CHEMICAL HERITAGE FOUNDATION

WILLIAM WEIS

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Helene L. Cohen

at

Stanford University
Stanford, California

on

7, 8, and 9 February 2000

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

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REFORMATTING:

Kim Phan, Program Intern, Oral History, Chemical Heritage Foundation. B.A. expected 2011, Anthropology, Cornell University.

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UNIVERSITY OF CALIFORNIA, LOS ANGELES

Oral History Interview Agreement No. T021600A

This Interview Agreement is made and entered into this 15th day of February, 2000 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 WILLIAM I. WEIS, having address at Department of Structural Biology, Stanford University School of Medicine, Fairchild Building, Room D 139, Stanford, California 94305, hereinafter called "Interviewee."

Interviewee agrees to participate in a series of University-conducted tape-recorded interviews, commencing on or about February 7, 2000, and tentatively entitled "Interview with William I. Weis". This Agreement relates to any and all materials originating from the interviews, namely the tape recordings of the interviews and a written manuscript prepared from the tapes, hereinafter collectively called "the Work."

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

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2. By virtue of this assignment, University will have the right to use the Work for any research, educational, or other purpose, including electronic reproduction, that University may deem appropriate.

3. Interviewee acknowledges that he will receive no remuneration or compensation for his participation in the interviews or for the rights assigned hereunder.

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6. All notices and other official correspondence concerning this Agreement will be sent to the following:

If to University: Oral History Program
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Attention: Director

If to Interviewee: William I. Weis
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Stanford University School of Medicine
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Stanford, California 94305

University and Interviewee have executed this Agreement on the date firs written above.

INTERVIEWEE

(Signature)

William I. Weis
(Typed Name)

Stanford University School Of Medicine
(Address)

Department of Structural Biology

Stanford, CA 94305

Date 2/8/00

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

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Date 2/15/00

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WILLIAM WEIS

1959 Born in Queens, New York, on 10 June

Education

1981 A.B., Princeton University
1988 Ph.D., Harvard University

Professional Experience

Columbia University
1989-1992 Postdoctoral Fellow, Department of Biochemistry and Molecular Biophysics

Stanford University School of Medicine
1992-1999 Assistant Professor, Department of Structural Biology
1994-1999 Assistant Professor, Department of Molecular and Cellular Physiology
1997-1999 Assistant Professor, Stanford Synchrotron Radiation Laboratory
1999-present Associate Professor, Department of Structural Biology
2000-present Associate Professor, Department of Molecular and Cellular Physiology

Honors

1989-1992 Howard Hughes Medical Institute
1994-1998 Pew Scholar in the Biomedical Sciences
1996-1998 Stanford University/Howard Hughes Medical Institute Junior Faculty Scholar Award

Selected Publications

Weis, W. et al., 1988. Structure of the influenza virus haemagglutinin complexed with its receptor, sialic acid. *Nature* 33:426-31.

Weis, W.I. et al., 1990. The structure of a membrane fusion mutant of the influenza virus haemagglutinin. *European Molecular Biology Organization* 9: 17-24.

Weis, W.I. et al., 1990. Refinement of the influenza virus haemagglutinin by simulated annealing. *Journal of Molecular Biology* 212:737-61.

Weis, W.I. et al., 1991. Structure of the calcium-dependent lectin domain from a rat mannose-binding protein determined by MAD phasing. *Science* 254: 1608-15.
Weis, W.I. et al., 1992. Structure of a C-type mannose-binding protein complexed with an oligosaccharide. *Nature* 3 60:127-34.
Burling, F.T. et al., 1996. Direct observation of protein solvation and discrete disorder with experimental crystallographic phases. *Science* 271:72-77.
Kolatkar, A.R. and W.I. Weis, 1996. Structural basis of galactose recognition by C-type animal lectins. *The Journal of Biological Chemistry* 271:6679-85.
Huber, A.H. et al., 1997. Three-dimensional structure of the armadillo repeat region of β-catenin. *Cell* 90:871-82.
Lenzen, C.U. et al., 1998. Crystal structure of the hexamerization domain of N-ethylmaleimide-sensitive fusion protein. *Cell* 94:525-36.
Misura, K.M.S. et al., 2000. Three-dimensional structure of the neuronal-Sec 1 /syntaxin complex. *Nature* 404:355-62.

ABSTRACT

William Weis was born and grew up in Queens, New York, the youngest of three brothers. His grandparents immigrated from Ukraine, Belarus, and Latvia, ultimately settling in Brooklyn, New York. A "frustrated architect," his father was in the United States Merchant Marines in World War II, where he learned electronics; he later earned a degree in electrical engineering at Brooklyn Polytechnic (now Polytechnic Institute of New York University) and worked in vacuum tubes until technology passed them by, at which time he began work for the New York City Office of Management and Budget. Weis's mother was an administrator in a volunteer social work agency and the administrator of a close family.

Weis always liked learning and school. He especially liked mathematics and science, even reading his older brother's entire anatomy textbook when he (William) was in sixth grade. In eighth grade he took a class of biology and chemistry together and fell in love with biochemistry. In high school he took two science classes every year and was on the math team.

Since a broad base of learning was important to him, Weis knew he wanted to attend a liberal arts college that also had strong science. He was accepted at Princeton University, and although it was financially difficult for his parents, he did go there and loved it. He majored in biochemistry and discovered spectroscopy, writing his graduation thesis on rhodopsin spectroscopy. Because DNA sequencing was new, many others went into molecular biology, but Weis liked physical chemistry best. He worked in Meredithe Applebury's lab, and she and Zoltan Soos were his major influences.

For graduate school Weis wanted a strongly quantitative school and one large enough to have a choice of labs. Matriculating into Harvard University, Weis liked all his rotations, but he found Don Wiley's crystallography lab perfect for him. Wiley was doing fascinating work and was extremely enthusiastic about science. There he worked on influenza hemagglutinin.

When he finished his PhD he decided to spend a year at Yale University, working with Axel Brünger on simulated annealing, getting a better model of hemagglutinin. From there he went to Columbia University Medical Center, to Wayne Hendrickson's lab, where he spent the "best four years of [his] life" studying the structure of C-type lectins using MAD phasing (multiwavelength anomalous scattering phasing or dispersion).

He accepted an assistant professorship at Stanford University, taking his research with him. In addition to managing his lab with its different personalities, he teaches some and has a few administrative duties. He likes writing papers and does not mind writing grants, of which he has received several. He has achieved tenure. He loves his work and spends most days in the lab, though he also takes time for his girlfriend. He feels he has met his goals so far, especially his professional goals. He thinks he would someday like to do community work, perhaps science education in earlier grades, particularly among minority students.

His current research comprises three areas: the C-type lectins; an interest in cell adhesion, specifically cadherins (calcium-dependent adhesion molecules); and intracellular vesicle trafficking.

UCLA INTERVIEW HISTORY

INTERVIEWER:

Helene L. Cohen, Interviewer, UCLA Oral History Program. B.S., Nursing, UCLA; P.N.P., University of California, San Diego/UCLA; M.A., Theater, San Diego State University.

TIME AND SETTING OF INTERVIEW:

Place: Weis' office, Stanford University.

Dates, length of sessions: February 7, 2000 (112 minutes); February 8, 2000 (104); February 9, 2000 (77).

Total number of recorded hours: 4.9

Persons present during interview: Weis and Cohen.

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's 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 since 1988.

To provide an overall framework for project interviews, the director of the UCLA Oral History Program and three UCLA faculty project consultants developed a topic outline. In preparing for this interview, Cohen held a telephone preinterview conversation with Weis to obtain written background information (curriculum vitae, copies of published articles, etc.) and agree on an interviewing schedule. She also reviewed prior Pew scholars' interviews and the documentation in Weis'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 technical background, Cohen consulted J.D. Watson et al., *Molecular Biology of the Gene.* 4th ed. Menlo Park, California: Benjamin/Cummings, 1987; Bruce Alberts et al., *Molecular Biology of the Cell.* 3rd ed. New York: Garland, 1994; Horace F. Judson, *The Eighth Day of Creation.* New York: Simon and Schuster, 1979; and recent issues of *Science* and *Nature.*

The interview is organized chronologically, beginning with Weis's childhood in Queens, New York, and continuing through his undergraduate work at Princeton University, his graduate work at Harvard University, his postdocs at Columbia and Yale University, and the establishment of his own lab at Stanford University. Major topics discussed include his research in the Don C. Wiley and Wayne A. Hendrickson laboratories, his application of simulated annealing to the study of hemagglutinin, and his current research.

ORIGINAL EDITING:

Ji Young Kwon, editorial assistant, edited the interview. She 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.

Weis did not review the transcript and therefore some names have not been verified.

William Van Benschoten, editor, prepared the table of contents. Kwon assembled the biographical summary and interview history. Deborah Truitt, editorial assistant, compiled the index.

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INTERVIEWEE: **William Weis**

INTERVIEWER: **Helene L. Cohen**

LOCATION: **Stanford University**

DATE: **7 February 2000**

COHEN: I usually start off with something really simple, like when and where were you born?

WEIS: I was born in New York City, in Queens to be specific. That's where I grew up. Then I moved to the suburbs when I was about thirteen or fourteen to go to public schools there. The schools were deteriorating in New York City at the time, so I went to high school there.

COHEN: We'll go into that in more depth, but before we do that, if you could tell me a little bit about your parents and maybe your grandparents—where they're from?

WEIS: Let's see, I guess I would be [third] generation. My grandparents emigrated from Russia, were Jewish. My mother [Anne Z. Weis]'s side [Isadore W. Zupnick and Flora P.Zupnick] was from outside of Kiev. My father [Martin Weis]'s father [Louis Weis] was from Minsk, and my father's mother [Celia Weis] was from, I think, Lithuania. My parents grew up in New York City.

COHEN: They were born in New York?

WEIS: Yes, they were born here. My maternal grandparents ran a deli actually on 34th Street and 9th Avenue. It's a food family.

COHEN: That's a good location.

WEIS: Oh, yeah, yeah. My mother grew up in Hell's Kitchen or around there, and then they moved to Brooklyn. My father grew up in Brooklyn, and his father was a children's clothing manufacturer. My mother actually went to college, sort of an adult education— She has a high school degree and then went to college—studied art history a little bit—but doesn't have a degree past high school.

My father was a sort of frustrated architect, but to support a family, he was actually in the merchant marines during World War II. He was a radio operator and he got very familiar with electronics, so after the war he went to electrical engineering school at Brooklyn Polytech [Polytechnic University of New York] and became an electrical engineer. Well, he was a vacuum tube engineer. He did that until transistors came in the late sixties and he lost his job. But he knew a lot about statistical analysis and process, so he got a job with the Bureau of the Budget in New York City. And that's where he finished his working days. He's kind of the quantitative one in the family.

I have two older brothers. One [Philip C. Weis] was a high school English teacher and quit that profession and became a lawyer. He's actually a legal secretary, so he writes opinions for a judge in New York state. My other brother [Richard J. Weis] has been kind of bouncing around. He basically is a bagel baker. He's really into food; he's a serious cook and wine collector. He has a bagel store; he was in New York and now he's up in Providence, Rhode Island. He actually studied English and Italian in college. So I'm kind of the oddball. [mutual laughter]

COHEN: The merchant marines was kind of an interesting—

WEIS: Yeah, he didn't want to carry a gun. So when you were drafted and you really didn't want to carry a gun and shoot people, that was an option—to work on one of the transport ships. That's why he did it.

COHEN: Which wasn't so safe either.

WEIS: That wasn't so safe either; a lot of them were sunk. But that's what he did, and that's how he sort of got into the whole thing.

COHEN: That's interesting. With your brothers, there are three of you. All boys?

WEIS: Yeah, I'm the youngest.

COHEN: What were you like together as kids?

WEIS: Well, the oldest and the middle one are separated by three and a half years and then I'm five years younger, so we're kind of spread out. I was just always the little annoying brother. [laughs]

COHEN: [laughs] The pest.

WEIS: Yeah, I got teased a lot.

In the sixties, particularly, there was a lot of skipping of grades in elementary school, so my brother closest in age actually was six years ahead of me in school. Really, by the time I was in junior high school, he was already in college. So once [I was] past elementary school, I was really sort of like an only child in a sense, because both of them were already out of the house.

But we got along fine. I mean, I endured lots of teasing as any little brother would [laughs], but we got along fine. And we still do. I'm not so close to my oldest brother just because there's a bigger age difference and we're just very different, but—you know— we talk and the like. My other brother and I are much closer in many ways, just in terms of our outlook on life, so we're in closer touch. But we're all kind of geographically really spread out, so it's hard. We don't see each other more than a few times a year.

COHEN: Are your parents still in New York?

WEIS: They're in New York, yeah, so I go to the East Coast when I can.

COHEN: Now, was your mother stay-at-home?

WEIS: No, she always worked actually. Well, I think when I was very young, until about five, she did stay home with the kids when she was raising us. But by the time I was in elementary school she had a part-time job, so she would be home by two or three to make sure she'd be there when I got home. But she worked, yeah. She always did. She worked in a social work agency. She was a sort of administrator at a volunteer social work agency in Long Island. She did that for about twenty years.

COHEN: Wow, that's a long career.

WEIS: Yeah. She's retired. Both my parents are retired now.

COHEN: What are your first memories of school? Did you go to preschool?

WEIS: Oh, yeah. I went to a nursery school; I guess that's what it was called then.

COHEN: They called them nursery schools then, right.

WEIS: Yeah, I have a vague recollection of very large blocks [laughs]; that's about it. Then I went to an elementary school which was literally across the street—PS 156, I still remember—in southeast Queens. I grew up across the street from the school, so I remember it reasonably clearly. When I started junior high school it was around 1970, I guess, and unfortunately the schools were kind of really deteriorating at that point. The school actually was a much bigger school than my elementary school and fed from a lot of different neighborhoods, and it became quite dangerous actually to go to school. It was really that bad. I was actually fearful of going to school, and I loved school as a little kid. I was actually literally ill from going. And my parents just said, "We've got to get out of here, William." So that's why we moved.

COHEN: Now, I take it your brothers went to that junior high? It must have been okay when they—

WEIS: Yes, that's right, it was then. But again, they were quite a bit older—the next one was six years ahead—and it was a big difference. So yeah, they did and they were fine. But by the time I went, which was again, about 1970, things had unfortunately really deteriorated.

COHEN: That was around the time, if I remember correctly—because I was living in New York around that time—that the whole busing thing started, a couple of years before that.

WEIS: Yeah, that didn't matter for me because, again, for elementary school, I literally walked across the street. And then to go to this school, just as my brothers did, you got a bus pass and you would take the public city bus there. It wasn't that big a deal; it was a couple of miles away. So no, I certainly wasn't affected by that.

But just the different neighborhoods that fed the school— Some of them had kind of deteriorated. It was really unfortunate because I don't think my parents ever really liked living there, but I certainly did. I had a lot of very close friends.

In fact, it was funny, we had all dispersed, obviously, by high school, but when we all turned thirty, one of them actually tracked us down and we had a big reunion. We were that close—the whole neighborhood. We had a reunion in a restaurant in Bay Ridge in Brooklyn.

COHEN: Oh, how fun.

WEIS: Yeah, it was actually pretty interesting. Everyone looked the same. They were just taller with respect to the tables. [mutual laughter] It was interesting. Yeah, it was actually a very close-knit neighborhood, and it was just unfortunate what had happened.

So I have an uncle [Alex Zupnick] who lived in Great Neck in Long Island, which is where we moved to, because they had really good public schools; that was the main reason. And that's where I went to junior high school and high school.

COHEN: Before we get to junior high and high school, you said you really liked school?

WEIS: Yeah, I always liked going.

COHEN: You did?

WEIS: Yeah.

COHEN: What did you like about it?

WEIS: I just liked learning. I mean, I always would read and know all these little facts. Apparently, I would wake up in the morning—everyone else would still be asleep—and I'd start spouting off facts about history or science or something like that and drive everyone nuts. Yeah, I think I just always liked learning.

COHEN: Did your parents think this was odd?

WEIS: No, they really encouraged it. They thought it was great. Probably I talked too much, but otherwise— [laughs]

COHEN: When you were in elementary were there any parts of it that stood out to you, any teachers or any particular subjects or incidents?

WEIS: Not subjects. I think there were some teachers I really liked, but there was no subject

that particularly stood out. I think I just liked learning of all kinds.

COHEN: So you were into everything?

WEIS: Yeah, yeah, yeah, I think so. I don't recall. I probably always had some predilection for math and science, but I don't think that was a particular standout versus other things at that time. I really don't remember though to be honest.

COHEN: Okay. In those days when you were playing with all these friends and whatnot, what kinds of things did you guys play at?

WEIS: Oh, it was mostly a lot of sports. You know, basketball—

COHEN: Stickball?

WEIS: Yeah, stickball, basketball, softball on the asphalt, handball. We did a lot of that kind of thing. Rubber-ball football with the crosswalks as the end zones on our block—a lot of that. And just riding our bikes around the neighborhood. I wouldn't say there were particularly intellectual pursuits or anything like that.

COHEN: Did you live in an apartment or—?

WEIS: No, it was a house. This was southeastern Queens, which is a lot of little detached houses.

COHEN: Now, a lot of these scholars that I've interviewed, when they were children, played at either building things or dismantling things. Did you do anything like that?

WEIS: I did, but not with my friends. Actually, this is really my father mostly, because I was the only one of the three of us who really grew up in a house, because we had moved from another part of Queens that was an apartment when I was born. So I really grew up in this house and I was the only one of us [who did so] and I would help my father around the house. He actually built me a workbench, and I would actually help do things. So that's when I really started doing things with my hands, and I really became interested in that kind of thing. That's certainly where that aspect of sort of doing experimental things came from. It was definitely

working with my father and helping him around the house.

COHEN: So your brothers didn't get the benefit of that?

WEIS: No, no, definitely not.

COHEN: All right. Well, you mentioned that when you were in junior high, which is usually around eleven or twelve, something like that— Yeah, I think junior high then was like seventh to ninth [grade] or—

WEIS: Probably eleven. It was sixth [grade], I think, at that time. Yeah, that's right.

COHEN: So you were probably about eleven?

WEIS: Yeah, that sounds right. Yeah, that's right.

COHEN: They moved to Great Neck. What was that transition like for you, because you did have to leave your friends?

WEIS: Yeah, that was— The upside was that the school was great. I made new friends there, although it was a little lonely at first, of course. You know, you don't know anyone, and everyone has come up through elementary school there together. I made some friends that were— You know, it was great. But the school was just really good. There were some really good teachers and I got put in an honors math class and things that I really liked, so it was very good from a learning point of view. Particularly, I remember the math and some of the science teachers were very good. I think it was around that time that I really started getting into math and science.

There was one thing though even before that, I think. I remember reading this anatomy book cover to cover. I think my oldest brother had taken some sort of freshman—he was living at home for his first year of college—biology or an anatomy course, and I read this book cover to cover. I just knew everything about the human body when I was about in sixth grade or something. So I had really gotten into it. I think that was kind of my first real interest in biology. I just learned it, and I knew that I was really interested in it. So I really got into biology when I went to junior high school. I remember this wonderful—this is seventh grade—science teacher [Henry Lewis]. When we studied biology and particularly human anatomy, I kind of knew it all already. In a funny way, I think I drove him crazy. [mutual laughter] I remember that class very

distinctly because of that and that interest.

Then two years later I really— The thing is I always really liked biology, but I really liked quantitative stuff, like math. And I don't remember how this happened, but I remember I got really interested in biochemistry.

COHEN: In junior high?

WEIS: In junior high, yeah.

COHEN: Wow.

WEIS: What happened was that this school was very kind of progressive, and they had a lot of different options for the science classes you could take—physical science versus earth science, whatever. There was one that was basically biology and chemistry, so I took that and I just totally fell in love with this interface of biology and chemistry. I think I really can date it back to that time—when I really wanted to do this—which is kind of scary, it's so early. But I really remember that very distinctly. There was this fantastic teacher named Miss [Vera] Randy; I remember her name. That was my first real exposure to it, and I just kind of got hooked.

COHEN: That's pretty impressive at the junior high level.

WEIS: Yeah, I don't ultimately really understand where it came from, but it just sort of clicked. I think it was partly this interest in biology and then really liking the more physical sciences as well. That's kind of why I'm doing what I'm doing now. It really hasn't changed.

COHEN: That's interesting. Now, when I was in junior high, the kids who were really way ahead in math and science were sort of— They didn't use the word geeky in those days.

WEIS: Yeah, nerds or—

COHEN: I think it was nerdy, yeah. Was that a problem at your school, or were those smart kids accepted?

WEIS: Well, it's all very cliquey, I think. I'm sure there were one or two incidents with bullies

or the like, but basically, this was a relatively wealthy community with parents who wanted their kids to succeed, and what happens, I think, in those schools—at least my experience—is that there is a core of these kind of nerdy students who do well, who get put into these honors classes, and it becomes kind of a separate little clique basically. Those are your friends, by and large, and those wound up being the people I socialized with. So it wasn't really a problem in that sense. I didn't feel isolated or anything like that. I could imagine a situation where you don't have those kind of honors-type classes. That's where I can imagine having more friction in a classroom. But they just did it this way. It's at one level elitist, but on the other hand it does solve that problem, I guess.

COHEN: What kinds of extracurricular things were you doing in those days?

WEIS: I was never into the organized stuff after school. In junior high school I would just go home and ride my bike and play basketball with friends and study. I mean, I really didn't do that much in junior high school. A lot of after school basketball—I remember that.

COHEN: In the neighborhood?

WEIS: Yeah. And just studying. That was kind of it.

COHEN: What about high school?

WEIS: What happened was we moved again to another part of town, so I switched. So there was a north and south in Great Neck. I was a south junior, and then I went to north senior.

COHEN: So you had to start over again with friends and stuff?

WEIS: Yeah, so that was, again, a bit painful, but I made friends there again. By that time I knew I was really into the science and math stuff, so I was taking two science courses a year actually. I took biology and an honors chemistry course. The next year, eleventh grade, I took college-level advanced placement biology and physics, and then I just kept going. I took all these science courses—I was really into them—and advanced math, so I was very happy from that point of view. I had friends, and I must admit, most of my extracurricular activities at that time were with my girlfriend [laughs]—my high school girlfriend. That was a major extracurricular activity for most of high school.

COHEN: That's pretty normal.

WEIS: Yeah, nothing out of the ordinary. So it was her and studying. That was kind of it. Again, I didn't really participate in much extracurricular organized stuff. Oh, I did— This is truly geeky— [laughs] I was on the math team.

COHEN: Math team?

WEIS: Yeah, they had these sort of competitive math— What are they called? Mathletes or something.

COHEN: Decathlon or something?

WEIS: Yeah. Basically once a month all the geeks from the different schools would get together. It was actually an organized thing then. They would have timed problems: "Okay, four minutes to solve this problem." They'd give you a problem and you'd have to work it out. I wasn't a star by any means. I mean, I'm not actually that quick at math. I just did it because my friends were doing it. We actually had a very good team because we had this absolutely brilliant guy who actually became a Westinghouse— He represented the U.S. in a math olympiad. So I sort of got sucked into it from that. That was my only sort of organized extracurricular thing.

COHEN: When you were getting ready to graduate from high school, you have to start thinking about what you're going to do next. Did you have a clear idea of what you wanted to do?

WEIS: Yeah, I think by that time it wasn't out of the question [that] I would do something nonscience, like literature, but I knew deep down in my heart I was going to wind up doing science. In fact, I pretty much knew I wanted to do sort of a biology/physics/chemistry-type interface thing even then. So I definitely applied to places looking for that, places that had good undergraduate biochemistry. But I also knew I wanted just a straight liberal arts education. I remember I interviewed at MIT [Massachusetts Institute of Technology] and absolutely hated it. I mean, just the idea of being in a place with no humanities was really oppressive. But I knew, ultimately, I was going to do that, so I did look for it when I was applying.

COHEN: Backing up for just a second, were there any special mentors along the way in high school that you recall, or anybody that influenced you particularly?

WEIS: Well, as I said, I did have a pretty strong, surprisingly focused interest in this area. But certainly I remember my advanced placement biology teacher, Mrs. [Gloria] Harrington, who was a wonderful woman, a wonderful teacher. I was this oddball junior taking this course that was all seniors, and I just sort of was way ahead of the class basically. She really kind of took me under her wing and advised me. It turns out her son was Bill [William] Harrington, who was a well-known muscle physiologist at Johns Hopkins [University], who died actually a few years back. She would say, "You remind me a lot of my son." We would talk a lot about these kinds of interests, so when it was time to apply to school she encouraged me [in] certain ways. I remember talking to her a lot about it. I had a really good chemistry teacher as well, my advanced placement chemistry teacher, Mr. [Tony] Tuori, who was the chairman of the science department. He was very encouraging as well.

