**: No, no, no, no. I think if you pay people more, if you give people a raise, they still wouldn't make the system work. I think that there's a cultural problem.

**HATHAWAY**: But that cuts across the board, too. I think that probably includes certain people who are in the situation where their response to something is not, "Oh, you can't tell me to do that better, that it's not working. I know what my job is." There are still some others who are taking a pay cut who are always still thinking, "How do I do my job better?" You could cut it, raise it, slice it five different ways, and they would be still-- As you say, that doesn't affect them so much as just the circumstances around. They read it as "I've got to do better and be more efficient because things are in trouble," regardless of what they do to their salary. It will be interesting to see what happens, whether these kind of deep cuts really kill it. A common response certainly from people in the legislature, I think, and other people who haven't got a vested interest in a job at a UC somewhere, or something like that, think the fact that the UC was really the stellar state program in the country, had these incredible things, that it was about-- Need to face up to reality. It will be interesting to see if it survives in any way, shape, or form as an institution that can be compared to its past--a place like Berkeley. Even a place like UCSC [University of California, Santa Cruz]-- In a sense you really have a long connection with it all, right? Now that you've got me really depressed--

We're coming to the end of the tape, and I don't—

**ALBER**: I think we're done.

**HATHAWAY**: I think we'd better stop now, even though it's depressing. I want to thank you for really what is one of the most wide-ranging conversations I've had, certainly, with your history-of-science background. It's been a real pleasure personally just to talk with you. Thanks a lot; I appreciate it.

**ALBER**: Thank you.

[END OF TAPE 9, SIDE 2]

[END OF INTERVIEW]

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