The American Association of Immunologists
Oral History Project

Transcript

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Williams: This is an interview for The American Association of Immunologists Centennial Oral History Project with Dr. Norman N. Eisen, who's professor emeritus at MIT.

Eisen: Herman N.

Williams: I'm sorry. Herman. I misread. My apologies.

We're at the 99th annual [ed. 96th annual] meeting of the AAI at the Sheraton Boston Hotel in Boston, Massachusetts. Today is Friday, May 4, 2012, and I'm Brien Williams.

Dr. Eisen, I thought I'd like to start by asking you a little bit about your family background.

Eisen: Okay. So I was born in 1918 in Brooklyn, New York, of parents who were immigrants from Eastern Europe. My grandfathers on both sides came from—one came from Lviv of what was then the Austro-Hungarian Empire, another one came from a city called Białystok, which was probably Poland or Lithuania, around there. They came in 1890. My parents were both children then, very young children.

I was born just as the World War I ended, when the flu epidemic was sweeping through the world. My mother had flu at that time and was left with a permanently damaged respiratory tract. She lived a long life, but it was a problem for her.

I went to public schools in Brooklyn. They were, by modern standards, I suppose, pretty good, but they didn't make much of an impression on me except for chemistry in high school, the only thing I remember about my early schooling, because that made such an impression on me.

Williams: How come? What was the . . .

Eisen: That there were atoms. That the world around me was made up of atoms and molecules. That seemed almost extraordinary. So I began to see things in terms that way.

Williams: Before we move on with you, what did your parents do?

Eisen: My father was in the garment industry, a small-scale manufacturer. I think he did well. My mother was a homemaker. She had four children, which in those days meant a pretty full-time, heavy-duty job. My father did very well during the 1920s, then came the [Great] Depression, and times were really very hard indeed, but we were never, I would say, in a state where food was a problem, so we survived it. Everybody around us was in the same state, so we didn't think of ourselves as being particularly impoverished.

Williams: So was part of your intrigue with chemistry due to the teacher or really just your own interest in the field?

Eisen: I can't answer that. It's probably both.

Williams: That was in high school?

Eisen: In high school.

Williams: So then what kind of a path did you take immediately after high school?

Eisen: Well, so in terms of career, I thought, "Well, I could be a chemist or a chemical engineer. Sounds like a reasonable thing." But you might have difficulty realizing it, but then there was a lot of bias against Jews in big industry, in universities, even quotas that were not spoken of. My father, who was completely unschooled, I think he had only one and a half years of schooling, was a voracious reader, had a library at home, actually, persuaded me that there wouldn't be jobs. I couldn't go very far in industry. I'd be better off in medicine, because in medicine you're kind of your own boss. [laughs] It didn't take too much persuasion for me to become a premed, although I was very young. I was in college before I was sixteen, which seems extraordinary now, but was not so extraordinary then. You were able to move ahead if you were a reasonably good student. I was really not a good student. I was really bored by the whole thing, but it must have come easily for me, so I graduated very early.

Williams: Explain your boredom. Were there other things that you were more interested in or just the whole idea of school?

Eisen: I was interested in sports, I read, but school didn't seem much of a challenge. It was not a real challenge.

Williams: So you decided to go to NYU [New York University].

Eisen: I went to NYU, and I went to part of NYU that no longer exists. It was up in the Bronx. It was called University Heights, and it was a very small special program they had. I guess you'd call it an honors program. It meant traveling an hour and a half each way every day from Brooklyn to there. I would say the education there was quite good.

Williams: Was it a science magnet school?

Eisen: No. It would amount to what we now call a liberal arts school, but I was interested in chemistry and in biology and in physics, and I could get plenty of that. Traveling seems like a big burden, but spending an hour and a half getting there and back, about an hour on the subway, you can do a lot of reading, a lot of

studying, so it really wasn't so bad. But then I developed tuberculosis about halfway through and had to take a year off. There was no treatment then except bed rest.

Williams: You didn't go to Lake Placid?

Eisen: No. I went there many years later for a different reason, but I stayed at home.