That was actually an interesting thing because we didn't have a lot of money. I mean, it was a real stretch for my parents to move to the suburbs and both my brothers— Well, my oldest brother had gone to SUNY [State University of New York], a state school, and then my other brother went to Cornell [University] but on basically a full scholarship, because my father was unemployed at the time. So when it came to me, my father was working and we really couldn't afford kind of an Ivy League school. And I actually didn't know much about them, to be honest, because I really just had my brothers. But among my peers in that school, the best students would go to Harvard [University], Yale [University], Princeton [University]—the elite Ivy League schools—and partly out of peer pressure, I got hold of the catalogs and I could say, "Oh, yeah, these places really have researched the kinds of things I want to do." So I applied to them as well as state schools, thinking, "You know, I can't really afford this."

When I ultimately went to Princeton—I was accepted there—it was a really, really tough decision for my parents, because we really couldn't afford it. It was a real stretch and sacrifice for them; I worked, of course, in college. We kind of really had to pull out the stops, but my mother felt I really should do it, and my teachers, particularly this guy, Mr. Tuori, said, "You really should do it. It's just going to open doors." My father was much more, "Well, I think state schools are fine." And I didn't really know myself. In the end my mother kind of won out.

And it was really a good decision because I think the exposure I got to a broader student base—international students—I wouldn't have gotten at a state school. And of course it was a research university and I really was able to do undergrad research at a level [that was] probably not available at a place like SUNY [at] Binghamton at the time. It was really important.

So I think the high school teachers who sort of pushed me in that direction were actually quite important in terms of the educational choices. And my parents certainly felt after a year there that it was absolutely the right decision. They were very happy about it in the end. But I remember that was kind of a really agonizing decision because of the financial aspect of it at the time.

COHEN: Well, nowadays people take out zillions of dollars worth of loans.

WEIS: Sure, that's what I did.

COHEN: That's what you did?

WEIS: Sure, although even with that— The way they would compute formulas for sort of a middle-class family were not all that favorable. My father had only been five years out of unemployment, and it was tricky. They didn't have any savings or anything like that, and they expected that we did. That made it kind of difficult. But we did manage; obviously, we did it. So that was important.

COHEN: Have you paid them off by now?

WEIS: Oh, yeah. The ironic thing, of course, is that I got out of college right before that hyperinflation—I graduated in '81—that was during the late seventies inflation. It was after that when inflation dropped—in the eighties—but the cost still kept escalating 10, 15 percent a year. So I got out right before the crunch. Even by the time I left, it was like ten thousand a year, so my total loan debt was less than eight thousand dollars—

COHEN: Oh, that's not too bad.

WEIS: —which I was able to pay off. Sometime right after I moved out here I was able to pay it all off. In retrospect it seemed awful at the time, but of course, it didn't kill me. [mutual laughter]

COHEN: So you ended up going to Princeton, and you lived there?

WEIS: Yes, it's a residential—

COHEN: What was that like—going off to be on your own?

WEIS: Oh, I loved it. When I was a kid we would go to summer camp—I went to summer camp every five years—and I always loved it. I never had sort of the separation problem with my parents. I mean, I love my parents, but it wasn't an issue.

I just loved being in college. The work was at the level I really enjoyed, intellectually; educationally, it was a great place. I absolutely hated it though, socially. I really found it an absolutely horrible place. [laughs] I felt it was very WASPy [White Anglo-Saxon Protestant], elitist. Basically, most people wind up being investment bankers on Wall Street. It was this whole preppy culture there in the late seventies, really conservative, and I really hated that aspect of it.

But fortunately, there were enough other people who felt that way there that it was kind of the same thing: that becomes your social group. In fact, all my best, lifelong friends are from college. In fact, there was a group of us that all lived together in one dorm freshman year, and most of my friends from college are from that group. We really became close and we had similar feelings about the place, so it was great. On balance, it was a great experience because educationally, it was terrific.

It was actually kind of a funny thing to go there because I didn't know anything about it. It was one of these things [where] there were people from my school who went there. I actually wanted to go to Harvard or Yale simply because they had stronger biochemistry departments—Princeton didn't have such a strong place—but I wasn't accepted to them. Then it was that or— I think Williams College was my other choice; my best friend went to Williams. But I realized I needed to be in a research university and not a liberal arts college to get the kind of research, science-type environment, so I went there not really knowing a lot except that it had a fantastic physics department, which was certainly an attraction.

Of course I went there and very quickly learned that I'm not cut out for doing physics. I'm not that smart. [mutual laughter] That was kind an eye-opener, dealing with that. So the first semester was a little rocky with the level of math and physics. But after that it was fine. I think getting used to that level of work— You know, I think everyone, or many people, go through that adjustment.

On balance I had a great time there. Well, not a great time. As I said, it was a very schizophrenic thing. In retrospect, I really do appreciate how good the education was. In fact, I think having been a graduate student at Harvard and seeing the undergraduate education, I was much better off at that time at Princeton, because I needed the kind of nurturing that— Harvard takes these kind of pre-formed people, very independent. I wasn't like that, and I think the sort of more undergraduate-oriented, friendly environment at Princeton turned out in retrospect, through complete sheer luck, to be a far better choice for me educationally. So I really did appreciate the experience from that point of view. But I really disliked the social environment of the place. Intensely.

COHEN: We'll come back to that in a second. But you said you didn't get into Harvard or Yale?

WEIS: Right.

COHEN: It sounds like you were a great high school student. What was that about?

WEIS: Yeah, but there are lots of great high school students. I wasn't the absolute top, I guess. I also certainly wasn't well-rounded in the sense [that] I didn't have extracurricular type things. I was obviously very, very strong in math and science and I was a good student in all the other subjects. But at some level I didn't care about them as much, I think. I'm sure all of that came through in interviews and stuff. You know, hanging around with your girlfriend is probably not something you write down in the extracurricular activities section of your— [mutual laughter]

COHEN: Yeah, that doesn't fly.

WEIS: Yeah, it probably doesn't fly. So I think it was a combination of all those things.

COHEN: Going back to Princeton, how was your social life in terms of dating?

WEIS: It was pretty abysmal. I think that was one of the things I really didn't like about it, because at that time it was probably only thirty-five percent women and just the whole culture of the place—this whole preppy culture—I really didn't like. I went out with a few people. Well, it was complicated for me because I was actually still going out with my high school girlfriend for about the first year and a half or two years. Then we broke up and that was kind of a total disaster for me. My grades really suffered, and I was really depressed for a good semester; the whole first two years was sort of that scene. It was kind of a mess. Then after that I was just, on some level, not really ready for it again. Yeah, that certainly didn't contribute to my feelings about the place either. But that's life.

COHEN: Were you involved in any extracurriculars there, like sports or fraternity or—?

WEIS: No, I wasn't because I worked. My free time was spent having to work to make sure I could pay for the place. In my first two years I just had kind of typical student— I worked in the rare books collection of the library, which was actually fun. That was actually much better than slinging hash in a cafeteria. I really enjoyed that actually, so I did that for two years. Then I got a job in the lab, and then I got a work-study job. That was my first real lab exposure. So that was my free time, because I had to pay for it.

COHEN: How was the experience of having to work? Because a lot of people got kind of a free ride. Do you think that that was useful, or did it take away from your study time? How did

you feel about it?

WEIS: No, because I think if I wasn't doing that, I probably would have done some other extracurricular-type thing. It definitely took away from some social time, I'm sure. I think it was a little annoying to see a lot of these rich Manhattanites being able to do whatever, not having to work, but I don't think it's a bad thing for people to have to do— I mean, look, a lot of people do that to support themselves through college. I didn't fundamentally object to it. Ultimately it was fine because I got to work in a lab and got that work experience. So no, in the end I think it's probably not a bad thing for anyone to go through as part of it. It gives you a little balance, perspective.

COHEN: Okay, you majored in biochemistry.

WEIS: Yeah. I mean, the real choice ultimately was either going to be chemistry or biochemistry. Effectively I really was a chemistry major—physical chemistry. I did all my electives in that and I took graduate courses, in fact, in physical chemistry; I liked quantum mechanics and the like. But what happens at Princeton is that you have to do a senior thesis and independent research. You can take classes in anything, but the major really defines what you're going to do your research in. And even though the biochemistry department there at the time wasn't that strong, I realized that I really wanted to do independent work in that. So that's why I chose that major. But it was fine.

COHEN: What was your thesis on?

WEIS: It was on rhodopsin spectroscopy. I basically purified rhodopsin from cow eyeballs—took out retinas in the dark—did laser absorption spectroscopy to— What happens is that rhodopsin, which is the pigment in the eye that is the primary light sensor, undergoes a series of transitions when it senses light, and we were looking at a transition on a millisecond timescale to try to characterize this transition thermodynamically. So that was basically just standard characterize the transition and determine how much of the two species do you get as a function of time, pH dependence. Very typical type of temperature dependence, very basic physical biochemistry.

COHEN: Was this your first real experiment?

WEIS: Yeah, in the lab. I worked in this other lab for a little bit; I didn't really do that much in it in the end. This was really my first serious research effort.

COHEN: And did you like it?

WEIS: I liked it, although it was funny, I was very— You learn a lot of about yourself. I was much more one of the book-smart people than a street-smart person at the time. And I was a little bit timid. I was afraid of making mistakes a lot, and I think that's a bad thing. You just have to go in and make mistakes and do things, and I always wanted to do things right on the first shot. I think that made me very timid about doing things in the lab. I'd get really upset if things went wrong, and it took me awhile to learn that that's just part of it. This is actually a phenotype I've seen [in] a lot of students, now that I'm on the other side of things, which is great because I can actually sympathize with them and I know that they're not lost causes. So it was a very, in some ways, traumatic experience doing that, but I learned a lot and it was a great experience.

My adviser [Meredithe L. Applebury] was wonderful, although it's funny in many ways. I wound up doing a lot of computer modeling along with it because you sort of had to computer-model the data. So I would end up spending a lot of time doing that and maybe not as much bench stuff as I should have. But my adviser was very supportive, maybe too much so, in the sense that I experienced some of the same problems in graduate school for a while—the somewhat timid approach to doing experimental things, which I certainly overcame eventually, but I'd say it did hold me back a little bit at first. Yeah, it was a very interesting experience from that point of view. But I loved the project, and as I said, my adviser was wonderful. So it was a very good experience. And that's the sort of thing—again, at a place like Princeton, where people are forced to take undergrads in their lab because all the undergraduates have to do a thesis—where I was very lucky to be able to get that kind of lab experience.

COHEN: What about the writing of the thesis? You know, for some people it's—

WEIS: I've always liked writing actually. I can be slow at it sometimes, but I'm actually pretty quick by and large and I feel I write fairly well and clearly. I always enjoyed writing in college, like in my literature courses. I always enjoyed doing papers in philosophy courses, so I've always liked it. That's something I know a lot of people really hate, that part of doing science. But I think communications are part and parcel of what we do. That's something I really spend a lot of time with people in my lab on. I drive them nuts, but I feel it's really important. So yeah, even at that time that was not a problem, except I had to type it all out on a manual typewriter. That was a bummer. [mutual laughter]

COHEN: Yeah, it's amazing, you couldn't even conceive of that now.

WEIS: I was really fast on those keys, I tell you.

COHEN: Were you? Yeah, I can remember doing that in college too. God help you if you made a mistake at the bottom of the page.

WEIS: Oh, yeah.

COHEN: Actually, I thought of something as you were talking about the research that you did in college: A lot of kids nowadays get exposed to this kind of thing even earlier through doing science fairs and things. Did you ever do any of that?

WEIS: No. I really don't recall even science fairs being avail— They probably were, it's just I don't recall that being an active thing in high school. It just wasn't there. I may just be forgetting, but I certainly didn't do it if it was there, except for things like the Westinghouse [Science Honors Institute]. I talked to my biology teacher a little about it, but ultimately the ideas I had just were well beyond the resources of the school, so it just wasn't feasible to do that.

I don't recall there being—or maybe I just didn't look hard enough if they weren't publicized—the kind of undergraduate or high school research opportunities in colleges that exist now. I don't really recall that being available. It was probably available on a more personal contact basis then. Now my sense is that it's reasonably well organized. I know Cold Spring Harbor [Laboratory] has a program for high school students to do summers there, and I don't recall anything like that existing. Maybe it did.

It was also [because] I had to work. I mean, I just didn't have the money to go off and do that kind of thing. I had a job in high school, and there just wasn't time. I spent weekends working in high school. I had a job in a hospital—it wasn't glamorous; it was just in central supply—sterilizing equipment and getting orders up to the nurses and stuff like that. It was a great job, paid a lot of money. Because of this interest in anatomy, I actually had always thought, "Well, maybe medicine is something I would do."

I'd say junior year of college, in fact, I actually went as far as to take the MCATs [Medical College Admission Test], thinking I might do an M.D./Ph.D. But by the time it came around to taking them—I did take them—I realized, "This is really stupid. I have no desire to be a doctor." In fact, it's actually something I didn't say before, but the job in high school did do one thing for me, which is that I realized I didn't want to be a doctor. Because that patient interaction which is so key to being a doctor— I didn't mind it, but it just didn't grab me the way it really needs to to be a doctor. Also, I really disliked the doctors I ran into—the arrogance and the culture of it. I really hated that kind of hierarchical M.D. culture. I realized that whole life wasn't for me at that time.

COHEN: That was in high school?

WEIS: Yeah, because that was my high school job. My last years of high school I worked in this hospital.

COHEN: But you apparently hadn't ruled it out completely because you—

WEIS: I hadn't ruled it out completely, yeah, because I knew intellectually, I had this interest in biology. It didn't seem unreasonable.

But also I just, on some level, got very cynical about the whole profession. I saw a lot of people doing M.D./Ph.D.'s because they wanted the letters next to their names, and intellectually, it just made no sense for them to be doing it. I just kind of really got turned off by the whole idea, and for what I wanted to do, it just made no sense. It really came down to that.

[END OF TAPE 1, SIDE 1]

COHEN: Before we go on to your graduate education, I just want to back up and pick up a couple of little things from earlier on. One thing that I like to ask everybody about is whether they had in their childhood or growing up years any formal religious training?

WEIS: Definitely not in my case. My parents grew up in fairly religious households, and they rebelled and didn't give that to us. It was kind of interesting because my oldest brother, being the oldest boy, sort of partly to satisfy my grandfather had a rather traditional kind of bar mitzvah and Hebrew school. When it got to the next one it was sort of done; it was more token and it was kind of a joke basically. Then when it got to me— By that time, I think partly just growing up in this family and having older brothers who were particularly very thoughtful people—we would discuss this a lot. Also, I had a lot of Jewish friends as well in junior high school who were getting bar mitzvahed. All they would talk about is, "Oh, I'm going to get all these presents and get all this money for my bar mitzvah." And I was just totally repulsed by it, because I felt this was just incredibly hypocritical. You either believe in it or you don't. So I just refused to do it. I actually took Hebrew lessons for a little while because— Well, my grandfather really wanted this. Then I said, "Look, this is just— I can't do this." And my parents were okay with that. It was a little bit tough working it out with my grandfather, but even he sort of accepted it in the end.

So that very much was not a part of me. I'm actually, I wouldn't say, actively hostile, but I'm really at some level very much uncomfortable with organized religion in general. It's just not a part of my life, and I don't want it to be basically. And it's not a matter of spirituality. It's just

the organized, formal part of it that I really don't believe in.

COHEN: But on the spiritual side, you said that a part you're not negative about?

WEIS: No, I can understand that. The spiritual side of formal religion I have nothing to do with basically, just the whole structure of it at all. On the other hand, I recognize that what makes someone a good person in our society ultimately comes from Judeo-Christian mores that have come down as part of our laws and our culture. I certainly don't deny that. I can accept that. There's sort of an—I don't know what to call it—anthropological basis of how to behave, which is fine, and I certainly believe in that. Maybe it's a little too clinical to sort of dissect it that way, but that's how I view it. So it's not that I think we should all be immoral and ignore society's morals about how to behave and ethics, but I just don't do it in the context of any kind of formal religious framework, I guess.

COHEN: Do you think that God and science can coexist?

WEIS: Yeah, I think I do. It's not something that troubles me personally. I think there are interesting theories about, say, the creation of the universe that don't require a God, for example. But also, I certainly respect people's beliefs that there can be, say, a creation event for the universe, and I think it's not incompatible—this idea that [there's] an initial creation and then that's followed by the current theories about how the universe is evolved. Ultimately, how life has evolved from that is certainly not incompatible with science. I think if you talk to thoughtful people in the clergy, a lot of them will say the same thing. The fundamentalist stuff is another problem I, many people, have. But no, I don't think they're necessarily incompatible. For myself, I personally don't feel that invoking that kind of divine creation is necessary. But I can accept it as a part of a healthy debate.

COHEN: The other thing I wanted to talk about from your childhood was what, if any, expectations your parents had for you and your brothers actually.

WEIS: They were great. I mean, they really believe that we should all go our own way, and we're all very different people and actually we're doing very different things—three completely different people from the same set of parents. They basically wanted us to be happy. Of course, they'd want to see us employed in the sense of having enough material comfort. But in fact, my father particularly has very strong antimaterialist feelings and we were certainly imbued with that, very much so. I'm certainly like that and my brother Richard is as well—the middle one. So we were never pushed to be, quote, a professional and make money. It was very much doing something you're happy doing.

Partly it was because my father, even though he became an engineer and did all those things and enjoyed it—he really liked the technical stuff—as I said, was kind of always a frustrated artist and architect. I think he was never totally happy with not being able to do that and he didn't want that to happen to us.

So they're absolutely thrilled that I'm doing this, because this is not the profession you go into to make a lot of money, obviously, but they know— You know, I love this. I mean, basically scientists get to do their hobby for a living, and they love the fact that I'm doing that and I've done well. The only pressure was to just do what— There wasn't any pressure actually. Maybe part of it was we were always self-motivated and good students and it wasn't an issue and they would help us out. But yeah, certainly that never came from them at all.

In fact, it was interesting— One of my mother's brothers—one of my uncles—raised his kids very much in the way, "Oh, you have to have a good job and be a success and make a lot of money." They would talk somewhat disparagingly of that. I'm not close to those cousins at all because they're just into that scene, which I— It's just not of interest. So yeah, very much [there] was not any pressure from my parents. If I had decided to become, oh, I don't know, a ballet dancer or whatever, they would have been happy with that, absolutely. And that's why we're doing all these different things.

COHEN: And they're equally proud of everybody.

WEIS: Oh yeah, absolutely, absolutely.

COHEN: Sounds like you came from a really loving family.

WEIS: Oh, yeah, my parents are just great. They really are. No complaints about them.

COHEN: That's great. Well, let's go back to Princeton for a minute. Were there any special teachers or mentors from that period that you recall?

WEIS: I had a couple. Zoltan [G.] Soos. He's a physical chemist, a theoretician. There were three of us, I remember—all of us are now research scientists, actually—in my class, who took organic and physical chemistry together as sophomores, which was kind of an odd thing to do. And this guy, Soos, was this wonderful quantum mechanics teacher. In fact, I probably did more physical chemistry than I would have if I hadn't had him as a teacher. I took his graduate course in it because he was such a great teacher. And he was a really nice guy. In fact, the biology teachers were actually quite weak. I think that's why I did so much physical chemistry at the time. I didn't have great experiences with the more biological teachers.

My undergraduate adviser, Meredithe Applebury, who actually is now at MGH [Massachusetts General Hospital], at the eye institute at Mass General or what is called the [Massachusetts] Eye and Ear [Infirmary], was wonderful. She was very supportive. She had come from a physical biochemistry background, so we, I think, really hit it off. She was surprised because— I think rightly so. A lot of the teachers in the biochemistry department there got very cynical because they had to take undergrads in their lab, because a thesis was required, and most of them were premed and they were really not interested. They were fulfilling the requirement.

So to have someone who really wanted to do science and also have this kind of funny interest in the biophysical stuff as well, which was very unusual at that time, because DNA sequencing had just been invented and cloning technology— Everyone wanted to do molecular biology. Here was someone who wanted to do this kind of stuff. I think she kind of found that interesting, so she was very, very supportive of me actually. She was great and obviously wrote letters for me. A really great woman. Scientifically those were the two people.

The other teachers I had who really were great were, actually, a philosophy professor named Richard Rorty, who is a very well known philosopher who I took several courses with, who's just a really fantastic philosopher and teacher actually. Then I had a couple of comparative literature professors [Theodore Ziolkowski], who were wonderful. You know, it was more actually the humanities people who I really, really enjoyed a lot and who made the whole experience at Princeton great. Intellectually it was those people. The science almost took care of itself, because I just had this pretty strong sense of what I wanted to do.

COHEN: Were you already clear about what area of science—? I mean, if everybody was suddenly going towards molecular biology, why didn't you go there with everyone else?

WEIS: Well, I think it was because I really wanted to do something more quantitative. I really liked the chemistry and the math and the physics and I ultimately wanted to be looking at biological systems, but I really wanted to approach it from a quantitative point of view. So it was just obvious that I needed to sort of take my undergraduate curriculum that way.

Ironically, since I do X-ray crystallography now, I actually worked for a crystallographer my junior year. My junior-year job was actually in a crystallography lab, although I didn't do crystallography, with a guy named [H.] Tonie Wright. But it didn't even register at the time. It was kind of funny.

In fact, I went to Harvard intending to do physical biochemistry, membrane biochemistry. I was really interested in membrane biology and cell biology; that's kind of always been there. But at the time of course, all this protein DNA stuff was starting to happen, and I was still interested in a lot of really interesting physical questions. So when I was looking for graduate schools I talked to my adviser of course, to Meredithe, and I looked for places that had faculty

[who] came from a more physical background. And ultimately my choice of graduate school was based on those kinds of people being present.

So yeah, I think it was certainly bucking a trend at that time, but it probably did me a big service, because when I applied to school I probably was a person who stood out from a lot of other people. It was definitely an oddball thing to do at some level, so it probably helped me get into graduate school, in part because it just looked weird.

COHEN: Now, when did you know that you wanted to be an independent scientist, because a lot of people major in biochemistry and then they go on to be somebody's lab tech[nician]. So when did you know?

WEIS: I don't know. I guess part of it is that I knew I didn't want to be a professional in the real world. Actually, during college I had some pretty stultifying summer jobs, like in a law office and stuff like that, and I just didn't want a nine-to-five-type career. And I didn't want to be a doctor; I knew that. I really just, probably in part due to the humanity professors, liked the idea of being an academic in a college environment, always around students who were challenging you. At that time also, if you think about it, in the late seventies and early eighties, the biotech[nology] industry wasn't something that was on the radar map as something you did, a career choice. So you say, "Well, why didn't you want to just be a lab tech?" Well, I guess culturally you figure if you're smart and you get a Ph.D., you become an independent investigator. So I don't think it was that well designed. I think that's just how it was. But I think in a more positive way, I really did want to stay in academics; I knew that. The life looked appealing from a distance; of course, the reality could be otherwise. But I think it wasn't that well focused. Probably it was in the back of my mind [that] I wanted to do that.

COHEN: Well, it's interesting that it was your humanity professors that sort of piqued the interest.

WEIS: I think that was part of it. I mean, obviously, I was much closer to the science people at some level. The idea of being able to do your own experiments— Actually, I think there was another big factor, now that I see it, which is that having had these jobs in high school and college, I really hated— I have a real authority problem. [mutual laughter] I really don't like having a boss. And I think part of the appeal of being independent was that I basically decide what I want to do. Not that I always had bad bosses, but I think the idea that someone's telling me what to do is not appealing. This is one of the reasons I didn't do—aside from probably a general lack of coordination—a lot of sports. Because I actually hated gym coaches, not because they're bad people—and I didn't mind sports—but I hated being part of anything organized actually. Even in high school I just didn't want to do this kind of militaristic, gym coachtype thing. And I think that has carried over. I knew I just couldn't have a boss. I think that was a big part of it, actually. So I think there was just a combination of all these things.

COHEN: You were pretty clear in your own mind about—

WEIS: Yeah. Oh, yeah, actually, which scares me. [laughs] But it's true. It really is true.

COHEN: So how did you end up at Harvard?