Williams: And you were just lucky that you beat it?

Eisen: Yes.

Williams: That had no long-term effect on you?

Eisen: Well, it had long-term effect in the sense that I had a very extensive impairment of my lung on one side, a lot of scarring. So functionally I've had one good lung.

Williams: Did you pursue sports at all?

Eisen: I was very interested. In fact, before I got sick, I was on the baseball team. I love baseball, played first base. I was a left-hander. [laughs]

Williams: But you had to give that up with TB?

Eisen: Yes. It was hard to give up.

Williams: So then did you have a break or did you go directly then into medical school?

Eisen: Then after that I went back to finish up and I went to medical school. Medical school was also a very good experience educationally, although I must say in many ways I learned more from my peers. It was a very good group of students. Getting into medical school was very competitive then as it is now, and so you really felt as though you were part of a specially chosen group.

Williams: Did you think of going elsewhere for medical school?

Eisen: No, because I'd had TB, I didn't even think of applying anywhere else except in New York. I was not accepted at Columbia [University] or Cornell [University]. Cornell I had no interest in, nor they in me. They didn't even interview me. But I was accepted at NYU.

Williams: Why couldn't you have had TB and be in Boston?

Eisen: I think because I was still at a stage where you couldn't really be exerted. You had to really be very—I lived at home while I went to medical school.

Williams: Just before we leave home, you mentioned three siblings.

Eisen: Yes.

Williams: What have they done?

Eisen: What did they do? Let's see. My oldest sister was a homemaker and a heavy cigarette smoker and died early. She's the oldest.

The next sister liked to write, became the editor of a small trade magazine, and then married one of the people she interviewed, a very successful businessman. She did a lot of designing, clothes designing, house designing. She's a very talented woman, and after he died, she began to lecture at a school called the Fashion Institute of Technology, FIT, in New York. It's a school that trains a lot of designers. It's quite a special school. She taught there until she was in her nineties. [laughs] She was a very charismatic teacher.

My brother became an accountant. During the war he was in the [U.S.] Signal Corps, and after that, he went into business with electronics in an electronics company.

Williams: Now, talk a little bit about being in school in the middle of World War II. What was that like?

Eisen: I started medical school in 1939. That's when Germany went into Poland, September 1st, 1939. So we were in medical school all during that time. We were enlisted in the Army of the U.S. That was without even a physical, all medical students were inducted into that. When it came time to be called up after graduation, I didn't pass the physical, and so I was stuck with doing medicine in New York, delivering babies.

But then I decided I would do pathology, so I went to Columbia PNS. That's the medical school of Columbia University. There I started to really have an opportunity to do some science, and I did. I did a few things. Then I went back to NYU as a resident, but at that time there was no real career path for science or a physician, except the role models for me were those few physicians who had practices of medicine where they earned a living and then worked in the laboratory or did research on the side. They were amateurs with a love for research. So that was a role model, I guess. So when I graduated, I went into practice. I had opened up an office close by NYU where I had a laboratory.

Williams: What kind of practice?

Eisen: Internal medicine at 37th Street and Park Avenue, very elegant address.

I think before I—I know what happened. This is really significant. When I finished my residency training, this was at the end of World War II now. It was in, say, '46 or '47. The government, the federal government, through the NIH [National Institutes of Health] had tried to expand support of research. I mean, during World War II, as we know now, research in scientific establishment was so important in winning the war, the experience everyone had with the development of radar, proximity fuzes, and finally the atom bomb.

We had made it obvious as a supporter of basic science it was really very important to national defense, and the experience at the medical end was also very prominent because in previous wars the deaths from disease were enormous, where they greatly exceeded the number of deaths from battle injury. But in World War II there was the benefit of immunizations against tetanus, for example. So whereas tetanus deaths were very common in the Civil War, they were unheard of in World War II because the vaccines were that good.

So the government expanded research not just in the physical sciences, but in biomedical stuff, and they started and I somehow qualified for one of the first NIH-supported fellowships, was called a senior research fellow. I don't know why. But it paid $3,600. If I had my calculator, I could convert that to present dollars. It wasn't bad. It might have been about fifty, seventy thousand dollars a year. So I had that kind of fellowship and I was able to publish a few things during that.