WEIS: The main thing, by far, was I knew I wanted to do this kind of more quantitative biology. I talked to my adviser, I looked at the people and what they were doing, and I basically said, "I'm going to the place." To this day I tell prospective students, "Don't worry about the location so much. I mean, location is important, obviously, in your other life. But the main thing about choosing a graduate school is to go to a place where you can imagine working for several different people, because some of them are going to be jerks and you want to find a place where you have enough choice of people you can imagine working for and one of them will work out."

At the time the Harvard biochemistry molecular biology department had more people doing the kinds of things I wanted to do. It was that simple. The only other place I really considered was Yale, because it had this very strong biophysics department there. It came down to those two places. There were a couple of people at Harvard that just kind of grabbed me more, I think. Then there was a location issue: I really wanted to try Boston. I hadn't gotten in there as an undergrad and I really liked the idea of living in Cambridge and being at Harvard and experiencing that. So it wound up being a pretty easy choice. I was accepted at [University of California] Berkeley and I think UCSF [University of California, San Francisco]—I don't remember—as well. I know I didn't apply here [Stanford University] interestingly enough, which had a very prestigious department—biochemistry—at the time. The only person doing anything physical was Buzz [Robert L.] Baldwin. That was a case where it was only one person—if I decided I didn't like it, I'd be stuck—so I didn't even apply here.

So it ended up being a relatively easy choice for me to make, and basically it was because— I can name the people. It was Jim [James C.] Wang, who's a physical biochemist at Harvard, Guido Guidotti and Lew [Lewis C.] Cantly, who were doing membrane biochemistry, and Don [C.] Wiley, who I ended up doing my thesis work with. I didn't know about him, but my adviser said, "This guy's really good, really interesting. You should talk to him when you go interview." I talked to him and I said, "Wow, this is amazing stuff he's doing," and I wound up working for him, even though I rotated in those other labs.

COHEN: So you were actually in Cambridge, not at the—?

WEIS: In the Cambridge side, that's right, not at the medical school. That's right, the arts and

sciences side. Anyway, that's how I wound up there.

COHEN: Tell me a little bit about what it was like being in Don Wiley's lab? You know, every lab is different.

WEIS: Well, my first year I made a huge mistake, which was not taking a year off. I was really not happy my first year. I think I was just kind of burned out, and I was really unsure. What happened was, again, this kind of timidity of benchwork that I mentioned before kind of came to pass and I started thinking, "God, maybe I really want to do just computation." I was really torn. In fact, I kind of blew off one of my rotations because I was just very unhappy and going through a lot of sort of personal problems with it.

I ended up doing a rotation with Martin Karplus, who's a theoretician in the chemistry department, and I realized, "Boy, I really don't want to do all computing either." Then what happened was my last rotation was actually with Don. By that time I kind of had— "You know, maybe crystallography is a good balance between bench stuff and computer work and more mathematical stuff." I worked in his lab and I really liked the project and I just realized this is what I should do—X-ray crystallography.

Also, at the same time I realized that all the questions I really wanted to answer, that I had on a particular problem, ultimately came down to knowing an atomic structure. So I said, "Boy, this is great. I can do exactly what I want to do on a day-to-day basis—some biochemistry, some computing, instrumentation." That's the level of question I wanted to look at. I realized this was a perfect match. Don was doing incredibly interesting stuff with influenza at the time, so I just joined his lab. That was it. That's how I joined it.

It was an interesting experience. It's a very high-pressure lab. Don and Steve [Stephen C.] Harrison had one big joint lab, and it was a very, very high-pressure place. There were things about it— And by that time— more generally at Harvard but that lab in particular— there was a lot of— What's the word? There was a kind of arrogance to the Harvard department at the time and also the lab there.

On the positive side, you need some arrogance to be able to do really hard things and take on hard problems and do it, and I took that away from the experience, I think. But there's a huge downside to it, which is that there was this idea that "No one else in the world is doing anything worth doing," that "We're the only ones doing anything." And I really hated that aspect of it. It was also just very, very high pressure. The lab was not a healthy place to work. It really wasn't. We would go out drinking all the time just to relax, four or five nights a week. You know, there were times it got really bad, and it wasn't Don. It was the combination of the whole environment there.

There also, I don't feel, was a lot of positive mentoring. It was very much, "Okay, great, show me what you've done." But you'd get ragged on for not doing stuff. There wasn't that much

positive mentoring, and I took away that very important lesson that that's something I would never do, like complaining about people behind their backs to other people, stuff like that, which is just very unhealthy. It was very good for me to work there because I took that away as something not to do. It's tempting at times, and I totally understand where it comes from [laughs], but ultimately, it would just get back to everyone because we were all very close.

What I did take away from Don in a very positive way is that he's one of the most enthusiastic people about science. Really enthusiastic. Just getting stuff done and staying really focused on a problem to get it solved—that's really important. I think that actually was the most important thing for me, because I knew I wanted to do certain things. And in fact I think it took me a long time to really get it down to the point where I could do things—the smarts to just do things. What I didn't have—and this is what a lot of people don't have, I think—is the focus to sort of focus on the problem and just get the thing done. I really took that lesson away—just to bear down and really do something. He was great at that. So he was a great adviser for me because I needed the push. I needed to get kicked in the pants to stay focused, to get something done.

I didn't really expect to have the day-to-day kind of mentoring, and the great thing about the lab was that the peers were wonderful. The other students in the postdocs were incredibly talented, and you learned from your peers. That's another way to run a lab, and lots of people do it. Obviously his lab has been very successful running in that mode, so you could learn all the stuff from your peers, and I was certainly not a great student. I would say there were just far better people in the lab. But you could really learn from people. Eventually I sort of learned at that end, but I was very slow. I've always been not a fast learner; I don't pick things up quickly. It takes me awhile to really get it down deeply, and it just took me years to really get it down as it were. But there were other people that were really good in the lab and you could learn from them. So Don was a great adviser for me because he gave me that sort of focus and the push to get it done while I could learn all the technical stuff from other people.

So I ended up, I would say, having a positive experience in the sense that I took those lessons away. I don't think it was great for the soul always, and I was very unhappy with the way a lot of people were treated in the lab generally. A lot of people I think got treated badly and unfairly in the lab, and I'm not happy about that.

I have a lot of problems to this day with the way that ran; I don't think it was necessary. But personally, I think I did pretty well in the lab, I would say. We also, though, have no real relationship. I mean, I've talked to Don about three times in the last seven or eight years. We just didn't have that kind of relationship.

COHEN: How big was the lab?

WEIS: It was very small when I started. When I started there were only six people in Don's lab and six in Steve's. By the time I left the total lab was about twenty-five, and it ballooned beyond

that actually by the time I left, so it became a very different place. When I first started actually, Don was around more, and to some extent I did work closely with him initially, so I don't want to be totally negative about that, of course. I think what I was saying about the way the lab ran is more general, not even necessarily directed at me. I did work with him more closely than a lot of people, actually, because I was one of the only people working on the influenza project at the time, which he was closest to at that time. So relative to other people in the lab, in fact, I did work with him more closely. But still, there were a lot of these negatives that I was very unhappy about there. And frankly, by the time I left, I had actually bought in, I think, to this idea that you have to have this very arrogant attitude to get things done. I had actually bought into that.

It wasn't until I was in my postdoc in Wayne [A.] Hendrickson's lab that I really realized how false that whole notion is and I got the perspective of a very different kind of lab, that you can do really great things and really be focused on a problem without that kind of overlay of this arrogant nonsense. So I definitely came close to getting brainwashed, I would say [laughs], while I was there. But I think I haven't been.

COHEN: You hear—I'm sure they're true because I have heard it from so many different scholars—about these horrendous working hours that people put in during grad school. Were you doing that?

WEIS: Oh, yeah.

COHEN: Fifteen, eighteen hours?

WEIS: Oh, yeah. Sure, we all do it. We still do. I mean, I work long hours now. There are a couple of things that I would comment on about that. One is that I never felt it was oppressive. I mean, it was a labor of love. And part of it was the culture of the lab. I mean, the great thing about the lab was that because it was this very tense environment, we all bonded. I think I'm much closer to the people I was in graduate school with than the people I was in postdoc with because we all sort of bonded, because psychologically the pressure of the lab was such that you had to do that. It was a funny lab. I mean, there was no one there before eleven and we'd all be there till about two in the morning, but we'd go out to dinner together and we'd go out drinking together and stuff like that. We would work very long hours, but it never felt like work at some level to me. It was just part of doing it.

Now, I should also say that there are different kinds of people. In that lab we were all single, we didn't have families, at least the core of us that constituted the bulk of the lab. We all worked like that. Certainly there are people that I've met subsequently, people in my lab now who have families, and they work fewer— You know, no one works forty hours a week; you can't get anything done in forty hours.

They'll work fifty or sixty and they'll get a lot done. They're just much more efficient. See, the thing about all these long lab hours is that yes, people work really hard. And there are crazy times where you just have experiments going, but you get into that. And even when you're not doing experiments, you tend to be hanging around the lab and socializing in the lab, so there's a lot of BS that goes on. So there can be these long hours, but that's partly under your control, and if you have external pressures, like a family, you can just work much more efficiently and get things done and it doesn't ultimately hurt or do anything.

It's kind of an interesting sociology. Different labs just work differently that way. That lab at the time was certainly a very much all-hours, crazy long-hours lab, but I didn't find it oppressive that way. I just kind of expected it. You know, you get into being— You're a lab rat. That's what we all are, you know. [mutual laughter]

COHEN: Next, I was going to ask you to tell me a little bit about the work that you did in Don Wiley's lab?

WEIS: My thesis work or what I actually started doing?

COHEN: Both.

WEIS: Okay. What happened was I started working on influenza hemagglutinin. This is protein on the surface of the flu virus. Flu is a virus that has a membrane and it's got two surface proteins, one of which is called hemagglutinin. This protein is responsible for binding the virus to cells, to its receptors, which turn out to be a sugar called sialic acid. Also, after it's bound, it's taken up by the cells; it's endocytosed by cells. Once it's inside the cell, in this compartment called an endosome, the endosome becomes progressively more acidic. That triggers a change in this protein that causes the viral membrane to fuse with the cell membrane, and the contents of the virus get into the cell. We wanted to look both at the receptor interaction and also the structural change undergone by this protein when it becomes acidic and fuses membranes.

The background of this is that Don and Ian [A.] Wilson, his postdoc at the time, who's now at Scripps [Research Institute], had solved the structure of the hemagglutinin in the state that it exists when the virus is free and you're breathing it. About a year before I joined the lab, they had published that structure. I wanted to then follow up that by looking at both these receptor interactions and also this so-called low Ph, acidic form that fuses membranes.

One of the things I tried to do—I think it was the first project actually— The details aren't important, but I was looking at this low pH form, which when it undergoes this change, aggregates because it exposes a piece of the protein that makes it hydrophobic. It makes it aggregate. That property is what actually is believed to make it go into the host cell's membrane

and fuse them. So you have to make this in detergent; you put it in detergent, mix it up with detergent, lower the pH, and then it will be happy. I was looking at basically finding the right detergent for doing that so we could try to crystallize the whole thing in this low pH state. I didn't get too far in that.

This was right at the time the first membrane protein crystals were solved, because the big problem with crystallizing membrane proteins is that you have to keep them soluble. That means they have to be in detergent because they aggregate otherwise. Harmut Michel and his colleagues had just crystallized the first membrane protein, so we were really excited about trying this. So I tried making this influenza hemagglutinin molecule in low pH and detergent and tried to crystallize it, and that didn't go anywhere.

Then while I was doing that there was another totally unrelated thing I worked on for about six months, which I don't need to discuss. No, I can if you want. It was actually quite an interesting problem. It was called signal recognition particle, which is this large ribonuclease RNA protein complex which is involved in targeting the ribosome to the endoplasmic reticulum membrane for allowing the secreted proteins to be passed through the endoplasmic reticulum membrane. It had just been discovered, and we were going to try to crystallize this whole thing, which was a very ambitious thing. I actually went down to Rockefeller University, where it had been discovered, learned how to take a pancreas out of dogs, make microsome preps from dog pancreas, and purify the protein. I brought [it] back, and we purified quite a bit of it and tried to crystallize it with no success. Then I started to actually work on this, but rapidly realized that the number of dogs we would actually need to make enough quantities just was prohibitive. It was not going to work at that time, so I decided to not work on that.

So what I wound up doing my thesis on after these first two [mutual laughter] failed things was looking at this receptor interaction. As I said, the hemagglutinin in this neutral pH form, as it's on the virus that you breathe in, binds to the sugar on cell surfaces called sialic acid. This is the terminal sugar on most of your cells. In particular, what's relevant in influenza is the respiratory epithelium. It's a respiratory virus: you breathe it in and it attaches to the lining of your respiratory tract through the terminal sugar on the carbohydrates that modify the proteins on these surfaces. That's called sialic acid, and it binds to that.

What we did was we took crystals, soaked them in solutions containing the sugar, and did their X-ray structure. That basically is the receptor virus complex; that's really what you're looking at in a minimal sense. That was really what a lot of the work I did was. There were mutants that we tried to look at. It turns out that different strains are specific for the way that sialic acid is linked to the next sugar on the chain, and we looked at mutants that had alternate linkage specificities as well, by X ray.

By the standards these days, this was something you could do in six months. Then, of course, it was more involved because of the technology; we had to collect our data on photographic film, and it was just more involved. It was actually a very great learning project for me because, of course, learning the basic crystallography— We also used synchrotron radiation a lot; this was the early days of using synchrotron radiation for protein crystallography.

Learning how to do all that was really interesting; I really learned a lot. The project also just required a lot of program modifications, and even though I knew nothing about the program—I was rotten at it when I started—I became a reasonably good programmer and did a lot of coding actually to modify things the way I wanted them to work to do that project.

Also, I had to refine them. I'll only explain this a little bit. When you develop an X-ray structure, you get an image of the electron density; that's what you're actually imaging. You interpret electron density by computer graphics with ball and stick models—the kind of thing that you only see in papers. You can sort of build by hand a rough model, but it's not that accurate. So there's a procedure called refinement where you can basically, mathematically, adjust the model to best match the experimental data. At that time refinement was actually relatively new; for proteins it was only about ten years old at that time. Wayne Hendrickson had really pioneered this, and we had his program. But influenza is such a large molecule, it was really prohibitive. Some initial stabs had been taken at it by another postdoc, but it really wasn't well refined.

So I took on this job, which was a really pretty major computation job at the time. We had to do it on supercomputers; this is when we were doing remote telneting over to supercomputer centers. So I learned a lot about refinement and protein and really got into a lot of the numerical methodology, which is, as I've said, something I really like. So it was a great project because I really got to learn it very deeply, and I really got into a lot of the crystallographic methodology as a result of all this. Even though it was a straightforward crystallographic project as a whole, you always do a lot of programming and I really got into a lot of the methodology. So it was really great fun doing it. I'm sure Don would have liked me to have it done three years before. If I was a faster learner, I'm sure that would have been true, but as I said, I was slow. But I eventually did figure out how to do things and get it done, and the most important work I did really with him was that. That *Nature* paper [Weis, W.I. et al., 1988. Structure of the influenza virus hemagglutinin complexed with its receptor, sialic acid. *Nature* 333:426-31] I had sent to you was the result of that work.

The other thing I did, which was sort of on the side, [was I] got back to this question of the membrane fusion. It turned out that our collaborator in London, John [J.] Skehel, had generated mutants of influenza that would actually fuse their membranes at a higher pH. We thought that would give some insight into the mechanism by which this transition occurs between the mutual and low pH forms in the molecule, so I actually did the structure of one of those mutants as well. It wasn't earth-shattering, but it certainly confirmed our ideas about how the thing would work—you know, knocked out a few salt bridges and made it easier to take apart a low pH so the pH rises; the pH, it just happens, is higher, needs less acid basically. So that was sort of a side thing I had done as well. It came out of that work. So that was graduate school. [laughs]

[END OF TAPE 1, SIDE 2]

COHEN: How long did you actually spend in your graduate work?

WEIS: I was there a little over six years total. So in Don [C. Wiley]'s lab, basically five years.

COHEN: That's pretty average.

WEIS: That's average, yeah.

COHEN: I mean, you make it sound like you're really slow.

WEIS: Well, I think the nature of what was accomplished— No, I guess it wasn't. But certainly I think by Don's standards— I think he would have been happy if things had happened much faster in retrospect, probably, but I just didn't know how to do a lot of things. For me to get things done, I need to really understand them in sort of a very deep way and I just get held up. That's not a good thing necessarily.

I've gotten better about that. I've actually found now that you can get things done, maybe not understand everything totally deeply, and then go back and later on realize— You learn that way too. You don't have to do it in such a rigid, linear way that I think I was doing at that time. That's something I really did take away from that lab, I think. It was very important, actually, because I think that is important. You have to make these judgments about when you should just leap ahead, and then sort of go back and look retrospectively, because it is just so easy to get bogged down.

COHEN: Well, here you are now, you're graduating from your doctoral program, and now you have to figure out—

WEIS: What to do. Well, as you saw from my CV, I did two postdocs. This is a little complicated. What happened was, because I had spent a lot of time working on this refinement stuff, I really got interested in it as a problem and I always had had this interest. As I mentioned, I worked with Martin Karplus a little bit in some of the computational stuff. What happened was that I met Wayne [A.] Hendrickson through— John Kuriyan is a very close friend of mine. He's a crystallographer at Rockefeller [University]. We were in grad school together, and John spent his whole thesis with Karplus in collaboration with Gregory [A.] Petsko, who was at that time at MIT [Massachusetts Institute of Technology] doing refinement methodology. So I would hang around with them a lot and I knew what was going on. Wayne actually came up from New York for John's thesis, because they had been in touch, and I met Wayne. Wayne was the person who kind of really invented refinement. I met him and we really hit it off, and I thought it would be a

really interesting lab to work in, because he was starting to develop this anomalous scattering methodology for solving the phase problem, which I'll come back to later. So I chatted with Wayne a little bit, and I decided that that would be a place I could really imagine doing a postdoc.

What happened was, also, when I looked around—and partly this was this kind of partial brainwashing that, you know, "there's no one else doing anything interesting"—really, the only two people in the end I really was interested in doing a postdoc with was Wayne and Dave [David B.] McKay, who's actually my colleague next door here, ironically enough, who at that time was at [University of Colorado,] Boulder, because he had done some really interesting structures in the mid eighties. So I went out to Dave's lab to interview with him and then I settled on Wayne's lab. I had actually done all of this while I was still in Don's lab.

But what happened was that I really wanted to do this refinement stuff. I wasn't real happy with a lot of the methodology we were using, and because of my contacts with the Karplus group, I had met Axel [T.] Brünger, who was at that time a postdoc with Martin Karplus. He and John Kuriyan shared an office, so I knew him kind of through John. John and Axel had developed this so-called simulated annealing refinement.

Let me take a few steps back. This problem of refinement is a multidimensional squares problem; it's a non-linearly squares problem. What that means is that you have a model that describes your data, and the idea is that you adjust the parameters of the model to best fit the experimental data. So you ultimately adjust the parameters of the model to best match the experimental observations. And that is not a well-determined problem in the sense that, in the case of a protein molecule, you can't just run this program and get the absolute best match of the data in the global sense. So you go into what's called the local minimum; you're minimizing the discrepancy between the model and the observation and you can just locally find the minimum discrepancy. That's a fundamental problem that affects many, many fields of this class of problem, not only in protein crystallography.

So in the early eighties a group at, I think, IBM [International Business Machines], based on some statistical mechanics analogies, had developed a thing called simulated annealing. Basically the analogy is that you take a glass, and if you just— No, sorry, let me stop there; that's not a good analogy for this. The basic idea is that if you take a system and you just minimize it, it would be like taking a liquid and then cooling it down and you get a glass. But the really lowest energy state would be a crystal, for example; everything's really well ordered or can be. So what do you do in practice, experimentally? Well, you would take that, you would anneal it, you'd heat it up, then let it cool down slowly and try to find something that would be more ordered.

Mathematically you can do the same thing by essentially imparting heat or energy into it—kinetic energy—heating up the system and letting it relax. What happens, if you think about a molecule now with balls and springs, is that if you just minimize your model, you're letting it relax to the nearest minimum and it's not going to drift very far because everything's tied together with springs. If you impart kinetic energy to it, the springs are moving all around and

it's going to search more of its kind of conformational space. Then you slowly cool it down and you may find a better minimum [that] more closely matches the data. That's called simulated annealing, the mathematical procedure.

Axel and John had applied this using what's called molecular dynamics simulations to the refinement problem, and I thought this would be a fantastic thing to do with this large problem of hemagglutinin we were working on. Axel and I had chatted about doing it when we were both still at Harvard [University]. I was writing my thesis then, he was moving to Yale [University]; we didn't have time.

So I decided to spend a year, the first postdoc, with him and work on this there. So I went down there for a year to work on this methodology, knowing I was going to Wayne's lab afterwards. What we did is we worked out the methodology, and we had to add some new things. It turns out there's something called non-crystallographic symmetry in this problem. In many problems where you have the same copy within the repeating unit of the crystal—so-called asymmetric unit of the crystal—you can have multiple copies of a molecule. Hemagglutinin is a trimer—there are three copies of it in the asymmetric unit—and you can use the fact that they all look identical as a restraint in this procedure. We had to build that into the program. So I spent time writing code to do that with him. We did that and it was very successful; we got a much better model of hemagglutinin out of it as a result. So that's what I spent the year at Yale doing.

I also started to work on some other methodology, which was later picked up by another postdoc of Axel's, in solvent corrections in refinement. I worked on that as well with him. So it was really sort of an extension of my thesis more than anything, but I really wanted to do this. So I spent a year there at Yale, writing code, working on the refinement. That's what the *JMB* [*Journal of Molecular Biology]* paper I sent you was [Weis, W.I. et al., 1990. Refinement of the influenza virus hemagglutinin by simulated annealing. *Journal of Molecular Biology* 212:737-61.]. Then I moved to Wayne's lab, basically a year—

COHEN: Which is at Columbia [University]?

WEIS: At Columbia Medical School, right. I was there for four years, which was fantastic. That was probably the best time of my life.

COHEN: Oh, really?

WEIS: Yeah, I was back in New York, which I had missed, and Wayne I just love. He's just great. The whole experience was fantastic.

I went there to— Well, there were two things. One is that all this anomalous scattering

methodology was being developed, and I had an opportunity to actually be very involved with it in the early days. I actually wrote some programs to sort of extend the methodology a bit. And I worked on this problem with Kurt Drickamer, our then collaborator, who's still my collaborator to this day.

What happened there was really that Kurt had come up to Harvard to give a seminar. Kurt works on what are called C-type lectins, these calcium-dependent lectins. I was working on carbohydrate recognition with Don at the time, and I met Kurt. We were chatting, and he was working on this family of proteins which included a very interesting receptor called the asialoglycoprotein receptor, which is found on the liver. It removes circulating glycoproteins from the blood. Kurt really wanted to do structures of these things; it was an unknown structure. He really wanted to get information about mechanism and this was a perfect match for my interests, carbohydrate recognition, self-cell recognition, which I'd really gotten interested in with Don. He wanted to do this, and he was just down the hall; it was a great situation to walk into. So I was in Wayne's lab collaborating with Kurt on those molecules.

Kurt had actually worked out an expression system for this molecule, another member of the family called mannose-binding protein. That protein is actually found in our serum, and it's involved in recognizing pathogenic cell surfaces. It recognizes sugar structures on the surfaces that we don't have, and it's a way of distinguishing pathogens from our own cells through carbohydrates rather than through an antibody response. Ultimately it triggers cell killing by mechanisms similar to how antibodies trigger cell killing, so it's a host defense protein. Kurt had figured out how to make the business end of this molecule, namely, the part that recognizes sugars, and we had a bacterial expression system. I spent a year trying to follow up with some bad crystals that another postdoc had grown unsuccessfully—you know, it didn't work out. Then we figured out we had to modify the protein. We did that and got great crystals and started working on it.

What happened there was that these proteins require calcium for their function, and we knew that. When you're doing a new protein structure, what you have to do is introduce heavy atoms into the protein to perturb the diffraction. If you can measurably perturb the diffraction with one of these heavy atoms, it turns out; if you can compare the diffraction of the perturbed and native crystals, you can extract the phase information you need to reconstruct an image of the protein. So you need to have these heavy atoms in there. So the obvious thing, if you have a calcium on your protein, is you put in something to substitute for the calcium that's heavier, which are called lanthanide ions. We put in lanthonides, and it turned out that— So that's a bit of the background for this.