Williams: What was the focus of your research?

Eisen: It was immunology. Because I had this experience with TB, I was interested in immunology. I remember being very much influenced by the sulfonamides then used to treat infectious disease a lot, but one of the drawbacks to them was that people became allergic to them with some very severe allergic reactions every now and then. So I wanted to use the small molecules like that as antigen-like structures for studying antibody production, antibody formation. That was what I was doing.

Williams: You did that, it looks like, for about two years.

Eisen: Yes, sounds like about right.

Williams: Then you went into Sloan-Kettering [Cancer Center].

Eisen: Right. That fellowship ended. I went to Sloan-Kettering, which I didn't care for too much, but it was productive, able to get some work done.

Then the Standard Oil Company of New Jersey provided money to NYU Medical School to support work in immunology of the skin, and I was offered that grant. So I went from Sloan-Kettering back to NYU. The grant was $10,000 a year, was

supposed to be provide a stipend, support for the lab, and I was forced to work half-time and support myself and practice half-time. That's when I opened that office at 37th Street and Park Avenue. But the work in the lab was really what I liked, and practice I did not find intriguing, so I spent all my time in the lab and would get to the office five o'clock. Supposed to get there at three o'clock, get there at five, six. [laughs]

Williams: I'll bet you had a lot of happy patients.

Eisen: Well, it's good I didn't have that many patients, not for long. I didn't do very well.

Williams: You were a one-doc shop?

Eisen: Well, I rented space from another doctor's office.

Williams: What were you particularly looking at? I'm trying to work a connection between manufacture of oil and skin disease.

Eisen: So they had a lot of skin problems, a lot of contact dermatitis. One of the commonest skin diseases is contact dermatitis. You probably know it as poison ivy, right? Well, people get it from handling dry chemicals, cosmetics. It's a huge problem in manufacturing.

Williams: So did you have some breakthroughs in—

Eisen: Yes.

Williams: Tell me.

Eisen: Yes, I had some very interesting results studying immune reactions of the skin, including my own skin. I could do experiments on myself and on guinea pigs.

Williams: So tell me just a little bit about what these discoveries were.

Eisen: Well, one of my great heroes in science was Karl Landsteiner, who had discovered many years before that that you could take small molecules. I don't know how much chemistry you know.

Williams: We're doing this for the historical record.

Eisen: Take small molecules like aminobenzene and convert them to diazonium groups, couple them to proteins, forming what he called haptenated proteins. When those were injected into animals and see if they'd make antibodies not just against the protein, which was expected, but also against the small molecule. So he was able to open up to study of the immune specificity the whole library of small

molecules that were then known, and it became an intriguing way of sort of combining good, clean chemistry with good, interesting biology and immunology.

One of the things that Landsteiner did toward the end of his life was to start looking at these small molecules when they're applied to the skin, being able to elicit very specific allergic skin reactions, like poison ivy. He hypothesized that that worked because the chemicals that were active in that way were able to make chemical bonds with skin proteins. He couldn't prove that, but that was the speculation and it was consistent with all his experiments.

When I got interested in doing that work, there was a seminar at NYU given by a man named Fred Sanger from Cambridge, England. Sanger was one of the really greats who found a way to determine that protein chains, a protein, made with a series of amino acids linked together in alpha peptide bonds. He did that by using a small molecule that was very active, reacted very effectively with the free amino group at the end of a chain of amino acids.

So at this little seminar in a room not much larger than this, he was describing it for the Department of Biochemistry at the medical school, and I was there. He talked about how he was able to decipher the exact sequence of amino acids in the insulin chain, the protein chain that made up one of the subunits of the insulin molecule.

So I decided I was going to use his approach to try to learn about the chain of amino acids in antibodies, but the chemistry is interesting here. Sanger had tried to use a molecule called 2, 4-dinitrofluorobenzene. That's what he succeeded with in getting these in making these derivatives of the amino acids that allowed him to sequence the protein. Before that, he had many failures using a similar molecule. He used 2, 4-dinitrochlorobenzene, and that worked sometimes, but not well enough. But when he got to dinitrofluorobenzene, that worked well. So I decided I was going to use dinitrofluorobenzene, of course, but you couldn't buy that reagent. He had made it himself. Wasn't hard to make, but he made it.

So I synthesized it myself, too, and in the course of synthesizing it, I became exquisitely sensitive to it. I got a real rash, not unexpectedly. But then I became very interested in that. That was part of that whole—related to that study with the Standard Oil Company of New Jersey.

Williams: So in layman's terms, at the end of your work in this area, what benefit did their employees gain from your research?

Eisen: Well, one of the things I was able to show using Sanger's reagent was that, indeed, Landsteiner was correct. It was a reaction with chemicals, a chemical reaction with the skin, so you had it if you deal with a bunch of chemicals of unknown properties or of partially known properties, it would tell you what to avoid, what's the likely sensitizer, what's not. You could find out easily enough

by trial and error, painful and expensive error, but there was a way of also predicting. Now, Landsteiner's work would have made that possible, but I think what we did made it absolutely clear that's the way to go.

But part of that, incidentally, was that I would test these various molecules for their ability to bind to skin protein chemically and to act as sensitizers. It was a very good correlation. But for some reason, I would confirm some of the tests on myself. See, because I was sensitive to 2, 4-dinitrofluorobenzene, I could myself as a guinea pig and do the kind of patch test that dermatologists do. I didn't have to go through any review boards or any kinds of regulatory licensing processes; just went ahead and did it. [laughs]

Out of this came something pretty damn interesting. There was one chemical that I could react with, a 2, 4-dinitrobenzenesulfonic acid that wouldn't work on guinea pigs again. It wouldn't react. It wouldn't elicit a skin reaction on them, but it would on me. So, why?

Well, I worked out the mechanism for that. The difference was that it's a water-soluble material. People have sweat glands in their skin, and those water-soluble materials can enter through the sweat glands of human skin. Guinea pigs don't have sweat glands. So this water-soluble chemical wouldn't react with their skin.

Williams: Were you married at this point in your life?

Eisen: I'd just gotten married, yes.

Williams: Did your wife know that she was marrying a super guinea pig? [laughter]

Eisen: She was too busy herself. She was an intern in pediatrics.

So that was a human experimentation which you could do. Then exploiting that and using that as these 2, 4-dinitrobenzenes as a takeoff point, I was able to build a series of papers that were clearly quite respectable.

Williams: Your next career move was then, according to my records here, to—

Eisen: Well, I was working in New York, at NYU in that small lab, getting pretty interesting results, and moonlighting in my internal medicine practice on Park Avenue. One time my income tax return was audited by the IRS. [laughs] They probably couldn't believe I made so little money with an office on Park Avenue, and so they came down to interview me, and they were in my lab at NYU. The end result was the guy shook his head in disbelief. They didn't owe me any money, but I didn't owe them any either.

Williams: So then you went to St. Louis, is that right?

Eisen: Then unexpectedly I got a phone call from somebody named W. Barry Wood, who you probably never heard of, but he was the chairman of the Department of Medicine at Washington University in St. Louis. Wood was a very charismatic leader in academic medicine and a member of the board of the Rockefeller Foundation. He had been a superb athlete at Harvard and spectacularly successful as a young scientist in biomedical research, and at the age of thirty-two became head of the Department of Medicine, one of the biggest Departments of Medicine in the country, at Washington U. So he was the chairman there and a remarkable guy.

He called me on the phone day and said he was in New York, could he come and visit me, and he told me that he'd gotten the Rockefeller Foundation to endow a chair in dermatology as a division in the Department of Medicine, and would I be interested in moving.

Well, I did make the move, finally, and I didn't hesitate so much, because I was getting pretty exhausted trying to have two jobs, and this was a chance to really go all out and do the kind of scientific work I wanted, without having to be in private practice. So we moved to St. Louis.