Wayne—[this is] one of the reasons I'd gone to his lab—was starting to develop this method called multiwavelength anomalous scattering phasing or dispersion phasing or MAD phasing. What this method does is— I just described that what you have to do to solve a structure normally is add a heavy atom and perturb the diffraction compared to the native. Well, there's a phenomenon that you can measure from heavy atoms called anomalous scattering, which is a wavelength dependent phenomenon where, when you're near the absorption transitions in the particular element—so-called absorption edge—you absorb energy of a

particular wavelength. It kicks an electron out of its inner orbital and then it relaxes back. So it absorbs the energy. That absorption actually has an effect on the measurable diffraction because, basically, normal X-ray scattering that we sort of would deal with, ignoring this effect, treats the electrons as though they're not even in orbitals, as though they're free electrons. So this is really a quantum effect of being bound in orbitals and kicking them out.

It turns out that that phenomenon is measurable. And it turns out that if you can measure this as a function of energy, or as a function of wavelength—same thing; energy and wavelength are the same—you can actually extract phase information from those differences. If you measured it one wavelength versus another, the difference in this anomalous scattering effect can give you the same kind of phase information that you would get from taking two crystals, one with and one without a heavy atom. The beauty of this is that you just need one crystal form. You just look at it as a function of energy.

This technology became available because of the synchrotron radiation, because when we make X rays at home, there's only one wavelength available. You make copper radiation. At a synchrotron it's tunable. And Wayne basically was— Well, actually, I should give credit where credit is due. The first person who realized this and published a paper on it was Keith [O.] Hodgson, who's in our chemistry department, who's now the director of the [Stanford] Synchrotron [Radiation] Lab[oratory]. Jerome Carl also had published some stuff, and Wayne also had done this.

So three different groups had sort of picked up on all this stuff, but Wayne was really the one who really pushed it and said, "I'm going to make this practical." This involves instrumentation, because you have to make tunable optics at synchrotrons, which is not trivial. Wayne developed a whole slew of programs to do this; he really pushed this into a practical method. So I was there when all of this was being developed, and we really wanted to do it.

So we substituted lanthanide ions. It turns out that they are incredibly strong anomalous scatterers, so it was a great problem, and we went off to France and did this experiment. We collaborated with a group in Paris—they had the optics to do it—and we did this and it was very successful, although we had a problem with the experiment: we didn't control the wavelength well. It was very hard to control the wavelength exactly. We actually had to write a refinement procedure to refine these anomalous scattering effects out of the data. It was kind of a real messy problem, but we did it. That was sort of my main methodological contribution, this refinement procedure. We wrote the code to make it more generally applicable. In fact, that idea is sort of used by everyone. We got a beautiful electron density map out of it and solved the structure from that, and that was actually the *Science* paper that I sent you [Weis, W.I. et al., 1991. Structure of the calcium-dependent lectin domain from a rat mannose-binding protein determined by MAD phasing. *Science* 254:1608-15]. So that was sort of the most important thing I had done.

Then what happened was, in fact, the crystals I originally grew were actually a co-crystal with calcium, with a big oligosaccharide that crosses the crystal together. Now, very quickly, we collected data on that and then solved the structure of the co-crystal so we could see how these

interacted directly with sugars. That was the *Nature* paper I sent to you from Wayne's lab [Weis, W.I. et al., 1992. Structure of a C-type mannose-binding protein complexed with an oligosaccharide. *Nature* 360:127-34]. That was the other major bit of work. That was the first structure done of that whole family.

Then we got the first information about how these actually interact with their ligands. That then has spurred Kurt and our lab to continue looking— We've been able to use that as a basis for engineering other specificities into that protein. We've done a lot of protein engineering to basically create new specificities to understand how the whole family recognizes its ligands. That's ongoing work now in our lab to this day.

Basically what happened is, Wayne was very generous. Kurt and I wanted to continue this collaboration, and Wayne let me take the project with me, which was actually very important for me to get my lab going. It was very important actually. And to this day, Kurt and I are still collaborating on this work.

COHEN: It was also very generous of him.

WEIS: Yes. Well, he had a lot of things going in his lab, and I think he realized Kurt wanted to continue with me anyway. Wayne just said, "Listen, this is fine." He agreed to it. I could've understood if he didn't want to, but he did and it was really great.

We have a really good relationship and I had a great time there. I consider him a really good friend. It was nice.

COHEN: We talked a little bit about Wiley's lab. What was the sort of milieu of that lab?

WEIS: Totally different. It was totally different. Wayne is very self-confident in his ability to solve any problem and didn't feel the need to have many people on one project or anything like that. Everyone had their own project, and what linked the lab was really the methodology that was being developed. It was a very interesting place from the crystallographic methodology point of view. Wayne just would, at that time, work very closely with everyone on their particular problems. He really left you alone, but when you wanted help and advice, he was there. And he was always really constructive. He would just have really clear thinking about everything. So he was a great mentor for postdocs, because you're already kind of pretty independent, and you could just really talk at a pretty high level with him and just kind of do things.

I don't think he was— Some of the students really floundered in his lab—the ones who needed more mentorship—because Wayne is just very kind of hands-off. I don't mean that in a bad way. He just was very busy at the time. He was involved in way too many things; even he

acknowledges that. So some of the students really were a little bit lost, because the downside of not having people working in related projects is that they don't really have direct peers to interact with and get help from. We would all try to help everyone else out, of course, but it isn't quite the same. And Wayne just wasn't around that much. He was gone a lot, traveling; he was involved in a lot of different activities. So some of the students really floundered.

The ones who did well though were fantastic. There were a couple of really terrific students there who did really well. [For] the postdocs, it was the same kind of thing. But for me it was great. I didn't need much day-to-day guidance, but to have someone who really, really knew crystallography at an incredibly deep level— Yeah, I just learned so much from the guy. It was just great being able to talk to him. Of course, I had the advantage of having Kurt down the hall. So on the sort of biological end of the project, I had Kurt; we would talk and we got along really well. It was just an ideal situation. It was really, really a happy situation for me.

You know, Wayne is very kind of calm, and he doesn't keep a high-pressure environment in the lab at all, probably not high pressure enough [laughs] for some people, I guess. I mean, as I said, some people can drift, but it was just a really nice environment and he's just a really nice guy and very constructive. It was just a very, very different environment from my graduate level. It was good. I think there were a lot of ups to that; there were some downs. I think having a little more cohesion on some of the projects that are going on— Also, I think people did have a tendency to drift a little bit in the lab. So again, I think from both labs, I took away positive and negative mentorship, and I think having those kind of very orthogonal lab experiences was very good, because I took away good and bad things from both labs. But on the whole, I just really loved Wayne's lab. I mean, it was just a great, great time. It was a great time.

COHEN: How was your social life doing at this point?

WEIS: It was fairly disastrous in graduate school. At Columbia it was good. I mean, I always had girlfriends there. I'm still not married in fact; I have a girlfriend here. But no, it was fine. You know, I worked very hard, [so] it was people at work that I knew at Columbia, that kind of thing. But basically, it was fine. Yeah, I just overall had a very pretty nice—

COHEN: Good time in your life.

WEIS: I mean, there was a very rocky— The last year I left was terrible because—well, no, two years before, I guess—I'd broken up with someone and that was very hard. I was very miserable, and it definitely affected my work and my interactions with people in the lab. I was very kind of withdrawn for a while. Very, very unhappy. And I had the additional stress of that's when I was looking for a job. So a lot of stuff was going on then. That was a bad period definitely. But aside from that, it was fine. I look back very fondly on my four years there. I really do.

[END OF TAPE 2, SIDE 1]

[END OF INTERVIEW]

INTERVIEWEE: **William Weis**

INTERVIEWER: **Helene L. Cohen**

LOCATION: **Stanford University**

DATE: **8 February 2000**

COHEN: I was reviewing the tapes yesterday and one thing popped out to me and I wanted to go back to it. You said you spent some time in Paris?

WEIS: Oh, that was just part of when we did that experiment in Wayne [A. Hendrickson]'s lab. At the time there were very few synchrotrons in the world that could do this tunable wavelength experiment, and the particular characteristics of that synchrotron and the particular beam line there allowed us to do it. That's why we went there; it wasn't anything beyond that. It's at the University of Paris, actually, right outside of Paris. I spent a month working there, and I got into Paris, I think, twice the entire time. [laughs]

COHEN: Oh, no!

WEIS: As I said, working on a synchrotron will take the romance out of Paris. [laughs]

COHEN: Oh, that's too bad.

WEIS: Yeah, I'd been there before and I love the place, but that was definitely a working trip. It wasn't too romantic.

COHEN: I think yesterday we finished talking about your postdoc pretty much, so let's move on and you can tell me the circumstances around you ending up at Stanford [University]?

WEIS: Well, let's see. As I said, I really loved working in New York, and I wasn't actually, at the time, even thinking about looking for a job. What happened was that I had been there—I have to think about the dates for a minute—I guess, for just about two years, and my friend, John Kuriyan at the Rockefeller [University], had gotten one of these "Dear Colleague" letters soliciting jobs at UCSF [University of California, San Francisco]. John knew I liked the Bay Area, and it was a good job.

So he said, "You really should apply for it."

I said, "Well, I'm not sure I'm really ready. I'm not thinking about it yet." He said, "Just do it, because this is—"

I thought about it and said, "Well, this is a great opportunity. How often do jobs at places like that come up?"

Of course, once you commit to doing something like that you actually have to be kind of serious. [laughs] So what happened was that I was really lucky, basically. It turned out that UCSF was advertising, and it turned out that this department at Stanford, which was called cell biology then— The biophysics department at Johns Hopkins [School of Medicine] also was looking for someone, and it turned out [University of California,] Berkeley was conducting a search too. So three schools in the Bay Area were looking.

Now, the Berkeley one had actually closed, but I made some inquiries and it turned out that they said, "Oh, come out. We'd like to see you." So I went to Hopkins and interviewed and came out to the three schools here and interviewed at all of them. Then I also got contacted—I think once these things start happening, people talk—by Ian [A.] Wilson at Scripps [Research Institute], and I went out there and interviewed. Then [Memorial] Sloan-Kettering [Cancer Center] came up—same kind of thing. I was contacted by them. I think that's the total list of six places.

If you think about it, that's incredibly lucky, because these are six really good places. You know, I wasn't even looking seriously, so I didn't feel any pressure. So it was almost the ideal circumstance. I really had it easy in other words. I didn't have to apply to a hundred places, and I figured, "These are all really competitive. If I don't get them, I'll do it seriously next year or whenever I'm ready."

And the timing was great because I actually hadn't published, at that time, anything. Although the work was done, we were writing it up, so it was all new and fresh and no one had heard about it. So it was just absolute fantastically fortuitous timing to present this work; it was all very new and it was a lot of new methodology as well as the new structure. So I got offers at, actually, all of them except Berkeley and UCSF, and I wound up coming here. So it was kind of very lucky and not stressful. You know, I had one of the luckiest times in terms of looking for a job because it just fell out that way.

The really agonizing thing came after I had these offers, which was that I really wasn't sure I wanted to leave New York for various reasons. I really agonized very hard about going to Sloan-Kettering. It was a very different opportunity because there, I would have been the first structural biologist—or first crystallographer, I should say. They had recruited an NMR [nuclear magnetic resonance] person from Columbia [University] already, and I would have been faced with basically designing and setting up a whole lab from scratch, which I wasn't really averse to doing, but it was not something I particularly wanted to do. You know, some people really want

to be the first and have it all under their power. I just wasn't that keen to do it one way or the other. Here, Dave [David B.] McKay was already here and there was a functional X-ray lab and I could add to it. I sort of really agonized over it for about five months and drove both places crazy, I'm sure. [mutual laughter] But in the end I obviously decided to come here, which I certainly don't regret. In retrospect, it was really the right thing to do.

COHEN: How did you know you liked the Bay Area? Had you been out here?

WEIS: Yeah, I had been out here. My best friend from college [Mark Moore] had moved up from Southern California to Genentech about a year before all this happened. So he was out here and I would visit and I had a lot of friends, it turned out, doing postdocs at UCSF and Stanford. So I knew the general area, and I knew I liked it.

COHEN: That's great, wow.

WEIS: Yeah, it was lucky. The other thing is that I knew I really wanted to stay in one of those two areas, particularly—at a minimum, on one of the two coasts. I really didn't want to live off of one of the two coasts. That played into it also. So as I said, when all these opportunities came up, it would have been stupid for me not to— Although I can imagine myself being that stupid without friends kind of kicking me. [mutual laughter] But that's really what happened.

COHEN: Well, what a nice place to wind up.

WEIS: Oh, yeah. As I said, it's been really good on the whole. I mean, all these things have ups and downs with starting out on a faculty, of course, but I have no complaints.

COHEN: Sure, sure. You also said yesterday that the postdoc was really like the best years of your life.

WEIS: Oh, yeah, no doubt about it.

COHEN: I've actually heard that from a few people, although not everybody realizes it while they're going through it. But I've heard a number of the scholars say that you go from that, which is the very best time of your life, to being junior faculty, which is absolutely the worst time of your life. Was that your experience?

WEIS: I guess enough of my friends had gone through it, so I had some idea [about] what to expect. But there are things that I think different people react to differently.

Our department when I came here was really in bad shape, it turned out. People were actually surprised I stayed as long as I did, because a couple of senior faculty left the department in the year between when I accepted the job and when I came here. The department was pretty much in financial deep straits and bordering on dysfunction. But I actually felt it was an advantage, because our department just didn't have the kind of nonsensical responsibilities that most departments dump on their junior faculty. We teach medical histology, which is a funny thing for us to be teaching, but we do. But I only do three lectures a year and they eased me into that one lecture a year. And Dave and I have taught a graduate course in crystallography every couple of years, but I didn't have to do that for the first two years. So I had very few teaching responsibilities. We have very few students, so I had none of the sort of committee-type responsibilities, although I actually was our department representative for the admissions. But it's not a big chore. So I just didn't have a lot of the kind of stuff—student oral exams and the like—that are a drag on your time.

Of course, the other big thing junior faculty run into is having to do grants. I was very lucky because, as I said yesterday, I was able to take this project with me, which was kind of something I knew was going to work. And of course, with the conservatism of the NIH [National Institutes of Health], I knew it would probably be a fundable project, because it was something that we already had proven could work. We were going to do the next things, which were really interesting and exciting projects, but also conservative in the sense that there was a pretty good chance that they were going to work. So I wasn't ultimately that worried about getting it funded.

So I wrote an NIH grant when I came here, and I got it funded. That was a bit of work because that was the absolute nadir of funding at the NIH. It was '92, '93—this was a really bottom time—but I got a really high score and it got funded. And I had a very generous start-up here as well to start up new projects, so I never really had the kind of money problems— Yeah, I worried about it until— It takes a year to actually see the money when you write a grant, but that came through relatively quickly. So after a year I was set.

The other thing, which of course no one is prepared for—and nothing prepares you for it—is the personnel management. That's by and large worked out pretty well. I think I run a lab in a very kind of informal way. I just kind of go around and talk to people; I don't have a very formal structure to it. We just interact and it's fine. And I've had, with one major exception, just great people.

So a lot of the things that wind up being a drag on junior faculty I was able to avoid to a large extent actually. I think part of it really was the situation of the department. It actually wound up working in my favor. And Dave McKay, my colleague, was really great in terms of helping me set up and being very supportive and helping with some resources in the beginning. In the end it was a pretty easy situation for me.

Nonetheless, I think what has happened over the years— The reason I still maintain that the postdoc was the best time in my life is that it's really the only time when you have no responsibility aside from doing research. You don't have money worries. You don't have worries about writing a thesis or being a TA [teaching assistant]. From that point of view, you just totally focus with no other distractions.

The thing I know I don't have is good time management skills. You know, I can't work on five things a day, and I really need to focus. That's what I found very frustrating. And I've sort of had to come to accept it. I've just had to sacrifice certain things: I don't do benchwork anymore. Fortunately, because the nature of our work with structural biology is a lot of computation and instrumentation work, I can still do that. I go to the synchrotron at the lab; I can collect data and get out of my office, and that's great. But I have had to sacrifice a certain amount of the wet biochemistry, which takes ten- or twelve-hour blocks of time. I don't have that. But I've just come to accept that, and it's not that big a deal because I'm still very much involved with the projects in a hands-on way.

COHEN: Well, you had said yesterday that you weren't that crazy about the benchwork anyway.

WEIS: No, I actually like it. I just found it boring full-time. That's not what I said. What I meant was that it really was a case where I couldn't imagine doing it— Because it does get very repetitive. But doing it along with— What I like in crystallography, in fact, is that you don't do anything all the time; you do some computations, some interpretation, some benchwork. I think that's why I like it so much, because doing any one of those would definitely bore me. The fact that it's broken up this way is one of the real attractions of it. But no, it's true, I really would like to be able to participate more actively in the wet bench stuff to some extent. I'm realistic; I can't do that. That's something I've just had to sacrifice.

That gets into having a big or a small lab. I've always wanted to keep a very hands-on lab, and it's grown slowly but steadily. I'm now at ten. I'm not sure I want it to get any bigger, because I think there is a point you cross over to being a full-time manager, and I don't want to do that. And I know I'm stretched too thin right now, but I'm so interested in the projects we're doing, I also need to keep enough personnel on them to keep them going. The problem is you need critical mass: if one person leaves or doesn't work out, the whole thing falls apart. So it's a hard balance, and I've never been comfortable with it, the balance. I don't know what the right thing is, so I just kind of oscillate. This size seems to be manageable right now. I'm still enjoying it.

COHEN: Well, I want to talk about your lab a little bit, but I just have a quick question before that. Are you on the medical school faculty or the—?

WEIS: Yes, this is the medical school. In fact, when I looked for jobs, with the exception of Berkeley, I only applied to medical schools. It was simple: I don't actually mind teaching, but I also don't want to do a half-assed job of it. I know to do that takes some real time and commitment, and I didn't want to do that because I wanted to basically stay as a hands-on person. I knew it would be very frustrating. Ph.D.'s in medical school tend to do much less teaching. The quid pro quo is that we raise much more salary from our grants and we don't get a nine-month salary. I was willing to accept that; I'd rather do the research and have to raise more of my salary from grants. That's just a choice everyone has to make, but I knew I wanted that.

COHEN: Okay, I'm trying to decide which direction to go in. Actually, before we talk about your lab, let's talk about these PI [principal investigator] responsibilities which you mentioned briefly. I want to go into each one in a little more detail. Since we're talking about teaching, let's talk about that first. Actually, I don't know if you ever got a chance to look at the materials from the Pew [Scholars in the Biomedical Sciences] that are about you, like your letters of recommendation, but I did.

WEIS: No, I'm assuming their confidential. I wouldn't have even thought to ask.

COHEN: Anyway, they're all very complimentary. But one of the things—or maybe this was on your résumé, I'm not sure—is that you got a certificate of distinction in teaching when you were a graduate student.

WEIS: Oh, yeah, I think when I was a graduate student, just for when I TA'd undergraduate biochemistry. It was just a thing— If the students give you good recommendations, you get a little certificate from the school. It wasn't any big thing.

COHEN: But a couple of the people that wrote about you said they thought you would be a good teacher. So tell me a little bit— You said you only teach three lectures a year in the—?

WEIS: For our medical course, I teach graduate [students]. I've actually taken on much more teaching since I started, of course. My teaching falls into a couple of different things. Our department collectively teaches first-year medical histology, which is kind of a funny historical burden of the department; none of us are ultimately qualified to really be teaching it. [mutual laughter] No, I shouldn't say— It's very basic cell biology. We try to relate tissue structure down to molecules, and it's very much a basic science course. Pat [Patricia C.] Cross, who's a professor of teaching in our department, actually runs the course. She's wonderful. Without her, it would fall apart, I can tell you that. She makes it very easy for us. There are good medical TAs. Basically the format is we lecture for an hour, and then there are two hours of lab after

that. She and the TA's run the lab; they take care of the exams. All we really have to do is lecture.

And I actually have really enjoyed it. The reason is that—it's funny—I've learned new things. See, I think the best thing about teaching is that you learn. So I came in and they said, "Okay, you're teaching the ear." I know nothing about the ear. [mutual laughter] But I learned it, and it's incredibly interesting. It really is.

Then I teach the skin and the eye. It turns out the skin has turned out to be unbelievably useful because most of my lab works on cell adhesion and it's just directly relevant to things we do. Now I can pick up journals and look at histological sections and see what's going on. So actually, that one has turned out to be incredibly practical and I really enjoy that one for that reason. Then we're doing some stuff related to some stuff, very indirectly, in the eye with some receptors. Of course, I worked on rhodopsin and eye work as an undergrad, so I had some familiarity with part of it.

It turns out with the ear and the eye, both of them, we teach tissue structure and how the eye functions as an optical element or the ear functions to transduce sound waves. So there's some very basic physics, which of course, doing the kind of thing we do, I can kind of explicate—you know, remind kids of their freshman physics, which they all hate of course. [mutual laughter]

But actually, I really do enjoy doing those lectures because they are just absolutely fascinating. They're incredibly painful to get together the first time—it's two and a half, three weeks of solid work—but I do it seriously. But that's the point. I mean, I actually enjoy doing it, but the time commitment is such that I think with all the other pressures, I wouldn't want to do a lot of it. But as I said, I actually do enjoy doing those—

Then Dave and I have taught, every other year, a course in crystallography, diffraction methods, which is kind of bread-and-butter stuff. I've found it useful, because to actually have to explain to people who don't really know it—stuff that you don't even think about anymore— It's a very useful thing to have to articulate stuff, even stuff you think you know. You realize you don't know it at a level you can truly articulate it in a simple way. It's a real challenge, and I think it's very, actually, good for your own understanding. I found that when I taught as a graduate student too. I taught physical chemistry for two years—I TA'd that—and actually having to explain thermodynamics to people who can't do math, say, is very good. So in that sense, it's very helpful.

What's happened more recently is that there's a movement among many of us in the basic sciences—this is over many departments—to revamp the graduate curriculum. We're trying to settle on the areas that all graduate students should know regardless of their particular discipline. Part of that is structural biology and very basic physical biochemistry. So I, with Dave, Jodie [Joseph] Puglisi in my department, and Dan [Daniel] Herschlag in biochemistry, put a new course together which combines elements of the course Dave and I taught on protein structure with enzymology and kinetics that Dan Herschlag taught, and [subjects] Rick [Richard W.]

Aldrich and Rich [Richard S.] Lewis from another department, MCP [Molecular and Cellular Physiology], have been lecturing on—diffusion and cooperativity and the like, things they're really expert at. We did it for the first time last year and we got a really good response, and we're trying to integrate this into a kind of core curriculum.

So I've wound up taking on a lot of teaching to do that. Then when Jodie Puglisi arrived in our department, we reorganized this methods course, and we're now teaching this every other year—this biophysical methods, which is basically crystallography and NMR. So I've been fairly involved, certainly relative to most of my colleagues in the department, in a fair amount of teaching partly because I just believe we should be doing a certain amount. You know, we are professors. [laughs]

COHEN: It is after all a teaching institution.

WEIS: Right. As I said, I just think the reality is that the time pressures that are brought to bear on you are such— I think people really do have true sympathy for the junior faculty, not here necessarily, but just generally in arts and sciences places. We all know this. The junior faculty come and they get dumped teaching these very low-level undergraduate courses with a huge number of students, and the time commitment is immense. And it strikes me that more established senior colleagues really should be taking on more of a responsibility, because we have so many other— You know, junior faculty have a lot of headaches getting used to the whole idea of running a lab, doing grants, personnel management, that I think to get that additional burden dumped on them—I'm sure you've probably heard this from other colleagues—I think, is really kind of unfair. Just because that's the way it was in the past when the senior people were doing it— It would be nice to break that cycle. I'm not complaining, because personally I've been satisfied with the responsibilities that I've had for teaching. But I do think that's an issue. I know people talk about this at other universities, and I think it's a legitimate issue and should be addressed.

COHEN: Now, in the course that you've taught—the histology—a few years in a row now—

WEIS: Seven, six.

COHEN: —is there much prep time for that anymore, or that's pretty much in the can?