Williams: Did this have an impact on your wife's career?

Eisen: Not seriously. We had at that point two children, so she was working sort of part-time. In St. Louis she continued to do that, and that was okay with her. In fact, she was delighted, because you know I was—the arrangement we had in New York would get me home at night, ten o'clock, or eleven o'clock at night, for dinner. It was no fun.

Williams: So you spent quite a few years at Washington U?

Eisen: Eighteen years altogether. I went there in medicine, and it was a time when medicine was quite different. I could be appointed as a dermatologist and chief professor of medicine at Washington U, dermatology chief at Barnes Hospital, and not have had a day's training in dermatology. It was done because there was such an emphasis on bringing science into medicine, on emphasizing research, and the federal dollars were there available for building up a scientific enterprise. Whether I qualified as being a clinician or not was almost beside the point, and there were good clinicians around, so I depended on them to run the service. It was a pretty happy service. They were glad to run the service and keep me. I didn't bother them. They didn't bother me. So that worked well for about five years.

Then the Department of Microbiology there moved en masse, practically, to Stanford [University]. I was on the search committee to look for a successor to the chairman of the Department of Microbiology, a very well-known scientist Arthur Kornberg, who won the Nobel Prize. So I was not a microbiologist, really,

but I was on the search committee, and I remember pushing a couple of people for the chair, but then it was offered to me and I took that. I was glad to move into a scientific department and leave clinical medicine behind me altogether.

Williams: Did taking that position result in you doing a lot less time in the lab or not?

Eisen: No, not for the beginning. I was able to spend a lot of time in the lab. It was a very small department, not like present-day departments. My lab was small but good. I was able to spend a lot of time on research. But then towards the end of that period then, I got unwillingly sort of caught up in administrative problems because Washington U and Barnes Hospital had a very close relationship, but like MGH [Massachusetts General Hospital] and Harvard [University], say, or the [Women's and] Brigham [Hospital] and Harvard. They're financially, in a sense, independent, but they're so intertwined, they couldn't exist without the other.

There was a new chairman of the board of trustees at Barnes Hospital, a man named Edgar Monsanto Queeny, who had the idea that the medical school was exploiting the hospital financially, and he created a real crisis. So it was in turmoil administratively for a while. I was a member of what was called the Executive Committee, because that's how the school operated, and I was going to meetings every week. It was not the thing I wanted to do, so I got a little bit tired of that.

Williams: So did that prompt your next career move?

Eisen: Yes. Well, it was interesting. My wife and kids wanted to get back east, my wife especially. St. Louis summers are notoriously hot, and we always arranged to spend a month in Woods Hole on Cape Cod. We ended up buying a house there, and I thought we'd retire there eventually. But around that time I was offered a job, two jobs, actually, one at Columbia Medical School as chairman of Microbiology there, and the other at MIT [Massachusetts Institute of Technology] in the Biology Department as just a professor of biology in the new Cancer Center that was being opened up with Sal Luria as the director.

So the job at Columbia was pretty interesting in a way. It was closer to Woods Hole, but also meant being the chairman of a medical school department, and Columbia was good. I liked Washington U better, but Columbia was fine. But then the folks at MIT said to me, "Don't make any precipitous moves. Wait. Things are going slowly at MIT." But they finally made me an offer. Well, I came to give a seminar and then they made me an offer.

Williams: So you came here in '73 and have been here ever since.

Eisen: Yes.

Williams: One thing you said a moment ago intrigued me. The move en masse from Washington U to Stanford, was that a very unusual event, or can you give me a little background on that?

Eisen: Yes. Kornberg, a terrific scientist, had discovered the enzyme that allows you to make DNA, and the physical conditions of his laboratory and office were pretty, I would say, pedestrian at best, and Stanford made him a pretty big offer, space, new building, all kinds of things. He had a very good small department. Actually, when I went to Washington U, my labs were not ready, but Kornberg gave me space in his lab, so it was a great experience for—I lived there for six months until my labs were opened up, were finished. So I knew him well.