WEIS: Yeah, they're relatively canned lectures. But what I do to keep it, actually, more interesting for me and for some students is I do keep up with things. Particularly with the skin, it's easy because I actually do read the literature and if there are really new interesting things—

What's happened, particularly in the ear, is there's been this explosion the last two years of finding genes that control hereditary deafness, which is of real interest to the students because it's clinically relevant and it turns out to illuminate a lot of the mechanisms we talk about. So I do actually keep up with that, and it keeps it interesting for me. It definitely does. It's starting to get a bit stale, I have to admit. I'll look forward to a sabbatical year, you know. But basically I do enjoy it.

COHEN: Well, a lot of people say that students have changed. That's a sure sign that you're getting old—

WEIS: Yeah, that's right. [mutual laughter]

COHEN: —when you say that. But what is your experience with the students? This is a very high-powered university, so—

WEIS: The students here I've been very impressed with. I'd say, on average, I don't actually see that much of a change to be honest. I think there's always wishful, wishy thinking about the past.

What I do find is that in our area, there are fewer— When I went into structural biology, it wasn't a very sexy thing to do, and people who went into it, a lot of them, were really from very hard-core physical backgrounds. As it's become a more sexy biological area, you have people coming into it now who don't have the quantitative backgrounds that we used to. They have a better biological background, and because the methodology's improved to the point where you don't need that, they can do very successful work in it. So in our little narrow area, I see that our students coming in don't have the strongest backgrounds anymore, quantitatively.

But I think part of it is also, just, times have changed. When I was in grad school, DNA sequencing was four or five years old. It was a big deal. A thesis would be to clone a gene. The fact is things have progressed, and you can do all this stuff with kits. You can say, "Well, it's really a shame that students don't understand how the kits work." I'm not defending that; I think everyone should. But there are just new frontiers and new problems, new methodologies that come up, and the fact that that stuff is now old hat—who cares? I actually don't have a problem with it, and if that's the level of objection, I don't know.

Now, a fairer question is, "Well, how many people are really the sort of supercreative types, and are you seeing fewer of those?" I'm not so sure. I think there always will be and always has been this sort of absolute upper tier of outstanding students that come along, if you're lucky, once in a class or once in every two classes. Everyone else is going to be really solid and do good work. I'm not so sure the average has changed, to be honest. Maybe I'm just not old enough to have the perspective, but I'm just not so sure.

I think what has changed, in part, is the culture a little bit in that our field—actually, [this] was one of the major attractions of it to me, frankly—wasn't very competitive when I started it. There were very few people doing it. It was hard, and you could stake out, "I have crystals or something." You stake out, and it would take five years to do structure. Now it's supercompetitive. It's gotten as bad as molecular biology. We've gotten beaten on a few projects; it's supercompetitive. You know, we've solved structures in as fast as a week, in good cases. Generally that doesn't happen, but it's happened. It's also taken us four or five years in some—

I think that level of competition has changed, and it attracts a different kind of person. My friend who used to be at Genentech [Mark Moore] actually said, "I could never do what you are doing because I have to have feedback. Every ten days I need to have a success from cloning. I need to see that sort of intermediate, tangible progress." And we don't have that. You get one thing at the end of the day: do you have a structure or not? And when I started in it, that was four or five years down the road and you just had to have the faith that you were going to do it. It's a different kind of personality. And I think in my little area, you have a much more typical kind of short-term gratification-type personality than you might have had when I was in grad school.

But going back to the more general question "Are students generally in the biomedical sciences different?"— Maybe the only other thing that's changed is that because the options, I suppose, are greater, it's now maybe somewhat more like chemistry. Not everyone is intending to go into academics and do supercreative work. They want to go into industry and maybe have a more structured nine-to-five-type thing, although not all biotech[nology] is certainly like that. A lot of it's much more like academia. But I think there are more options. Maybe it's attracting more students who are more interested in a more basic kind of "I want to be technically trained and do a career in this but not be an academic and do any of that kind of cutting edge—" So maybe that kind of student in the latter category has gotten diluted a little bit. I suppose that may have happened, because I think the general pool of students, numerically, has probably expanded.

And I think there was a time when times were really tough. I think it still has the reputation of being really tough, that it's a hard row to hoe. I mean, grants are supercompetitive, and there's no question a lot of the best students still go into medicine or law. Really bright people are doing those things, and all of us at some level probably bemoan that "are we always getting, potentially, the best students?" But of course a lot of success in science is, as I've said, mind-set; it's not raw talent. So I don't know. I'm not so sure it's changed that much. Maybe the pool has gotten a little diluted.

And there are more good places. So maybe when you talk to people at really good places, they're competing for students against many more places and there are just more options. In any one institution, it could be that the pool of the best students has gotten diluted that way because there are just more options now than there were ten or fifteen years ago in terms of quote, "elite institutions."

COHEN: One of the things that I've heard a lot of people say, and I know it was my experience teaching, is that the students argue about grades and things—things that I never would have thought of doing when I was a student. Does that happen here or are they more—?

WEIS: Well, I'm really insulated from that because I don't teach undergraduates and we don't deal with medical students. I think, in fact, our course is probably pass/fail. I don't even know; Pat takes care of all of that. But certainly at the graduate level, none of those students care. The school requires they carry a B or B plus average, so they will care if they're flunking. But [otherwise] they couldn't care less. I tell them, "Look, I've never been asked for my graduate school transcript." I don't even know where my diploma is. [mutual laughter] That's not what matters at this level, and I think students do know that.

Frankly I doubt it's changed with undergraduates, despite what everyone says. Because I think what happens is that when we were students, we probably cared less about grades, and then people who are teaching undergraduates, who never cared about grades, now are facing these undergrads who do care about grades for medical school and saying, "Oh, it's terrible. It wasn't like this when I was a student." But I bet it was. Only it was their peers doing it, and they just didn't care; they didn't know. Because when I was a biochemistry major in college, most of them were going to medical school and of course they were worried about their grades. I know that. I don't think it was any different. I was friendly with a lot of professors and graduate students when I was an undergrad, and they would complain about it. I doubt it's changed. I don't believe that.

COHEN: Since this is a private university as opposed to a public, what is the distribution on campus of ethnicities and gender?

WEIS: Well, again, I really don't have exposure to the undergrad campus. I'm sure it's whiter and generally more upper middle class than a public university. I'm sure that's true. But I really, statistically, have no idea.

In the medical school it's hard to know. I mean, I know there's a very active and very effective recruiting program for underrepresented minorities. But curiously, my sense—and I may be completely off base here, not being a doctor—is that this is not a great medical school to come to if you want to be a practicing physician rather than someone who's a little more academically oriented. There's some very high fraction of the medical students who do research here. It's like 25 percent or something—some number which I found truly astounding. It's a more academically oriented medical school. And let's face it, if you're working ER [emergency room] here, you're not going to get the kind of spectrum of patients that you get in an inner-city hospital. It's just different. And if you want to be that kind of doctor, this is probably not the kind of place you want to be. I suspect that that may affect, to some extent, the distribution of minority students, because if it's the kind of thing where you want to have underrepresented

minorities going back to their communities, which, realistically, tend to be in more urban areas, maybe this isn't the best place to come in the first place, you know? But I actually may be completely off base; you know, I just don't know. That's just my gut sense looking around and talking to some people.

At the graduate level, I think we don't do as well as public universities. I'm getting hit with this right now, having just taken over a training grant in biophysics. I know we were trying to work out ways of really improving our minority recruitment, because we get only a very few qualified applicants each year and of course we're competing with many places for [them]. And talking to some people who choose not to come here, I think there is a sense that this is not as friendly a place as maybe Berkeley, for example. That's understandable at some level. I'm not sure it's true; I don't think that's a reality. But look, Palo Alto is a white, upper middle-class area, and I can understand that it's not as attractive as a more integrated kind of area [like] a Berkeley or a UCSF even. That's a real frustration actually for me—not just to make the grant succeed of course. I think we do offer opportunities here for training that are unique, and I hate to lose any student for a reason like that, but we do. I'd like to improve that, but it is a struggle. That's a general concern I have.

It goes beyond that though. This is something maybe you want to discuss later, because I think the whole pipeline issue of K- 12 education is really the big problem. We simply can't remedy it at this level with affirmative action or anything like that. Really, just the pool is far too small, and it really has to go way back educationally. That's something I hope I can get more involved in later on, because I think that's a far bigger problem than worrying about it at this level.

COHEN: Do you see yourself doing community work?

WEIS: I hope in the longer term. Right now just the pressures of our work— We're sort of in a time when I can't do that, but I can imagine doing that in the future. I'd rather do something like that than serve on a lot of corporate boards. I know that that's something that you get asked to do more, and I would much rather be doing something like that. I'm not sure what the tangible things I would do right now are, and that's just because probably I haven't worked hard to find out. I'm hoping through this training grant to get more familiar with what one can do. I want to put some programs in place at Stanford to try to do that if I can, but more generally, in the community at large, I'd like to see what could be done.

And I'm not sure, to be honest, because I think we're fighting a lot of cultural things. Right now—and this is not just minorities—I actually don't think it's as much color as it is economic class. [For] people from lower economic classes, I believe, there's much more community and family pressure, I'm sure, to do a profession that makes money. And getting people from that background into science is a hard thing, because this is not a profession, as I said, that you go into to make money. And I think you have a double whammy going against you. I'm not saying maybe that doesn't matter and maybe we have enough scientists already in

the pipeline. But if we're going to worry about that and want role models, people who have come out of lower economic classes, we have to do something about it.

But how does one change the culture and say, "Well, gee, money isn't everything" when, of course, if you're coming from a real poverty condition, it is everything to get out? It's the first thing. My parents' [Anne Z. Weis and Martin Weis] generation came out of that, and of course they worried first and foremost about better economic [conditions] and providing a future for people like me to then go and do what we want. Maybe it is a several generation issue, and maybe we can't worry about it at this level.

As I said, I'm not sure there is a solution for that reason, but I think it's worth trying to think about for the future and to do something about it. I, right now, don't have any concrete ideas, but I want to learn more.

COHEN: In terms of the less formal teaching that you do, which would be with your graduate students, you just said a second ago that you think the training opportunities are unique here. In what way?

WEIS: Well, I was referring specifically to the physics-biology interface. What's happened here in the last few years is we've really improved the biophysics community at Stanford. It's largely by faculty recruitment, but also we have some unique things here. We have the [Stanford] Linear Accelerator Center as a unique resource. We have all the people who do single molecule work, which is the big, sexy area now—being able to image single molecules and their dynamics: Steve [Steven] Chu, this Nobel laureate here who invented optical tweezers, is in the physics department here; Steve [Steven M.] Block just moved here from Princeton [University] last year; and W.E. [William Esco] Moerner came here from [University of California,] San Diego. We've got, basically, three of the biggest people who really pioneered these methods, and we're seeing it in our applications actually in the biophysics program now. We also have a relatively small faculty and a small graduate program, and I think it's just much more personalized here than it is in larger places. But it is largely what I said is really unique to Stanford—this biology-physics interface. And there's just been a lot of invention—physical, physics, and engineering-type invention—that's gone on here that is kind of unique to this place. It's a very interactive place.

Ultimately, one of the big reasons I came here is I realized—and I'm very happy here—having trained on the East Coast— I don't know if this is Stanford or just a West Coast thing. It's just much less, certainly at the faculty level, this kind of ego and arrogance—people forcing their egos on you. I think it's very interactive. You know, I came here and I wanted to work on certain things and I walked into some colleagues' offices and I said, "Hey, we should collaborate on this." It's like there aren't these kind of walls and fiefdoms that I found at Harvard [University] and elsewhere. Harvard's, I think, particularly egregious that way. And I just really enjoy it because I think there are just far more opportunities here for this kind of interdisciplinary interaction; it's just easier to do here. I actually really try to emphasize that to

students who come through, because I think that is a unique thing about Stanford, and as I said, maybe it's a West Coast thing rather than Stanford.

But versus, say, Berkeley or UCSF, Stanford has one thing, which is that the medical school sits on the campus, and I think that's an enormous advantage for someone like me working in a kind of interface area between physical science and biology—that we don't have to travel across the Bay Bridge. We have the medical people here and all this great biomedical stuff going on with the physical scientists. It's wonderful. Those are the kinds of things I feel are unique here and have made it very attractive.

[END OF TAPE 3, SIDE 1]

COHEN: Were you finished with why it was unique here or—?

WEIS: Again, I just feel that one of the other reasons I wanted to be in a medical school is just, really, I wanted to be immersed among the biologists. I find it's just much more stimulating to be immersed among biologists.

The year I spent at Yale [University], which was a wonderful working environment for structural biology and biophysics— In a funny way, the community was too big. It's a real powerhouse, but in a funny way the community was too big and it became a kind of isolated little island where people simply talked among themselves in terms of structure and methodology. I didn't feel there was as much, potentially— Partly it's probably because I was really doing methodology there. But I could see that there wasn't as much interaction with the biology community, and I'd rather be sort of the way we are, where we're just kind of thrown and sprinkled among all these great biologists. It's just much more interesting and stimulating for me.

That was another reason I actually wanted to be in medical school, or at least a biology department, versus a chemistry department. In fact, when I interviewed at Berkeley it was actually in a chemistry department; that was another reason I didn't want to—aside from the teaching load which would have been horrific— [laughs] But really, intellectually, I just didn't want to be with those guys versus the biologists. Yeah, that's certainly part of it. But that's not unique to Stanford. I mean, anywhere I would have wanted that.

COHEN: Well, we talked about ethnicity in terms of the students. In terms of the graduate students, how does the male-female breakdown work?

WEIS: It's pretty good. I don't have the statistics in front of me obviously, but there are a lot of women in biomedical science—applying—and in graduate school. In fact, strangely enough,

right now my lab has two men and nine women, for example. You know, it varies, and I think that's a good thing.

Obviously we all know that there's an enormous discrepancy at the level of tenured faculty, which is partly a historical thing, because that of course is predicated ten years back. Hopefully that will change. Here the faculty is certainly predominantly male and I'm sure a bad thing for the female graduate students in terms of role models. But that's something that just has to improve slowly over time. Hopefully more and more women will really step into the system. I don't see women leaving the system because of it, but that's from a very limited— You know, seven years is not a long time to see that kind of long-term trend. Certainly I have a number of female friends from graduate school who are on great faculties elsewhere.

But it is true that in our field, which is more physically oriented— Of course, we all know that girls starting in junior high school, I think, tend to drop off in physical sciences for, I guess, somewhat known reasons. That does lessen the pool of students we see there. But we actually have a surprisingly— This year I think the prospective students we invited for interviews in biophysics has got to be close to half women. I think that's a great thing.

In a funny way—I guess when someone asks me—I will think about it, but it's never an issue. We just look for really good students, and we've been lucky. I mean, I've certainly had terrific graduate students, male and female.

COHEN: Well, pretty much everyone that I ask this question to says that the women are represented roughly equally with men at the graduate level and at the postdoc level, but clearly not at the faculty level.

WEIS: Absolutely, yeah.

COHEN: You suggested that that might be historical, that it's going to take some time to catch up, but— Have you ever been on faculty search committee?

WEIS: Oh, yeah.

COHEN: And are there as many women applicants?

WEIS: Definitely not, definitely not. The two I've actually shared— One was in our department, and then one was at the [Stanford] Synchrotron [Radiation Laboratory], because I'm on the faculty there. That was a funny position, though, up there. That was a very physics kind of thing, and I think there really aren't as many women in the physical sciences, the

quantitative sciences. That's just a fact.

In our department as well, because it was physical—although we certainly had some very strong women who applied and we interviewed in fact—it turned out we did hire a man in the end. Partly he was a kind of unique situation. It was someone we brought in at an associate professor level, not as an assistant, because we really needed to establish NMR here and the school I don't think would have gone for giving the millions of dollars it required to set up an 800 megahertz magnet for someone who wasn't already established to some extent. So I think it was unusual.

When we had a search, we had some very strong female applicants, I would say. In fact, I would say in our final list—I don't remember the breakdown—it wasn't fifty-fifty, but it wasn't far off. I couldn't tell you the numbers off the top. So that's very encouraging.

But I also know it's true [that] there's the pressure of— A lot of women want to have a family, and of course the system is not geared to giving time off and having the time period on a day-to-day basis to do it. Now, I think it depends. I've seen it work. For example, my friend Pamela [J.] Bjorkman, who is another Pew scholar, who's down at Caltech [California Institute of Technology], and her husband, Kai [G.] Zinn, are both on the faculty there and they've had two kids since they've been down there. And the school was great. I think if I remember right, they gave Pamela an extra year in terms of her tenure and Kai as well, so he could spend more time— So I think if the schools can be accommodating, that's great. But there are a lot of things that are beyond the capacity of the school. I mean, there are just time constraints; you've got to get stuff done for your grants. You know, NIH grants don't give you time to go off and be on maternity or paternity leave.

COHEN: Yeah, they don't care if your kid had any—

WEIS: They couldn't care less, they couldn't care less, and that's a genuine problem. And even with the best kind of marriage, where people are sharing the work fifty-fifty, there's still a lot of work to be shared. I think it goes for men and women. Of course, we know it's obviously biased against women. We all know that that's true. And that's a really tough issue because the system is not set up to help out. I don't know what you do about that, to be honest, and I'm sure that's a major discouragement for women. You know, not being a woman and not having kids, I can't speak to any personal experience, but I know that that's an issue. And the women who do succeed, who actually do have families, really have a much tougher road to go, I think. But there are a fair number of women in some of the departments here, and they're obviously doing well.

COHEN: Does Stanford give people extra time on their tenure?

WEIS: I actually don't know what the policy is. It wasn't an issue for me, so—

COHEN: I was surprised, interviewing one scholar, to find out that Harvard does. But there's also a difference between giving someone time and then, in subtle ways, punishing them for taking the time.

WEIS: Yeah, I think there are a lot of subtle things that go on. But even as I said, beyond that, I think there's just so much of the fundraising and the external pressures that even if they give you teaching relief— I mean, there are a lot of things that schools can do that are positive and they should do. But nonetheless, it's hard. I don't know how one solves that, actually. I really don't. I think it does take an extra level of commitment in that regard.

The thing is—I have heard it from senior colleagues—I think there is still in this day and age, surprisingly, bias against women. I really do believe that. I've heard it from people. Not everyone obviously, but I've heard it.

COHEN: Well, there was that thing at MIT [Massachusetts Institute of Technology] just a couple of years ago.

WEIS: Sure, that's right.

COHEN: Well, now that we've talked about teaching, let's go back to the other things that take up your time. You mentioned grant writing. It sounds like in the beginning you were a little bit lucky to get that stuff done. But right now at this point, because you're probably no longer eligible for all these young investigator things, how much time do you spend in trying to get money?

WEIS: It goes up and down. Basically, right now I have three R01 grants from the NIH.

COHEN: Three? Wow, that's a lot.

WEIS: Yeah. Basically I had this one from a work, which is still ongoing, and I've just renewed it. It's for the work I started as a postdoc. Then when I came here, I got two other things going that I really had wanted to work on, and that was totally dependent, basically, on the Pew. A little later on the Howard Hughes [Medical] Institute gave Stanford a pot of money to give two-year grants to junior faculty. It wasn't a direct thing from Hughes; they just gave Stanford money. So they had this [Stanford University/Howard Hughes Medical Institute] Junior Faculty Scholars [Award] program you could apply for. Those two things allowed me to get other stuff

off the ground—the Pew [Scholars in the Biomedical Sciences award] being the first one and probably the more critical one actually.

It was actually quite interesting—I'll show you how important this stuff is—because I wrote to the Pew and also the NYI [National Young Investigator]. This is the NSF [National Science Foundation]-sponsored National Young Investigator award. And my sense—I may be totally wrong—is I felt that that was less competitive than the Pew. I may be wrong about that; I just don't know. I wrote to those two the same proposal. The Pew said, "Great, this is really interesting." I think the Pew kind of awards partly on more a track record; I figured all these young investigator things do. The NYI came back basically like a peer-reviewed NIH grant saying, "Well, you haven't showed us any preliminary data yet, and even though you're a wonderful guy, it's not clear you could even do this." And I thought that that was the whole idea of these young investigator awards. I was shocked to get this thing back.

At the same time I was very fortunate to get a really good postdoc, actually from Pamela Bjorkman's lab, who wanted to work on this problem. So he wrote to the usual suspects—the cancer agencies for postdocs—and he got a very prestigious one. He got the Jane Coffin Childs [Memorial Fund for Medical Research]. [He also] wrote to the American Cancer Society, which is not as competitive, and he got the same review, saying, "Well, there's no reason to think you can do this."

I immediately knew, seeing that, that there was no way I was going to get an NIH grant, because this is the kind of peer review you're going to get. So the Pew was absolutely critical for doing that. We actually got it to go successfully, which I knew we were going to be able to do, actually. Then once we had it going to the point where I could write an NIH grant, I wrote one and I got it; it was that kind of thing. So I guess because of the Pew, I ultimately didn't suffer on that project because I knew that— You know, it did exactly what it was supposed to do—the Pew and then this Howard Hughes thing. Then it got funded for a shot once we had enough. So I already had two and was rolling along with that.

Then the other project we worked on, which is involved with intracellular vesicle trafficking, was a very interesting case because that, again, got going— I collaborated with a Hughes investigator; he helped out with a technician basically. I tried to get my own money for it, and I spent a lot of money from the Pew and this Howard Hughes thing. Finally, I felt we had enough preliminary data—certainly at the point I had written the catenin grant—to go to the NIH. So I wrote an NIH grant and it got a very low score.

Basically it was a completely, in my opinion, flawed review, because basically it said, "One project's great. The other one you don't have enough data for." What they're supposed to do then is cut out the money for that subproject and give me the money for the rest, because they didn't have any scientific criticisms. Instead, they just gave the whole grant a low score. So I felt this was kind of ridiculous. I said, "Okay, easy enough to rebut. I've now lost nine months," because you have to go through the cycle. But fine, I wasn't too panicked. I write the thing, I cut out the project, I send it back. There was nothing to respond to. I get the review back, same low score. Now they're complaining that "We wanted to see more stuff." And that is

basically illegal as far as I'm concerned, because you're supposed to, on a resubmission, respond.

So then I called up someone at the NIH, someone I knew on council, and said, "Well, what do I do?" Well, I won't name the study section, but the study session is well-known in our community to be a disaster. So I talked to my colleague, Richard [H.] Scheller, who's my collaborator on this, and said, "Look, just send it to a different institute, because this is obviously hopeless." So I did, and then it got funded.

I know this is not unique, and I was lucky because I already had two other grants. I mean, I have had lots of friends who have gone through this with their first grant. So I've been pretty fortunate and I understand that I have been. But it just shows how important this kind of unrestricted money really is, because you just run into this nonsense. You know, Harold [E.] Varmus and all the reforms he's trying to do— Terrific. They want them to look more at track record and innovation and stuff. But fundamentally, the people reviewing these are conservative, and that's part of the problem.

I don't know what was going on with that grant. I mean, it was odd. The whole thing with that was just— I actually, in part, blame whoever was the administrator at that time, because I think that administrator should have said, "No, this is just a blatantly unfair review." I think there are just a lot of flaws in the system. I'd be much more up in arms, but obviously I've done well by the system. But I can really sympathize with the frustration of many of my colleagues. I have junior faculty colleagues here who I've tried to help out, reading their grants, but you just run into these peer reviews and you don't know what to make of them.

I think the system does break down. Of course, you always think if your grant doesn't get funded, "Oh, they're all a bunch of idiots." [mutual laughter] That's, of course, not true either. But in a case like this, I just thought it was really flawed at a very basic level in terms of being really unfair given the way the whole thing turned out.

So that actually set us back in the sense that I had to spend time reworking these grants three times, and ultimately the grant that got funded was fundamentally no different. It really wasn't fundamentally different from the one I had submitted twice. That's very frustrating. And in fact, that was the project we actually got scooped on, and I really do attribute that in part— not completely, but in part—to the time I couldn't spend working on the stuff. I mean, I basically was wasting my time writing the same grant three times, and that's very frustrating.

Another project I've been trying to do, which is a very high-risk thing— We've submitted a couple of times to programs that said, "Oh, yeah, we don't expect you to be that far along, because this is very high risk." This is crystallizing a membrane protein, which is a very, very high-risk thing. NIH has a special program to fund work in this area, and my collaborator and I submitted a grant and it got turned down. So even though they say they're doing this, it still seems rather conservative. That's a real frustration—to waste time on stuff like that when you'd be much better off just being able to do stuff.

Then what's happened is that in our field— Particularly those of us who are supported by the NIH are competing against these labs funded by HHMI [Howard Hughes Medical Institute], which are fundamentally unrestricted in a sense. They don't spend their time dealing with this, and that playing field is very nonlevel. I think that's true of other fields as well, but it's certainly true in ours. And there are terrific people funded by that, of course, but the reality is that it does create a rather unlevel playing field when you have to run into these buzz saws at the NIH and have to spend a lot of time rewriting what are fundamentally pretty reasonable grants.

I actually don't mind writing grants, unlike, I think, a lot of people. I think there's nothing wrong with having to articulate and justify what you're doing, and I feel I can do that pretty well and I've been successful at it. So that aspect of it I don't mind. But when you run into this kind of thing is when it really does get very frustrating; you see yourself not spending time doing what you're supposed to be doing. On balance, I've done well by it. But certainly I've had my share of frustrations with it at the same time.

COHEN: Has there ever been a time when you thought you might not be able to keep things going financially? I mean, three grants is more comfortable than one grant, for sure.

WEIS: Sure. Well, actually, it's never enough. I mean, our catenin grant is not a big grant, and I hope when I renew it I can get more money for it, because we only had sort of one thing really working and I just couldn't ask for a lot at that time. In fact, they said, "Well, you're not far enough along on this other thing to fund another postdoc." I'm chronically short of money on that, but I've managed.

I never worried about the whole lab collapsing. I've certainly worried about not being able to pay people from time to time, but I've been very conservative. If people want to write to me about doing postdocs, I just say, "Look, I can't do this right now because I want to know that if someone comes here, I don't want to have to stay up at night worrying about whether they can eat basically." Even if I think there's a good chance they'll get their own money, I won't do it. Or I'll say, "Look, I can guarantee it for one year, [and then] you have to get your own money. If you're willing to come under those circumstances, great. But I won't hold it against you if you decide not to come because you don't want to take that risk." So I've been kind of risk averse that way. But on the other hand, I can sleep at night.

The reality is with the Pew and the HHMI Junior Scholars Award, combined with the first NIH grant— Until I got that second one, I was never really so worried about it. I always had a fair bit of unrestricted money, and I was very careful about spending my start-up money as well, which I still have a little bit leftover of actually just for a rainy day. So I've been very conservative about managing the money because I don't want to get in that situation. Yeah, I've never really worried about it collapsing. I mean, from time to time, but never in a kind of prolonged way.

COHEN: Okay, you sort of glanced over some of the administrative responsibilities. It sounds like you had relatively few at the beginning, but I'm told these things tend to snowball. What kinds of administrative responsibilities do you have, and how much time do they take up?

WEIS: The only thing I really had administratively before was graduate admissions. We were joint with the biochemistry department, so they actually ran it; I just sort of had to read some applications. It was no big chore.

Almost since day one I was asked to serve on the biophysics executive committee, which is basically a glorified admissions committee, so I was always involved with that. That was actually run by the chemistry department, by Steve [Steven G.] Boxer in the chemistry department. Chemistry is a very different culture from biomedical sciences. They have hordes of students come in, they flunk a number of them out after qualifying exams—certainly at Berkeley they do that; I don't know how Stanford works—and they support them for a couple of years by teaching. We don't do any of that. We actually interview them beforehand, we actively recruit them—because it's a small pool of these very good students—and we spend a lot more effort at it. What basically I did over the years is I got biophysics kind of drawn into the culture of the biomedical side. It was very successful actually. We've been, actually, one of the most successful programs in all the biomedical sciences in recruiting over the last couple of years.

Steve had been running it for twelve years and he was sick of dealing with the training grant stuff, so I was asked to take it over and I agreed to do it. So I'm now running that graduate program, which has turned out to be a little bit more work than I anticipated. I'm going to have to write the training grant renewal for it, which is going to be a big chore. Particularly we have some real deficiencies, as I mentioned, in terms of minority recruitment, which I'm trying to figure out how to deal with now. So that takes a fair bit of time. As a percentage of total time, it's not that big. But it's constant little interruptions—students writing to you from overseas or wanting to know more— You have to respond. Just little things like that. I'm lousy at time management, so I've found it to be a bit annoying. It's just a skill I'm going to have to learn to do better.

On the plus side, I'm praying it will give me moral authority to say no much more when I'm asked to do other things. [laughs] So I think that's good. I pray I will never have to do chairman of the department or anything like that. I think this is a far less onerous task. So that's all good, and if I can keep it just to that, that's fine.

I haven't been asked to do study section work yet. I'm sure that day will come, which I'm dreading. I think I would not do it while running the biophysics program. I would just ask to defer that until I stopped doing that, because I don't think I can do both of those. And that's pretty much it in terms of administrative stuff.

The rest of it's the lab itself and making sure we're not overspending our grants; you know, we get help from our business manager. I would ideally like to be able to spend 90 percent of my time doing research. It's not that high, but it's also not 50. It's somewhere between

50 and 90; I don't know what the number is. I think that's pretty good, considering.

COHEN: Yeah, I should say.

WEIS: Yeah, that's the way I want it. Largely it's because of the teaching. I have a very concentrated period of teaching in the fall quarter, and that quarter is kind of taken up doing that. Then around this time of year the biophysics admissions is a lot of work. But aside from those two times, it's really pretty good.

I really try not to travel too much. That's the other thing. A couple of years ago after we solved ß-catenin, which was kind of a big thing, I had a fair number of seminar invitations. In fact, I was told at my third-year review by one of my colleagues, "The one thing you really should do is travel more," which I hate doing because I just find it very disruptive. This is the one sort of mentorship thing that I had. They said, "Well, for your tenure, you should probably just have a few more things on your CV in terms of invitations and stuff." I just never really cared about that, but I said, "Okay, fine." So I did it, and I found it incredibly disruptive, because I took ten or eleven trips that year, which is ridiculous. You know, being away once a month for a couple of days is really a lot in terms of just disrupting the flow of the work. So since then I just really avoid it as much as I can, and I'm much happier.

COHEN: Do you mind the speaking, or you just mind the traveling?

WEIS: No, I actually enjoy giving seminars and talking about the work. Visiting, generally, I don't mind. And if it's a good conference, it's great. But it's just so disruptive. It's just this balance. It's a tricky thing. You don't want to be a hermit. I'm never really very concerned about my reputation in the end, but I recognize that you want to publicize the work enough that you can continue to get a stream of postdocs applying for positions and stuff like that. It is, unfortunately, part of the game—not one I actually relish, but it's a reality—and I accept that. But I'd really like to minimize it as much as I can.

COHEN: Now, what about writing for publication?

WEIS: Yeah, that I actually like. Again, the only thing I don't like about it is the time pressures. Right now—it's a funny thing to say—it's been kind of a not so enjoyable writing period, because we're having too much success. We sort of have this string of things: We're just getting the fourth of what will be eight papers out the door. We just got three major things out the door. One of them we're trying to write, and it is a very important paper. And it was while I was teaching, and that was really hard because actually, I really do like writing. But generally I do like it. I feel I write reasonably well. I can do it reasonably efficiently if I have nothing else to

do. That's a big problem with time management though because when I get distracted, it's very hard. One of the things that's been difficult in the transition from the postdoc to the PI is writing—other people's papers. I want to teach them how to write. Some people are good at it, and some are not, even though they think they are. And that can be very frustrating with major arguments about papers. It's kind of a joke in the lab that when you're writing a paper with me, the best thing is to break into my office and hide all my red pens. [mutual laughter] But I think it's just really important, and I am very fussy about it. I had a recent paper with one very good but very obstinate graduate student, which was extremely painful to write, for both sides, I think. In the end I said, "Look, this is just stuff we've got to do." And I'm not as happy with that paper as our other ones, but it's fine. And the work's really good, so—

COHEN: So they write the papers and you edit?

WEIS: They do a draft, yeah. I find it much harder to write that way than writing it myself from scratch, of course. Styles are different. But even with that, I actually do take a lot of satisfaction out of pointing out how to reorganize this to make it more clear and saying, "These are wasted words. These are wasted sentences. The flow's getting lost." When they come around to it—you know, how to really put it together—it's great.

My first graduate student, who was a fantastic guy actually— His first paper was kind of really all over the place. Then we worked on it and our collaborator worked on it as well. The next three papers he wrote I almost had to do nothing. He really got the message. It was great. When you see that kind of improvement, you feel like you've done something. So that was great. And I really like that, because that's one of the mentorship things I think we are really, truly responsible for. Because most of the students here know how to do research—we direct them, whether or not they think so—but the writing is something that a lot of them don't know how to do. So that's actually something I do spend time on. I very consciously spend time on it with them.

COHEN: Is tenure here at the associate or the full professor—?

WEIS: Associate level.

COHEN: So you're tenured?

WEIS: I'm tenured, yeah.

COHEN: How was that in terms of stressful or time-consuming or—?

WEIS: Neither. The honest truth is I really didn't think about it at all until about my fourth year. Partly because of sort of the dysfunctional nature of our department at the time—I was supposed to have a third-year review—it hadn't been done after my fourth. Of course I didn't even keep track; I didn't even know this. So it kind of got done in a very haphazard manner. And in the end there weren't really too many problems. They said, "You should really try to get some of this stuff written up," because they knew things were progressing. They actually even for that got outside letters. I guess there were no major red flags at that point.

The year before that we had a pretty important paper come out, the *Cell* paper, the ß-catenin paper [Huber, A.H. et al., 1997. Three-dimensional structure of the armadillo repeat region of ß-catenin. *Cell* 90:871-82]. I figured, "Well, that was a fairly major piece of work." We had the *Science* paper on this phasing methodology [Burling, F.T. et al., 1996. Direct observation of protein solvation and discrete disorder with experimental crystallographic phases. *Science* 271:72-77]. And we had this one other thing coming down the pike—the NSF [N-ethylmaleimide-sensitive fusion] D2 domain, which is this other *Cell* paper [Lenzen, C.U. et al., 1998. Crystal structure of the hexamerization domain of N-ethylmaleimide-sensitive fusion protein. *Cell* 94:525-36]. I don't know if I sent you that one or not. Anyway, I sort of figured, "Well, if that one also came out, then everything's fine." Everyone was telling me, "There's no problem." So I had no indication that there was going to be a problem, either from my external colleagues or people here, so I really wasn't worried about it. It wasn't even on the radar screen until that point.

But then I figured, "It would be really good to get this paper out." And this was the one major personnel disaster I had. I had this postdoc who basically didn't do anything and tried to get everyone in the lab to do everything for him. Basically, I had to let him go in the end, but I had to do the entire project—solve the whole structure myself and write the paper and get that out the door. We actually had the electron density map something like nine months before we actually got the paper written, because I kept waiting for him to solve it and he didn't. Then basically I just had to take over the project and do it. Of course I was doing a lot of teaching at that point, so it really slowed me down. Then I figured, "This may be important for the promotion." So I just really got it out the door. We rushed it out the door, got it out and accepted, and then I knew everything was okay. That turned out to be a good thing, because in fact, unbeknownst to us, one of our competitors actually had just solved the same structure. It turned out they came out together, so no one got hurt. But the reality is we just should have had it out months and months before, which is very annoying.

Anyway, I ultimately didn't really worry about it. I got asked for materials and all the usual stuff—a CV, some reprints.

COHEN: You didn't have to do a seminar?

WEIS: No, here they don't, at least in this department— I guess they do it in a lot of departments, but that wouldn't have been a problem anyway; I certainly wouldn't have minded it.

In a funny way, it's certainly not meant to be this but I know it is— There's this thing called Wednesday Club, which originated in the biochemistry department. Now it's our department, them, and developmental biology. We meet for lunch on Wednesday at noon and one faculty gives a research presentation—informal, but they're pointed questions. I participate in this, so the reality is that there are people looking at your progress sort of through that funny mechanism; it's certainly not meant to be that way. The senior faculty do it too, but people do kind of know what's going on. Also, I have some really wonderful collaborations here, so I have some good advocates in the MCP department, who, in fact, have now made me a full faculty member in that department as well.

Yeah, it was never really a stressful thing for me. Obviously, I think people know how things are going and what their peers think of them at some level. And unless it's something really pathological in the department, which certainly happens— When I interview job candidates when we have faculty searches, people [who] start asking about that is a sure sign to me that this is not someone I want to deal with, because there are people you meet who really are totally obsessed with that from day one and that's just not healthy. I mean, the only thing you should care about when you're starting out is getting your work done. I think that's always true, but you do find that phenotype and that scares me.

COHEN: You said a little while ago that your nine-months salary isn't guaranteed here. So what does tenure mean anyway?

WEIS: Well, tenure doesn't mean a lot in medical schools frankly. Frankly, I don't understand it—[that] is the real truth. I do think your salary is ultimately backstopped at some level—maybe 80 percent. I guess the way it works here is that you are expected to raise some fraction of your salary from grants or outside sources. That number is actually a moving target from year to year as the medical school income goes up and down actually—it's been very different than the time I've been here—and I don't know if there are any formal stated rules as to what tenure means in that regard. It certainly means space. I suppose if you lost all your grants and they had to support you for x number of years, they could take your space away as punishment. I'm sure that's true. But I think, ultimately, your salary is backstopped at some level. But let's put it this way, to have a lab space, a functional group, you are expected to raise whatever fraction of your salary they're telling you, and if you raise more than that, you don't get it back. So actually 90 percent of my salary is off of my grants at this point, which is higher than I'm required. But if you list yourself as some fraction or percent of the grant and you get the grant, that's what you take.

COHEN: Oh, that's a shame, because otherwise you could spend that extra money on other

people.

WEIS: That's a relatively recent policy change. That's the way they save money; that's the way they do it. But when I came here, I was negotiating a start-up. I was guaranteed three years in case I didn't get a grant salary. A grant came through after a year, so that was fine.

COHEN: Well, you said that you're really bad at time management. I think under the best circumstances, it would be hard to juggle all this stuff, but when you say you're bad at it, what do you mean?

WEIS: Oh, I just think that if I could go from one thing to another and then back again— So I'm writing alone, then I have to have a two-hour meeting about a training grant or something, and when I come back to it, I lose the flow, that kind of thing. Or when I'm teaching, I find it very hard to get very much else done. That kind of thing I find difficult. I'm getting better. It's clearly an acquired skill, at least for me it is.

It's funny though, one of my students is working on sort of two projects and she's fantastic. She can just drop something, do something else, come back and just— I really admire that skill. I could never do that in a lab. It's one of the reasons I know I can't do benchwork anymore. It's the same thing. I just don't have that skill.

COHEN: I can't remember where I read this, but I'm sure it was in the lay press somewhere, like *Newsweek* or something. But a couple of years back I read something that said that men and women are really different that way, and it's interesting that your graduate student that can do this is a female. Apparently, men are a little more linear in the way they think and women can do these fifty-two things at the same time.

WEIS: Well, I guess I could cite myself as an example. What can I say? [mutual laughter]

COHEN: It wasn't a scientific study.

WEIS: Right, right. In fact, as I said, I enjoy writing less now than I used to for that reason, because I love totally immersing myself in writing and really trying to get a coherent thing. It's very hard for me to get my head around a whole paper anymore and just spend hours focused on it or days doing nothing else. The only time I have to do that anymore is when I'm writing grants, because when you're under an absolute deadline, you have to. That I can manage. But even that I've gotten faster at. I mean, my first grant probably took me six weeks to put together, and now I've turned around in two weeks. I've definitely gotten faster at that.

COHEN: Two weeks of concentration?

WEIS: Yeah, yeah.

COHEN: Now, I know you're not married, but how does all this work around impact having a social life of any sort?

WEIS: Oh, it's terrible. I've certainly sacrificed that, not in a conscious way. I mean, I'm sure I must be at an unconscious level, but I never considered myself sort of career driven. It's more like I just have goals, like I knew I wanted to do this and I wanted to be in a good place with good colleagues because I know I'm just one of these people who needs the constant stimulation of people who are smarter than me basically. I think I was ambitious in that sense, to be in a place like this. I definitely take much more out of the place than I give back, I suspect [laughs], in that sense. So I've always worked hard, but it's never been with that goal in mind. It's just been because I really want to do the work. I definitely am a workaholic, I guess, in that sense, and it's definitely had an impact in terms of relationships and stuff like that. It's definitely a problem, which I— I mean, I'm forty now. I probably should work on that a little more.

But I really do think things are slowing down. There was just this huge bolus of work that sort of built up over the last few years—crossing through tenure and all of that. I think once these last papers are out the door, we really are going [to slow] down. We have a lot of new exciting stuff coming down, but it's not going to be quite at the intensity level and coming all at once that it has been. That will be good, and I'll hopefully get my life a little bit more in order.

[END OF TAPE 3, SIDE 2]

COHEN: Do you have the goal to have a family at some point, or not necessarily?

WEIS: Not necessarily. I think with the right person— I guess I'm not a person who is that goal oriented. I mean, if it comes along and it's right, I would do it. Yeah, I don't have a goal one way or the other. I could see not having kids; I could see having kids. I have to see how the circumstances develop.

COHEN: Well, let's talk about the makeup of your lab a little bit. I think you said ten people?

WEIS: I think right now it's ten. Yes, that's right.

COHEN: Who are those ten people in terms of—?

WEIS: In terms of job description, there are two technicians, four students, and at least four postdocs, so it's kind of evenly split at the moment.

COHEN: Okay. I know yesterday when we were talking about the labs that you had worked in, you said you had figured out a few things about how not to run a lab. But how do you run a lab?

WEIS: Something approaching chaos. [mutual laughter] As I said, it's pretty informal. I have a pretty good idea what people are doing, certainly on a week-to-week basis, but almost on a day-by-day. I talk with people every day. It's really at the level of just wandering around and saying, "What's up?" Even if it's just more of the same, great, and I leave. But usually we get into some, hopefully, interesting conversation. I can suggest something to do, or I'll sit down and start working with them on the computer and look at things. It's really kept that informal.

We have joint group meetings with Dave [David B.] McKay's lab. They're actually not for me to find out what's going on. They're really two things: I like to get feedback from other people. I'm happy to have other input into projects, of course—that can be very valuable; it has been in the past and I'm sure it will continue—not only from Dave, but also just from other students and postdocs. Also, I think it's important to have such presentations because people have to learn how to give formal presentations. I think it's actually almost more important for that. So that's really the extent that I formally run it. That's all that we do.

I've tried, partly because of my chaotic life, sort of subgroup meetings. We have three major areas of study in the lab, and with one of them we've tried to have submeetings where we talk about things and go over literature more. But that hasn't actually been too successful. That's largely my fault. I hope we can get back to that, sort of more keep up with the literature. But that's pretty much it.

In terms of mentorship—on the formal side, how to give presentations—the other thing is that we started what we called the molecular biophysics group, which I started with a couple of other faculty. We have once-a-month meetings with pizza and beer Wednesday evenings, and we have two students or postdocs from participating labs give presentations. It's a tough audience—this is faculty—and it's in an auditorium. To give more formal presentations, also, [there are] our department retreats. Those are two of the forums where they can do this. I will sit down with them afterwards and say, "These were problems with your presentation. This wasn't clear. This is how you should do it." Most of them take that criticism to heart and really improve their presentations. Like [with] the writing, I try to do that.

The actual science is done much less tangibly. It's thinking up new experiments, new ideas and stuff, but it's really just on a one-to-one conversation. So I wouldn't say the formal training is obvious to them in that regard, but it's happening. In a way, I think that's best, because I did come from labs where you had a lot of independence and I do think that's important. I know plenty of colleagues who will do that to the extent of virtually writing out day-to-day protocols for people. I will not do that. I think there has to be independence. People have to flounder around to some extent, but I also want to sort of guide them, like channel their thinking. You know, you need to make mistakes, but you also want to not drift and be all over the place. So I think striking that balance where first of all, people really have to feel the project's in their own hands— They're not my projects; they're theirs. I think it's legitimately true. That's not a sham. But of course I want to be guiding them, and what I'd like people to have is a sense that it really is their own work, because it is. But I think there is training that happens in a very intangible way by just having these kind of daily conversations—you know, what to do or not. And if I say something and they say, "Boy, that's a really stupid idea," that's great. I love to hear that and be challenged.

I think what happens from labs—this happened in our lab when I was a grad student and my postdoc— Actually, Tom [Thomas A.] Steitz at Yale [University], one of my colleagues, put it best. He said, "I know a graduate student's ready to leave when they think that I'm an idiot or I have nothing more to contribute to their project," because in that kind of environment, you're never conscious of being trained, but you are. And it's not only from the PI [principal investigator]; it's from your peers as well.

But graduate student training is very odd. It really is, because it's ultimately independent work, and all we can do is kind of channel— My definition of a successful scientist is someone who can increase the probability of something working from, say, 1 percent to 10 percent; I don't know what those numbers would be. Mostly you're failing on a day-to-day basis, but it's sort of increasing the probability that you might succeed at some experiment. And how to sort of channel it so that things will work is very intangible, but people do pick it up. I mean, it's part of being a graduate student and a postdoc. That's all I feel I can really do.

Occasionally I'll step in and really do much more, like when I had this disastrous postdoc. I'll write programs for people who aren't really adept at writing programs, help collect data. Some situations are tricky. Like when we're at the synchrotron, beam time's really precious, and [if] it's a less experienced person, I'll just have to step in and say, "Look, this is the way we have to do it," because we really are so constrained with this beam time. I try not to do that, but it happens.

COHEN: Now, you mentioned that you had this disastrous graduate student—

WEIS: Postdoc.

COHEN: —postdoc, who wanted everyone else to do the work. How do you do quality control, because these people are working pretty independently and yet whatever they do comes out with your name on it?

WEIS: I look at all the data, and I do know what's going on. It hasn't really been an issue. This guy was a different situation simply because I knew what he was doing, because either I was doing the work for him or someone else was and I kind of knew that. In the end, when we write a paper, I better understand everything that's in that paper. I want to know that the data's there. I mean, I'm hands-on enough that I do know I would never— If I ever got to that point, I'd leave because I'd feel very uncomfortable doing that. So quality control is just sort of staying on top of it basically on a day-to-day—certainly a week-to-week—basis. There's nothing real complicated.

COHEN: So on any given day—

WEIS: That I'm not being interviewed?

COHEN: —that you're not being interviewed, right [mutual laughter], that you're not spending two hours doing this, what does an average day look like in your life, from when you get up in the morning to when you go to bed?

WEIS: Tons of coffee before I leave, so I don't get on the road and kill anyone.

COHEN: Do you live around here?

WEIS: I live in Mountain View. It's not too far. I used to bike in—I lived in Menlo Park—and now I have to drive, but it's good.

I get in— Depends on the day. One of my collaborators is in England, so if I have to call him, I come in very early. But generally I come in somewhere between eight and nine thirty, depending. I come in, deal with phone messages and E-mails to the extent possible, try to get all that nonsense out of the way. Then it's actually quite variable. That's actually one of the fun things: it isn't stale. If we're writing a paper, I'll start working on a paper. If I'm supposed to be helping someone in the lab work on the computer graphics or doing something in the X-ray lab, I'll do that. That's really the hands-on stuff, and I just try to maximize my time doing that. Of course, I have some of these administrative meetings; I have to do them when they come up. There are tons of seminars around here, but they come and go and I certainly don't go to all of

them. It's pretty variable actually. I don't really, in a funny way, have a typical day. I don't plan things out too far in advance. I just come in and deal with what I have to do to the extent that I can be really doing—

Right now all I've been doing for the last couple of months in terms of in my office is writing papers, because we've just had a lot of stuff going on. That actually involves work in the sense that I actually have to be looking at results and data—helping to interpret them. So I would call that hands-on in that sense, even though it's writing papers.

Then, hopefully, if these ever disappear, I can go back to actually doing— I have one thing I did five years ago that I haven't had a chance to write up. I'd actually like to go back and finish that off. But yeah, I bounce around basically from day to day.

COHEN: How late are you usually here?

WEIS: Usually till eight. It's a pretty long day. And I'm here— Boy, actually, honestly, in the last two years, I've been here seven days a week.

COHEN: Really?

WEIS: Yeah, yeah, pretty much. I try to get to a period where I have at least one day off. I did that for a while, but things have really snowballed, again in a good way; there's just been a lot of successful stuff happening. I try to take Sundays off when I can, and Saturdays I don't work a full day, obviously—Sharon [M. Halfon] and I can go out and stuff. It's tricky. But that comes and goes. The next little while I want to slow it down a bit.

I don't work at home either. I did it in graduate school, and I really avoid doing [that], which was a major quality of life improvement from graduate school. I work very long hours, but I don't take work home generally. I don't have a modem at home. I have a little laptop. If I have to write grants or something at home, I'll do it. Or I'll take a paper back to review at home in the morning when it's quiet.

COHEN: But you can't log on.

WEIS: I can't log on, and that's very intentional. I really want to keep it separate. It's one of the reasons I'm here so much. I know a lot of my colleagues aren't here as much, but they work at home. I mean, we all work this hard, I think. But I don't have a family I have to sort of be taking care of, of course.

The other thing is that I really try not to come back after dinner, so I have the evenings free. Even though I eat late, that's something I found made an enormous difference, because I did that for graduate school and I somehow realized somewhere late in graduate school or in postdoc that just, "Okay, come in, get your work done, and then go home." Then you really feel like you have—even though it's not much of a life outside—much more. You can go out to a movie or dinner or do things—you know, cook—you like to do. I found that really helped. That may be why it doesn't feel oppressive even though I work long hours, because I do have a divider that way; when I'm home, I'm not working.

COHEN: So what do you do for fun?

WEIS: I like city things: museums, going out to eat. I'm a big eater, despite my size.

COHEN: Lucky you.

WEIS: Yeah, that's right. [mutual laughter] It's a good thing actually. Until two years ago—this is just, again, my total workaholic nature over the last two years— I have a shoulder injury, but I swam a lot as sort of a major exercise-recreation thing. I haven't been doing that actually, which is bad. Occasionally I try to get out to the coast to hike around and stuff like that. I like outdoor stuff. A lot of city stuff though. I just love cities and San Francisco, in particular. I go up there a lot on the weekend. Sharon lives up there of course, so it makes it easier. And music a lot. I like listening to music, both at home and live, so I try to do that. Those are the major things.

COHEN: What kind of music do you like?

WEIS: Everything. Rock, blues, classical, jazz. I'm really into jazz, so I do a lot of that. But all of it actually.

COHEN: Do you play any instruments?

WEIS: I did. That's one thing that's been sacrificed after becoming a scientist. I played guitar for a long time, which has been sitting, gathering dust in a closet for many a year at this point. Somewhere after graduate school it just kind of got put aside and never picked up again, which is unfortunate, but it happens.

[END OF TAPE 4, SIDE 1]

[END OF INTERVIEW]

INTERVIEWEE: **William Weis**

INTERVIEWER: **Helene L. Cohen**

LOCATION: **Stanford University**

DATE: **9 February 2000**

COHEN: Yesterday you talked quite a lot about collaborations and also a little bit about competition in the workplace. I wanted to explore that just a little bit more, because it sounded like when you first went into this field, it was something that not too many people were interested in, and then it became very hot after a while. So kind of in a global sense, how do you see competition impacting the study of science?

WEIS: Well, there are obvious positives and negatives. The obvious positives are that people are human and are to some extent competitive, and to the extent that it actually spurs people to do things, it can be a motivation. Many people function like that.

The downside is that many people crumble under such competition. So it goes both ways. The obvious downside is that it's globally inefficient. If two labs are working on the same thing, then resources are being put into the same thing instead of two different things. That's just the reality of how things work, and I wouldn't defend it. I think if everyone really got along and could be sufficiently motivated just by the work itself and not have the extra spur of competition, things would be better. But that's the way it works.

Of course there are external forces that I think come into that competition. It's not just people's egos, although that's certainly part of it. It's things like, "Well, if I don't get this done, I'm going to lose my grant because I've written a grant to do this." Particularly in structural biology it's a real problem, because the very long-term project has basically one payoff: the structure. There's no second place in something like that. You might go on and do some good clever studies after that, but it's particularly devastating in this field to be second if it's really the same molecule that's being studied. That kind of thing is a problem.

As I said, I think I'm someone who doesn't particularly like the competition. But I also recognize that from time to time it's probably spurred us on to do things not necessarily better, but more quickly. Unfortunately, the system does in part reward speed rather than thoughtfulness in many cases. And I must say a lot of my colleagues do thrive on it, not all, but there are definitely people who do get a rush out of working on things like that. It's not an attraction for me and, as I said, one of the reasons I went into this—an attraction of structural biology when I started in it—was that it was very much noncompetitive and cooperative the way it is not anymore. I'm not sure I'd do it again. Well, I probably would. But I'd probably give it more thought. At least that positive aspect of it wouldn't be there anymore if I was starting out

again.

COHEN: You mentioned in your own work that you got scooped once.

WEIS: Oh, yeah, yeah.

COHEN: Or more than once?

WEIS: Yeah, it's happened a couple of times. One major thing.

COHEN: How is that? I mean, it sounds pretty disappointing to me.

WEIS: Yeah, it was very disappointing, but it wasn't unexpected. What happened is that this was a case where there was an obvious target. Four labs were working on it, it turned out. I found out three other labs also got beaten; we weren't alone. You just move on.

I have sort of, now, a track record and the people I actually worry about far more are the people who are really in the trenches doing the work. In that case, the postdoc doing that project had to move on to something else. It's far more devastating for them. I think that's where it really impacts more. I mean, if you're the postdoc or student doing it and you get scooped— For me, personally, it's less of an issue. I mean, it impacts grants and the like; in that case, it wasn't a disaster. But I really worry much more about them, and that's why I really try to avoid it and try to work it out if I know we've got competition, because that's a far more important thing.

COHEN: What happens to a student [for whom] this is going to be his dissertation and, suddenly, it's old news?

WEIS: Well, then it depends if there are clever follow-up things. Sometimes what happens is that people are working on related things, but they're not the same. Then the comparisons turn out to be quite interesting, and it's quite often that that second paper can be the more interesting one. That happens. If it's really the identical thing, then it's really a matter of whether you're in a better position, say, than the competitor to kind of move on and do the follow-up work and the studies. Salvaging something is maybe too negative a word, but at some level, that's what it is. It depends. I've never really been in that situation where someone's been so— This postdoc is an example, but he's now working on other things and he's doing fine.

That's just something that you have to deal with on a case-by-case basis, and I certainly

would never keep people in the dark about it. People in the lab need to know that this is an issue; some of them actually do get motivated by it. It's just something you have to deal with, and it's not a good thing. It really isn't. We've been very lucky because two of the three areas we work in, really, we've never had significant competition. We've gotten scooped on little things here and there, never any major— The other thing has been very competitive; it's the first time I've really experienced being in this situation.

I've been on the other end of it a few times, where we've kind of beaten other people and we legitimately didn't know there was competition. I mean, it wasn't that we did anything intentional. We just didn't realize someone else was working on it until it was basically in hand. That's happened a couple of times. So I really haven't been, with this one exception, on the bad end of it very often. But it's always there, and I think it's only getting worse in this field. But [for] the people who do cell and molecular biology, where the time scale of projects is much shorter, this is something everyone lives with.

COHEN: Now, do people ever try to—well, I guess this is my editorial—be courteous and copublish if they know that someone else is really close also?

WEIS: Well, in fact, in the project where we got beaten, the lab—Axel [T.] Brünger's lab—that we were competing against— We have simultaneously published two absolutely identical structures—the two labs. The first time it happened we literally didn't know the other was working on this particular molecule. The second time we did know. They were a little bit ahead of us, so I talked to him and said, "Look, I just don't want anyone to get hurt," because no one got hurt because everything came out at the same time and it was fine. I asked if they were interested in copublishing, and they decided not to do that. You know, we were clearly behind them by a little while and they didn't want to do that. In the end we were able to get it submitted about—I don't even remember the timing—three or four weeks after them. It wound up being accepted before this came out, so there was no problem again. So at least we were communicating there. I still think it would have been better if they had agreed to slow down, but that's their choice and they chose not to. But in the end it was fine because, again, all the papers did come out about the same time.

COHEN: Well, it seems to me that there is potential in a very competitive system for people to cut corners and not always behave, let's say, in the most ethical fashion.

WEIS: Yeah, you hear about such things.

COHEN: Have you run into that in your—?

WEIS: Personally? No, no. Also, we're doing X-ray structures. There is an answer basically, and you can't really cut corners. You either have it right or you don't. There have been cases where people have made minor mistakes because they were in a rush. I know of other competitive situations, not me personally, but labs I've been in, [where] people got a little sloppy. But fundamentally they had the right answer. Yeah, that's always a worry. I mean, we're not in a field where we could fabricate data certainly. There can't be that kind of outright fraud. It's just impossible. It's just the nature of what we do. But yeah, I think there have been some sloppy things.

Even for myself, the fact is that this thing that we knew we had competition on, we probably wrote that paper a little faster than I would have liked to in terms of being able to think about some of the implications. But in the end we got, I thought, a nice piece of work out, and it was fun. I think for me, personally, we probably do sacrifice a bit of rigor perhaps in thinking about the problem and analyzing it and writing the best paper possible. I think that definitely will get sacrificed in a situation like that.

COHEN: But the data is what it is.

WEIS: The data is not the issue there, yeah. It's just sort of the presentation and the analysis thereof; that's more of a problem.

COHEN: Well, the flip side of competition is collaboration, and it sounds as if, from what we spoke about yesterday, you've had a number of very fruitful collaborations.

WEIS: Yeah, that's right. In fact, one of the things, particularly when I started in this—it's not quite as true now—[is that] it's a very technically complex area, X-ray crystallography, working out three-dimensional atomic structures. We are, at some level, tradesmen or craftsmen specialists, whatever you want to call it; there's a long time investment in learning how to do this.

The flip side of it is that—at least my generation, where we really invested years in just learning the methods because they were really being developed still—most of us are not well-rounded biologists. We're really on the most physical reductionist end of the biomedical research spectrum. I am absolutely fascinated with various problems in cell membrane biology—that's what we work on—but I'm not a cell biologist; I would never claim to be. So having collaborations with such people, good collaborations, is much more than the sum of the parts. It really is synergistic; that's the ideal thing. It's very stimulating from a purely abstract, intellectual level—just talking with colleagues and people in their lab, learning a lot from them—and we, I think, give that to them as well in the other direction. It's actually one of the most enjoyable things for me, that kind of interaction.

These collaborations really have run the gamut. Our work on the C-type lectins that we do with Kurt Drickamer is really close. They do a lot of the molecular biology and some of the protein work; we do the X-ray work and some of the protein work. We really have, at a practical level, a very close collaboration.

On the catenins, we have a collaboration with [W.] James Nelson. All the sort of practical stuff's been done in my lab, but as we've been accumulating the structural data, now we talk to James a lot just sort of about the biology of things. We're now going to be, in the future, in a position to take our results and our models and go back into cells with their lab, which is their expertise, and really do things. And it's certainly going to be far better than anything we could do by ourselves.

Part of that is a matter of personality. There are people who really want to have total—you know, the control freaks—complete control over it. And I understand there are egos involved in this, but I just kind of want to see the problem solved. I actually really take away a lot from interactions with colleagues, so I really like that kind of collaborative environment. I think it just varies for different people, the degree to which they do that.

On the other hand, I've had some pretty bad ones where people have said, "Okay, we should do this and we'll give you molecules to try to work with to crystallize." Then they decide, "Oh, this is actually pretty expensive and pretty time-consuming for us to be doing." And then they just drop it. So we've had bad ones as well, and I've learned to be very careful about who to collaborate with. You just don't know sometimes, of course. But by and large, I've been very happy. Things have worked out really well.

COHEN: Well, I want to talk a little bit about your current work, because you said yesterday that you have three different things going—three grants, three areas, three projects. Maybe you can fill me in a little bit on what's going on in your work?

WEIS: The oldest one, which is the stuff that, as I've said, dated back to my postdoc, is this family of carbohydrate binding proteins, called C-type lectins. The C means they're calcium-dependent; that's just how the family is named. These are molecules. Basically [in] all eucaryotes—actually, in procaryotes too of course—cell walls have carbohydrate modifications. It turns out that those are used as molecular recognition determinants.

A couple of examples: When white blood cells traffic through the body and they go from the blood into the lymphatic system, they have to get out through specialized tissues. That happens through an interaction: it's a multistep process where the cells are zipping along in the blood and then they hit these tissues and they start—it's actually a remarkable phenomenon—tumbling along the endothelial walls. That interaction, that tumbling, is actually mediated by this interaction of this family of proteins—they're called selectins, the particular family members—and they interact with specific carbohydrate structures that are expressed on those cells. That slows them down, they start tumbling, and that induces other adhesion molecules.

Eventually they get stopped dead and then they crawl out between— It's really a remarkable process. That's an example of one of the things that happens. I got into this actually through my graduate work with Don [C.] Wiley, because in the virus I mentioned, hemagglutinin, the hemagglutinin protein on the flu virus binds to carbohydrates in the respiratory endothelium; that's how it attaches to cells and gets in and infects.

Another group of molecules that do this that we also study in the C-type lectin family are proteins found both in the serum and on macrophages. You exploit the fact that pathogenic organisms have sugar structures on the surfaces that are different from us. It's a way of distinguishing a foreign from a self independent of an antibody response; it's called primitive immunity. We're basically looking at all these molecules and trying to understand in a detailed chemical molecular sense how they actually specifically recognize certain carbohydrates. That's been a long-standing effort, to understand this family.

Then there are other aspects of that family: A lot of them turn out to be endocytic receptors, which means that they— Let's say these macrophage receptors that will actually bind, say, a bug at a cell surface and phagocytose it for destruction take their cargo into a vesicle in invagination on the surface which pinches off to form a vesicle. The vesicle is delivered to a particular area, like a lysosome, to get destroyed, and the receptor actually recycles to the surface. So there's this reversible transit where it binds, has to release, and then go back. Actually, many receptors are mediated by pH because these vesicles that get pinched off get acidified, and that turns out, in turn, to be related to this calcium dependence and binding—the acid actually titrates the calcium off the structure—and it turns out to induce changes in the protein structure. We've basically been trying to understand how all that works, both in terms of structure and thermodynamics and kinetics. That's one of the areas we study; I was working on this when I came here.

Then I had this interest generally in cell adhesion, and when I moved here I met James Nelson. There's another class of adhesion molecules called cadherins; it's an abbreviation for calcium-dependent adhesion molecules. These are so-called homophilic adhesion molecules. These are transmembrane proteins that sit on cells in solid tissues. They have lots of different kinds and the same flavor of cadherin binds to itself on another cell. This is what knits the same kinds of cell together in a solid tissue. For example, when a liver is developing, cells differentiate into hepatocytes, they express a particular kind of cadherin, and then they know that they belong together in one solid tissue. It's the way multicellular organisms actually differentiate into specific tissues. I got very interested in that problem.

The specific thing we're doing in the case of these lectins, these carbohydrate binding proteins, is we're looking at these extracellular portions and how they interact. A number of labs, including Wayne [A.] Hendrickson, my old boss, had been looking at the extracellular domain of the cadherins and how they may interact. But I got interested in a different problem and that is that these molecules do not work unless they have an intact cytoplasmic domain. On the inside of the cell, they have to have an intact cytoplasmic domain, which is actually very highly conserved. That's because these have to be linked to the cytoskeleton. So you imagine basically what these molecules do is you have a tissue full of the same kind of cell with rivets

which are basically these adhesion molecules. The sort of structural steel, the girders, are the cytoskeletons. You have to have that whole network to actually provide mechanical strength and integrity to tissues. I got very interesting in understanding how the cytoplasmic side of that is put together, because it turns out that a lot of the regulation of adhesiveness comes there.

For example, in cancer, one of the things that happens when cells become metastatic and they have to get out of tissues [is] they have to de-adhere. They lose contact, so-called contact ambition, and they get out. These junctions have to fall apart so the cells aren't adherent anymore. Not surprisingly, these assemblies are highly regulated. It turns out that the cytoplasmic domain of the cadherin is not linked directly to the cytoskeleton but through proteins that are collectively called catenins, from the latin "to link." We started studying these and the goal of our work is basically to understand in biophysical terms how these cell junctions are assembled and how they're regulated.

It turns out they're regulated by phosphorylation, most likely. We really want to understand how all this works, how they're put together, how phosphorylation affects them. We started by looking at this molecule, B-catenin, which binds to the tails of cadherin, and then to another molecule called α-catenin, which is unrelated, which links us to actin. There are lots of other proteins involved, but that's kind of the linkage.

We started working on this and what happened—we've been continuing to do this work; I don't need to go into the details of that—was very interesting. It shows you how you can just go in new directions in a sort of fortuitous way. B-catenin, when it was isolated and cloned around 1990, turned out to be a homolog of *Drosophila*, a fruit fly, protein called *armadillo.* Now, *armadillo* is a so-called segment polarity gene. It affects the body plan during early embryogenesis of a fly larva. No one understood what it did at that time, but everyone knew it was homologous to the structural component of a cell junction. It turns out now that in flies it does the same things in junctions, so everyone thought, "Well, maybe"—at least, I thought—"what it might do is be directly involved in adhesion." When you develop multicellular organisms, cells adhere and de-adhere. Tissues remodel. But it turns out that it has a completely separate role as well—and it turns out to be true in vertebrates—which is [that] one of the down stream affectors of a growth factory signaling pathway controls cell fate determination in embryogenesis. So not only is it a structural component of cell junctions, which is how we got into it, but it's a developmental signaling molecule. That's gotten us into looking at that pathway as well, which is actually very complex. We're looking at interactions in that system as well and trying to understand how it functions there. So starting from the cell adhesion got us into this whole interest of signaling networks and developmental signaling pathways. So we're working in that area. We've kind of gotten happily dragged into it; it's not where we started. That's a lot of fun because I've learned a tremendous amount of stuff I knew nothing about. And now it's really becoming a really big part of the lab.

Then the last area we're working on is intracellular vesicle trafficking. Basically, in all eucaryotic cells, cargo gets moved around, say, from the endoplasmic reticulum to the golgi, through the golgi apparatus, golgi to plasma membrane, to lysosome, whatever. Conversely, endocytosed vesicles have to move to particular places. What happens is that cargo gets

delivered and these vesicles have to get targeted specifically to a membrane and then dock and fuse so that the contents of lumen gets dumped into the next compartment. There's a whole machinery that controls that not surprisingly.

I was very interested in this, again, back from Don Wiley's lab actually, because of the fact that influenza and other viruses like HIV get into cells through this membrane fusion mechanism. I was really interested in how that works. So when I came here we started collaborating with Richard [H.] Scheller, who's one of the main people in this field, and we've been working together on trying to understand some of the molecules involved in that process.

Those are the three main areas we're involved with. We have a fourth thing, which is really mostly happening in a collaborator's lab. It's actually hard because it's back to undergraduate days—our interest in 7 helix receptors and rhodopsin. One of my colleagues, Brian [K.] Kobilka, is also in the MCP [Molecular and Cellular Physiology] department. Brian Kobilka works on beta-adrenergic receptors or, generally, adrenergic receptors. He's been very interested in trying to get structural information, so we're working with him to try to get structure. These are integral membrane proteins, so as I mentioned the other day, it's a very challenging problem, mostly, actually, at the level of expressing enough protein to work with at the quantities we need. We've been working with him, trying to get enough and trying to crystallize it.

Eventually that's going to tie into other things we're doing. For example, in the signaling pathways, a lot of times there are 7 helix receptors. They are representative of a much broader class of receptors, so a lot of these things are going to tie into one another over time. But everything we're doing is ultimately cell membrane biology in the most general sense. That's really the interest of the lab.

COHEN: Now, yesterday you said that the Pew [Scholars in the Biomedical Sciences] money in particular allowed you to do something that you wouldn't have otherwise done. Which of these was that?

WEIS: Well, I wrote it actually on the cadherin-catenin project. That was the main thing. That's how I justified the request for the money. [laughs] No, it's true, that was it. Then I certainly used it also with this Howard Hughes [Medical Institute] support, that junior faculty grant, to work on the vesicle stuff as well, although Richard Scheller contributed a technician to this early on; we have kind of a joint postdoc between us now. So that's been sort of more integrated in terms of the financial support as well. But particularly the cadherin-catenin stuff just wouldn't have happened without the Pew.

COHEN: Well, the things that you're working on right now—I know there are different things, so this may not be a simple answer—how are these things going to contribute to our understanding of cellular mechanisms?

WEIS: Cell biology? Well, structural biology, biophysical mechanism, is really, again, at the most reductionist end of biochemistry. Can you take a system apart and understand it at the level of chemistry and physics? That means understanding specificity, say, in the lectin case. You know, what are the atomic determinants that allow these molecules to only selectively recognize pathogenic cell surfaces and not our own so you're only killing the right target? Specificity is one thing—really understanding biological specificity at a very chemical level.

Mechanism as well. What is the mechanism by which this machinery that fuses membranes—? How does that all work? How do these proteins come together to work? How do you set up a regulatory system? How do you target specifically? That's a question that has to be approached at whole cell levels—biochemical, genetic, structural. We're contributing in that global picture, trying to really understand it at that basic level.

In the case of the cadherins, it's really, again, trying to understand the nature of these cell junction assemblies. That includes how do these things bear loads? What I'd love to do with this—this is what I'm planning on doing once we have some basic structural information—is basically reconstruct a cell junction in an artificial system to the point where we can actually, in a controlled way, exert forces on single assemblies and really understand the mechanical loads. This is just fundamental to understanding why tissues are strong or not, how you strengthen or not strengthen tissues.

And again, the regulatory mechanisms. If you know phosphorylation affects these, how does phosphorylation of some of these proteins affect their interactions quantitatively? What does it do to the structures? What does it do to their binding affinities? Very, very basic level information. That's really what I'm interested in. Those are the kinds of ways that they contribute to that field. The best case structure really does. I'm not saying it's going to happen in all of these, but I think particularly in the catenin system, it will give such a new way of looking at things.

There are sort of two kinds of structural biology: In one you know all the biochemical parameters and you kind of know how the system works and you're filling in a lot of details. I don't actually find that that interesting to do. It's a perfectly valuable thing to do, and for certain practical things, if you're worried about drug design, for example, that can be a very practical thing. You have to know those details. But I'm more interested in problems where we just take a totally different view of the world from, say, a cell biologist, where we start from structure and try to gain some insight into how it might work and then go back up and try to really see where the biology might come from. It's a different approach. I think it's not any more or less valid; it's just a different way. We can bring that to the problem and complement what, say, the cell biologists are doing. That's where the most fun stuff happens.

Of course, there have been some spectacular examples. The most obvious impact of structure, I would say, in the last twenty years was in Don Wiley's lab—the MHC [major histocompatibility complex], the structure of the histocompatibility antigens—where seeing that

molecule and this peptide bound in that groove, you just got an insight into how T cell recognition worked and how you generate T cell responses. That was one of the most spectacular examples.

But of course, a lot of it is fortuitous timing. That came along at exactly the right time to where the immunological research was. Sometimes it's incredibly synergistic. More often than not, things are a bit out of sync. But I like to be out of sync at the level where we don't know quite know so much about the biology and you try to bring it to a new mechanistic level.

COHEN: You actually light up when you talk about this stuff, so I can see it's very exciting for you. Now, what about practical applications? I mean, we know about the histocompatibility of things—everybody knows about that now—but what kinds of practical applications could you see coming from this?

WEIS: For example, with the selectins— I'll tell you the ups and downs of this. The issue of specificity and designing inhibitors is one that is broadly, in theory, applicable. In other words, if you knew atomic structures and you knew something about how to make new synthetic molecules, in principle, one could design something that will fit and have the right shape—fit into an enzyme or a target—and act as a rationally designed inhibitor. In fact, when selectins were discovered and right around the time we solved our structure, several companies wanted our coordinates, because they wanted to try to understand the interactions. That is a very practical use of crystallography. In fact, it was a real interest of mine when I was in Don's lab. We'd worked out the sialic acid receptor interaction with hemagglutinin and said, "Boy, drug design."

It was kind of the early days then, and it wasn't clear how it was going to pan out. But frankly it's been a pretty big disappointment in that it's really due to a fundamental thing, which is that we know a lot about atomic structure, but the link between atomic structure and thermodynamics— Ultimately the problem is you have to make something that binds more tightly, has the right thermodynamic. I mean, forgetting bioavailability and all that other stuff that comes into it, which is critical of course, the fundamental thing is you want to be able to design something that binds more tightly, displaces the natural ligand to act as an inhibitor. And there is a fundamental lack of understanding between structure and thermodynamics. That's the realm of statistical mechanics, and that is just not a sufficiently developed area, theoretically, to allow you to do that in a good way. There are a lot of really smart people working on that problem, but it's been disappointingly slow—the progress on that—actually, because it's very hard for many, many reasons.

There have been a couple of spectacular success stories with structure-based design, the influenza neuraminidase inhibitor, the antiflu drugs that have just come out. HIV protease inhibitors are a really spectacular example, because there was a lot of knowledge about protease inhibitors and proteases that led to that. So those are important applications.

COHEN: But there was a dismal failure too, because I remember in the early days of HIV, people were trying to prevent adhesion of the virus to the cell wall by giving soluble CD4.

WEIS: Yeah, that's right. That wasn't the kind of rational design I was talking about, because that was based on a known biochemical property: You knew CD4 bound to it. Can you just inhibit the interaction? This is stuff where you're designing molecules knowing atomic structure—designing small molecule inhibitors to stuff up an interaction. And the lectins have their own peculiarities, which basically makes it a very, very hard problem. That's why all the drug companies bailed on it actually to make anti-inflammatories; well, it seems like they have. But that still is a big area. All the drug companies have crystallographers and people doing modeling and the like, but it has actually not been a success in the sense that "Gee, I know the structure. I can design a molecule."

Where it is very useful though—and I do believe in it at this level— If you think about the old days of screening for drugs, you would take a random, huge number of molecules—a million—and you basically had to screen them to see what worked. I think that at a minimum, what structure will give you is a way of reducing the number of things you have to look at. You won't find the answer, but if you can even reduce your search from a million to ten thousand, you've got a huge gain there. I think that kind of thing is very important, and I'm actually optimistic that the methods will get better and better for this kind of rational design. It's certainly not there yet, but in a combination with a lot of combinatorial chemistry, I'm very optimistic that that's going to happen.

Those are kind of practical applications. Knowing molecular structures is just an integral part of that kind of inhibitor design process. It remains to be seen how wildly successful it will be, but I think it will happen. I must say that practical stuff is really not what motivates me personally, but I recognize it as an application.

COHEN: One of the things you mentioned sounds like someone ought to be working on this—this business of preventing metastatic events from happening. Is that in the pipeline with any of the companies?

WEIS: That's really out of my area of expertise. I don't know. I can imagine it. Again, I would hope that if we get to the bottom of how the adhesion events happen molecularly, that may be at least a new avenue to explore in terms of drugs. But I must say, I just don't know. I mean, we all know that most of the anticancer drugs these days are basically aimed at inhibiting just the growth essentially; it's more DNA targets and the like. But yeah, that would be a wonderful new avenue if that comes to pass, and it would be great if we contributed to that in some way. I could see it happening, but it remains to be seen.

COHEN: Now, I noticed you didn't put on your résumé any patents.

WEIS: Yeah, we don't—

COHEN: You don't have any? If something were to develop out of something that you discovered—quite a few of the scholars do hold patents—do you have any interest in that sort of thing?

WEIS: I guess if it came to pass, I would probably be interested. I don't know; I would have to see. I mean, I'm just not really motivated by money. I guess if someone else were going to profit from my idea, I'd probably want to do it just [because of] the principle, but it's not something I've given much thought to frankly. If it comes to pass, sure, I guess I would. What often happens of course with these things is that patent or not, you wind up sort of consulting with companies that are doing more practical development. I think that would actually be very interesting, to see the science applied that way. I would love to be involved with it at that level, but it remains to be seen.

One of the main things we do, of course, is molecular structure, and despite, I think, certain people's desires, I feel it's not a patentable thing. We're basically looking at natural molecules and how they work. From time to time I've heard rumors of people talking about patenting structures, but I think that's not going to happen. I hope it doesn't.

COHEN: Well, people patent gene sequences.

WEIS: Right, it's that same flavor. I'm really a believer in public dissemination of these things, but it remains to be seen what will happen.

COHEN: It does bring up the question of does anybody own scientific ideas?

WEIS: Yeah, that's right, that's right. I believe it is public domain. I really believe that very strongly. And I think the ethics of it are very difficult when you talk about being supported by public money, particularly NIH [National Institutes of Health] money, to then turn around and do that. I guess it's a little stickier of course with things discovered in companies. It's one of the reasons I would never work in a company myself. Yeah, I'm really a believer that that stuff should be public domain. I really do believe that.

COHEN: Well, one of the things that I think happens, probably more than people realize, is the

role of—you can call it whatever you want—fate, serendipity, in scientific discovery. There are some really classic historical examples of it, but has your work been affected by any serendipitous events?

WEIS: That's a good question. No, not in the sense of a discovery that we've come on because of luck. It's kind of the nature of doing what we do though. I mean, we take a problem—how do I put this?—we kind of go at it in a fairly rational way, and we have the answer. There can be some real surprises in the answer that we get out of an atomic structure. I mean, I've been surprised plenty of times—what the thing looks like; you suddenly realize, "Oh, this is how it works"—but that's not a chance discovery. In other words, we've gone ahead and sort of done the structural analysis and then done it. It's kind of the nature of our work that those things don't happen. You know, we don't do so much of the mixing things in test tubes and suddenly some odd result comes out. I mean, we do a certain amount of that, and to the extent we do, that hasn't happened for us.

What can be lucky is sort of the connections that occur, like we were working on the B-catenin problem and then all of a sudden learning about all this signaling stuff. It's that element of chance that's taken us into this new direction of looking at this developmental signaling. So there's been a real role of chance in the way the lab and my interests have developed. You work on some interesting molecule and it takes you into directions you really didn't anticipate. That's actually a lot of fun, and that's great. But in terms of making discoveries, no, that really hasn't happened.

[END OF TAPE 5, SIDE 1]

COHEN: Well, I think in order to take advantage of something serendipitous, you have to have—I think it was Einstein that said this—the beginner's mind or the open mind. You must be receptive to whatever comes along.

WEIS: I think that's certainly true. In practical terms, we certainly have exploited observations we might not have expected just in practical ways of when we make our molecules and think about how to approach a problem. Certainly that happens all the time. I think that's what you want to be doing as a scientist—being able to have a good sense of where to take a problem and how to get it done. In that sense, having that kind of open mind is really important. But again, in my career so far, that sort of next level of actually making a fundamentally new discovery by chance really hasn't happened.

COHEN: Well, when I look at the pictures of what you do, which are all over the wall there—

WEIS: Festooned—

COHEN: Yeah. They're very artistic in a way, particularly the color photographs. You could almost frame them and put them on the wall as a piece of artwork.

WEIS: People do that.

COHEN: Do they? It brings up a question that I'm interested in, anyway, which is the relationship of creativity, which most people usually associate with the arts, in science. I think in order to be really good at this, you have to be pretty creative. Do you see any relationship here?

WEIS: Yeah, I actually think—who is it?—C.P. [Charles Percy] Snow, the one who divided it in the first place— I think it's largely a lot of bunk. It's maybe a different half of the brain, but the fact is I've known people in the arts, and people who function as artists or as creative scientists are not that different, because there's a real obsessive quality to all of us. We're totally consumed by our work in a good sense. I mean, it's not a job. As I've said, it should be a hobby or a passion. People look at scientists and say, "God, you work nutty hours." But the best musicians and the best artists have that kind of dedication as well. The sort of mental attitude to it, I suspect, is not very different. The skill set is totally different, I'm sure, but I don't think in terms of outlook that there's the division that is made out to be by the media or anyone else.

This is probably a rotten analogy, but I'll make it anyway. Ultimately, our reality is grounded in sort of the physical world, so we have to be creative under a constraint; ultimately, it's data and experimental observation. And maybe it's something akin to these Japanese paintings where there are rules about particular brush strokes. It's almost like that. It's creativity but under constraints. You think about the wild-haired artist flinging paint at a canvas; that's certainly one form of creativity. But it's just a different mode. I think at its spiritual root, it's not any different. I really believe that. At the highest level of artists and scientists, I really don't think there's that much of a difference.

COHEN: Do you have any idea—some people do and some don't—where your ideas come from?

WEIS: Well, in the vaguest sense, just general curiosity. You look around the world of biology in this case, and say, "Gee, that's a really interesting thing. How does it work?" That takes you down a path of thinking about "How might it work?" Then you start thinking about "How could this work in molecular terms?" And that just starts spawning ideas. Then you do experiments and that of course eliminates— That, maybe, is another difference between that and a sort of

pure artist: you actually have to do hypothesis testing and eliminate things. But still, you are having to creatively think about a problem. But where those sort of creative thoughts might come from— Hard to know.

COHEN: Well, some people have them in their sleep. You know, they get an inspiration or they daydream or—

WEIS: Well, for me, to the extent that I've ever had them [laughs], it's kind of more like a vortex. I start up here and I start thinking about it and thinking about it and I eventually sort of work my way down to it. It doesn't just come to me. There's this kind of evolution of thinking along a path down to something. I just walk around with the problem for a while and think about it and hopefully it will come. Sometimes it never does—how to solve a particular problem.

But again the kind of stuff we do in structural biology is a funny business relative to a cell biologist or a biochemist at some level. They are strictly hypothesis driven. I have an idea, here's this and this— Our view of the world is we want to start from knowing a structure and then develop hypotheses from that, but the data gathering aspect of just knowing the molecular structure is much more like field biology: you just go out and you're collecting, in this case, atomic structures and then trying to put that together in a framework. It's kind of different from going out every day, "Okay, here's test tube A and B. I have a hypothesis, here's this and this, here are the controls." It's just a very different kind of thing. So we have elements of field biology in what we do, actually. It's very useful of course, and it's a very enjoyable aspect, because if you're an evolutionary biologist, it's actually quite hard to then go back and do an experiment. We can actually generate a hypothesis and test it. So we kind of have the best of both worlds in a funny way.

COHEN: Your work is very dependent on technology—

WEIS: Oh, yeah.

COHEN: —more so probably than many of the other areas of work. Obviously there have been great advantages to many of our technological improvements. Is there any downside?

WEIS: Well, I can tell you how the field evolved. X-rays were discovered and then the Braggs [William Henry and William Lawrence] basically— [Max] Von Laue realized that crystals would diffract X rays. For a good part of the century you could just do very small, little problems, like salt—measuring data and then doing the calculations—by hand, because they involved these Fourier transforms. Anything the size of a protein means you can't do Fourier transforms by hand. So this field is absolutely, completely dependent on the development of

computers. It just would never have developed. Then the X-ray detection technology has improved, so it's gotten faster, more accurate—better synchrotrons now. The computer is the one thing that the field was totally dependent on—just literally wouldn't exist. And of course all the other technological improvements— So what's happened is that it just is faster now. And over the years the numerical algorithms for doing the computations have gotten to the point where there are now, in this day and age, pretty good computer packages, and structures can be solved quickly.

The one downside—this kind of relates to what I was mentioning the other day about kits for DNA sequencing—is that people really now, on a straightforward problem, can solve the structure without having any idea how it works, or pretty close to it. I'm not an old-timer, but I guess in this context I am. You don't have to know what you're doing anymore. And I think there is still room for people like me who do, who are more sort of technically trained this way—people my generation and older—because there are really hard problems that really require a level of expertise. But it's actually falling; the methods are getting so much more powerful that it's getting easier and easier. It used to be, when I went into it, that crystallography was a full-time job. You were a crystallographer. That is just not true anymore. Now you have people who use it as a tool like anything else. That's great. Of course, we do a lot of other things aside from crystallography in my lab. It goes both ways.

So the physical technology and the computers were one thing. Then of course recombinant DNA, the ability to basically take rare proteins and make them in large quantities by recombinant systems, was the other major thing. Until that technology occurred, crystallographers were limited to studying things that were basically available by bulk biochemistry: you grind up a brain, isolate an enzyme—you know, a couple of pounds of brain, because you need milligram quantities and most proteins don't exist in such quantities. Now you can take any gene and try to express its protein product. That's really been the other major thing. There have been some other technological improvements along the way, but those two things really made the field explode in the late eighties. So there are mostly upsides: just more structures are being done. The real downside is that crusty old farts like me can sit and say, "Oh, these young'uns don't know what they're doing anymore." And it is true.

Actually, there is a downside really, and I've talked about this with people in my lab. The expectation when I was a grad student [was that] a whole thesis could be just toward getting a structure or maybe solving one structure. The expectation now is you can do several structures and the associated physical chemistry cloning as part of a thesis project. It's a more biologically integrated project than it would have been when I was a student, when it was really very much you did a structure. So the expectations of the students are to get more of this stuff done, and of course there's more competition, there's more pressure to get things out faster.

The computers run faster. A typical thing we have to do is we measure diffraction data and we have to take a lot of redundant measurements and scale them together, sort of a least squares problem. When I was a student, I would submit a computer job and go home, because it would be, in real time, about twelve hours on a time-sharing machine. What that gave me time to do was sit down and read the papers and really figure out how the programs worked. The

programs weren't as well done in those days, and you always had to monkey with the programs a little bit to get them to work or write your own programs from scratch. Now everything's really kind of canned and it works. And now that same scaling job that might have taken twelve hours when I was student is ten seconds. So people don't have that time to think anymore about the methods, so they're just not learning at that deep a level. That is a downside in terms of the technological training.

The upside again: More structures are getting solved. There's more of the ultimate thing you care about, which is the structure. More of them are happening. So viewed from the community as a whole, it's only good. But for those of us who actually enjoy the technological aspects of it, it's a little bit disheartening. But you do find students who really want to learn it at that level, and it's fine.

COHEN: Well, what about something as simple as the Internet? I mean, that, to me, can be a time-saver in many ways, but it can also be a terrific time sink.

WEIS: Yeah, I don't have the surfing addiction. Certainly for molecular biology, the ability to just rapidly do sequence searches and database queries and stuff is fantastic. "Gee, I want to look at another protein structure." I go to the protein data bank and I just pull it out. When I was a grad student, they would ship a tape of all the new structures and you'd get an update every six months. It's fantastic. So the tools are great. The computer graphics that make all these pretty pictures, of course, are that much more powerful; you can really get a lot of insight into things. So generally it's just been a terrific tool. I'm not a particular addict of it, fortunately. Of course, the other thing is just literature searching. What a huge difference that makes, just the ability to not have to go to the library. Just search for articles and retrieve them. It's just terrific. That's had a huge impact for me.

COHEN: Well, when you look at where you are—let's start with professionally—how do you think you're doing in terms of meeting your goals?

WEIS: Basically fine. I mean, I have a secure job, and I'm doing basically the work I want to do. You know, I'm not naive. There are certainly the time pressures and a lot of aspects of it that are difficult. But basically I'm very happy with things. I think I'm pretty much where I would want to be. I'm in an institution I really like with colleagues I like. It's worked out well.

COHEN: How about in terms of your productivity?

WEIS: Well, I guess all of us are so driven, you always want to have more done. Stepping back, I'd say we've gone through, as always, cyclical up-and-down periods, but right now we're in a

very productive period. So it's been good. I'd say overall, integrated over whatever it is—six, seven years I guess—it's been fine. For our field, I think we've held our own in terms of productivity. It's neither high nor low, I guess—depends who you ask, I suppose. But I'm satisfied with that. We're making progress on things. We've had a couple of really hard problems, but we've gotten them done. So I don't think we've been grossly stalled on projects—you know, "Oh, god, this is going to take us far longer than I anticipated." Yeah, I'm pretty happy with it actually.

COHEN: Sometimes people talk about going down a blind alley where they'll start something and then somewhere along the line they realize that they're heading for a dead end. Has that happened to you?

WEIS: Not really. Again, it's partly the nature of what we do. We're not as hypothesis driven. So if not everything you're doing every day is hypothesis driven, then the chances of making the wrong hypothesis and going down a blind alley are lessened of course. Sure, we have ideas and we test them and they turn out to be wrong. But we move on. We haven't really taken what I feel is a bad turn that way.

I think in our field, what it is more is, "Did you pick the right problem?" I think that's where a lot of the sort of skill in structural biology is—knowing where the right problem is. Is there a problem that needs to be answered by structure? That's not always true. And that's something not everyone gets. I don't think all structures are equally interesting. Part of it is blind faith, this idea that you start from structure and then you get ideas about how things work.

What does happen sometimes is that you say, "Okay, I still don't know what's going on." It hasn't actually told you anything and you have invested time in it. That really hasn't happened to us, but I can imagine it happening, because a lot of it you do go on gut intuition; this seems like it's going to be really interesting and important and you hope it might. But you've got to face the reality: sometimes it's just not. But it depends on what motivates you. I mean, all structures are interesting from a purely aesthetic and structural point of view. But if you really try and understand a biological problem, as I said, they're not all created equal, and I think it's knowing which problems to pick. Having a good sense of it is what makes people in this field more or less interesting.

I'm sure we will make a mistake. I mean, some of the things we've done are less interesting than others, I'm sure. But I think we're doing a fairly large, complicated system where we have intermediate points along the road. Some of those intermediates might actually not be that interesting, but in the longer term we hope that we will be able to build ourselves up to something that really will give us some insight into how it works. So it varies.

COHEN: One of the things that you hear people talking about, although the scholars themselves don't talk about it because they're all doing pretty well, is how somebody takes a

wrong turn in something and then that's the end of their career. That, to me, sounds like a lot of pressure that one might have to face.

WEIS: Yeah, not being harsh, but it probably doesn't put enough blame on the person, because I think one of the things about being a successful researcher is knowing when to stop. That's as important as knowing where to start. Even when you have a successful project, you have to say, "Okay, I can study this in more and more detail, but what's the cost-benefit? How much more insight am I getting into the problem by tracking down every little detail?" That's something that everyone has to make their own decision about. I think the blind alley thing falls into that; it's recognizing that you're in one. I think the good scientists tend to realize that "This is not a good thing, and I'm going to cut my losses." Cutting your losses isn't necessarily an easy thing to do when you have invested manpower resources as well as financial resources into something, but that's just something you have to come to terms with. I really think that's an important skill that you hope people pick up as they go along.

COHEN: Now, the same question but on the personal side. When you look at your life and where you are in the more personal aspects of you life, how do you feel?

WEIS: Well, I think I'm surprised that I'm not more settled down in my personal life. I figured I would be, and that's been hard at times. It's, in some ways, tied up with the nature of the work. I went into this because I liked the idea that I had my own independence and freedom. My time, of course, is very precious. I think one of the aspects of working sort of the crazy hours we all work, at least as perceived from the outside, is that there's a real difference between working twelve or fourteen or sixteen hours a day when it's your own motivation versus someone telling you. There's an enormous difference there, and I am very happy with the idea that I am my own boss. It's largely a lifestyle choice: I just don't want to have a boss and be controlled. I work too many hours, I'm sure, but I find that notion very calming. I'm happy with the idea that I've been able to achieve this and just have that kind of life where I'm in control. The fact is, I can walk off and just sort of chill out for a while if I want to do so. Obviously there are external pressures on that limiting you. But fundamentally, I'm pretty damn lucky to be able to do that without having a boss to tell me I have to be some place at a particular time.

COHEN: You could work all night and sleep all day if you wanted.

WEIS: Sure, yeah. And I just prefer to work six or seven days a week and then just take time off. That, unfortunately, seems to happen less and less often over the years, but in principle, just that notion is very comforting—to know that, actually. I know that was a major motivation for me. I didn't want a job where I had to have a ten thousand dollar wardrobe of suits, and I'm very proud of the fact that I own one tie.

COHEN: One tie? [mutual laughter]

WEIS: Yeah, I'm very proud of this. No suits and one tie. There's definitely a lot of attraction in it just in terms of the work environment and just the freedom you have. That was very consciously, actually, an aspect of choosing this career for me in addition to just the basic interest in it of course. Having had some lousy nine-to-five jobs in college, I really know I would hate that at so many levels. So in terms of that aspect of my life, it's really great. I wouldn't want it any other way.

COHEN: Well, if you were to gaze into your crystal ball of the future, do you have any idea what kinds of things you might be doing, say, five years from now?

WEIS: I think some of the problems we've taken on we'll still be working on in five years. They're pretty long-term problems and we'll be continuing. I really want to study these systems down to a point [where] I'm really satisfied we understand them. And I hope this work on the receptor starts to take off and really get back to looking at how those work.

Beyond that, I hope I don't know. I kind of like the idea that there are twists and turns that I can't predict, like with ß-catenin getting into this whole interest in developmental signaling pathways and trying to look at these large assemblies and these signaling networks. I hope that keeps happening. There are things I can't even anticipate doing because that's what keeps it really fresh. Because on the one hand I really take a lot of satisfaction about studying something really deeply and in-depth, but I can imagine, also, that getting stale after a while. So I think that balance of having the kind of ongoing problem but also maybe running into some new things would be great. It remains to be seen.

COHEN: Well, there's no point in asking you about ten years then.

WEIS: No, because I'd give you the same answer. I mean, I know what I don't want is to be—I'll probably live to eat my words—one of these people who spends much more time doing administration and editing journals and sitting on corporate boards, which is certainly something a lot of people by the time they're fifty do. I would really hope that I'm still interested enough in doing the day-to-day science that it stays that way. I'm pretty sure about that part of it. I don't want to get disconnected from that, because it's the day-to-day stuff that's really interesting. As I said, maybe I'll live to eat my words. I hope not. [mutual laughter]

COHEN: You mentioned, I think it was yesterday, about getting more involved in the community later on in life. Is that a goal?

WEIS: Right. Yeah, that's something, as I was saying, as opposed to sitting on corporate boards—you know, when things are a little more settled— I really don't know what's going to happen, as I said. I don't have any good insight into what form that will take honestly. But I hope to be able to do something about that at some level, with science education and the like, because it just is important. But I must say, I haven't thought about it deeply enough to know what form that will take.

COHEN: Do you ever entertain thoughts about doing anything else?

WEIS: No, not really. Not in a serious way. I mean, I can imagine having serious time off to do— Actually, one of the nice things about this profession is you do get to travel a fair bit, which is nice. I've always enjoyed that. I'd love to just have more time to read just for pleasure and not work. But aside from just having more time to do that, in terms of a major career change, no, I can't imagine doing that.

COHEN: Well, one of the things that always sounded very appealing to me about the academic life—but then I have a great wanderlust—would be taking a sabbatical and going somewhere completely different for a year. Do you ever think about that?

WEIS: Oh, yeah, I can imagine doing that in fact. But right at this time in my life, sabbaticals would probably mean, hopefully in a nice place, being able to learn something new, going someplace different intellectually, obviously in the context of our work. I'm actually going to be eligible for one after another year, I think. So yeah, in that sense, definitely. But in the sort of longer term, would I ever drop this and just do something very different, like become a corporate CEO [chief executive officer]? There's no way I would do something like that.

COHEN: Or go to biotech[nology]?

WEIS: No, no, that's just not— I'm not saying it's a bad thing. It's not a moral judgment at all. It's just I know that's not for me. It's just not me. That I know.

COHEN: Well, one of my questions was, what would you do if you weren't a scientist [mutual laughter], but I don't know if you have an answer to that. Do you?

WEIS: Probably it would have been something that would give me the freedom that I have

now. It probably would have involved teaching in some form, I suspect, even though I don't teach a lot and, as I've said, I don't really have a desire to do a lot of teaching. But I think the general academic life, where you actually can keep learning your whole life and always be around people smarter than you, is really important to me. I probably would have wound up doing something like that—literature or philosophy or something along those lines—because I just know I would not want to just have a normal job. I mean, that I would hate. I do know that much.

COHEN: Well, you may have already said this, but I'll give you the opportunity in case you didn't: What is the thing you like the most about being a scientist?

WEIS: Probably the constant stimulation. It's hard and it forces you to really think every day and it keeps you young basically. You know, I like learning. I think that's it more than anything. There are certainly aspects of the sociology I don't like in terms of competition and the like. But I really like the general lab environment and the informality of the workplace; certainly, all that's very important to me. When it comes down to it though, it's really the work, just doing something challenging and different every day.

COHEN: And if you had to dredge up the thing you like the least, what would that be?

WEIS: I don't know. Probably dealing with things like the competition and some of the nonsense that you deal with, like study sections and grant reviews and stuff like that. As I said, I don't actually have a fundamental problem writing grants; I think that, in principle, is not a bad thing. But the practical aspects of how that works in this day and age I find very frustrating at times, even though I've been reasonably successful at it. I just find that aspect of it kind of annoying. And I certainly have enjoyed, even though it's disruptive, some of the aspects of the travel and just being able to get out and about; that's a nice aspect of it. Sort of comes under the whole freedom of just being able to move around.

COHEN: Well, I think I have just about run out of questions for you.

WEIS: Good, T'm out of answers. [mutual laughter]

COHEN: At this point T'd like to offer you the opportunity to—

WEIS: Retract everything? [mutual laughter]

COHEN: —add anything that you might like to add that we might not have covered.

WEIS: No, not really. T think it's fine.

COHEN: Well, thank you.

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