But when he moved, it was with the whole department. It was a small department, and they were all very good. He had recruited them all, and they moved together. It was very unusual because the department was depleted. So when I was offered that job, it was a pretty big challenge, but I didn't really think about it very much. I sort of liked the idea of moving from a clinical to a preclinical department, and it was a fine move for me, it turned out.

Williams: Before I ask you to talk more about your MIT career, this might be a good point for me to ask you to reflect on the state of immunology from the time you entered the fields until now.

Eisen: Yes. Let me preface that a little bit by telling you one little anecdote, in a sense. I'm old enough to tell anecdotes. [laughs]

When Washington U offered me that job as chairman of Microbiology, it was essentially an empty department. To sweeten the whole deal, they said, "We'll send you on a recruiting tour, anywhere you want to go with your wife, to Europe to look for some good American postdocs who were working there." So I went to Paris to the Pasteur Institute. I had met Jacques Monod before that, so I knew folks there. Then I went to Cambridge, England, the MRC, which was a hotbed for great research in biochemistry and microbiology.

Fred Sanger was there. I told you I'd heard Fred Sanger's lecture years ago. So I met with Sanger and said, "You know, it's amazing to me to realize when you made the switch working with DNCB, which wasn't very effective, to DNFB, how did you know about that?"

So he said to me, "It was obvious, because I read Landsteiner's papers, which were all published in the *Journal of Experimental Medicine*." Now, that doesn't strike you maybe as very unusual, but he was a guy, Sanger, a terrific organic chemist, very successful chemist, reading the *Journal of Experimental Medicine* where Landsteiner published.

Science was small then. People talk about convergence now into disciplinary research and make a whole big commotion about it. Well, people did it then, too, because the field was so small. So a chemist reading biomedical literature and he picked up Landsteiner's work, and he saw Landsteiner had seen that DNFB was more reactive than DNCB with proteins. So that's it. That's how I was saying I got to DNFB.

Williams: There were probably fewer publications in those days too.

Eisen: Far fewer. A fraction of them. Immunological literature was limited to *The Journal of Immunology* and the *Journal of Experimental Medicine*. If you were very adventuresome, as I was, you also looked at the *Journal of the American Chemical Society*, but you didn't see immunology there, except rarely.

Williams: So what were the giant leaps over the period of your activity?

Eisen: Well, the biggest leap for me, and it was a blind alley, was Linus Pauling's work. Pauling was very interested in immunology, and he developed a very elegant elaboration of existing ideas but giving them great chemical fecundity because he was so brilliant chemically. But he was absolutely wrong in his basic ideas, it turned out. Nevertheless, he influenced me a lot.

One of the first things I had done when I was back at NYU, to give you an idea what immunology was like then, I was working in a biochemistry lab with this NIH-supported fellowship, and that was working on the sulfonamide drugs as sort of haptens which you could raise antibodies against them. A guy working the bench next to me, a man named Fred Karush, was studying the binding of detergents to serum albumin. He was interested in protein interactions using a technique called equilibrium dialysis.

Well, I got the idea that we could use that same technique to look at binding small molecules to antibodies, and so I teamed up with Fred Karush, and we did that. I mean, I raised the antibodies against some small molecules, phenylbenzene, arsanilic acid. Fred provided the dialysis bags. The technique was incredibly simple. We did dialysis. These first experiments were fantastic. They worked. We were able to measure the number of binding sites on the antibody molecule and the binding affinity in terms of good physical, chemical measurements, including constants in molar terms, and published that in the *Journal of the American Chemical Society* as a short note.

So Pauling, who was the Nobel Prize winner and a great leader in this whole field, sent us a letter of congratulations, but with a very curious twist. He said he was delighted to see our results, and I forget exactly how he put it, but he said he was so pleased to see us confirm his ideas. [laughs] Now, what's his idea he referred to? That an antibody molecule had two sites, two binding sites. That's what we found quantitatively. There'd been speculation before that, could have one site

per antibody, multiple sites? There're a lot of arcane reasons why people were debating it. We came up clearly with two, unambiguously with two. So that delighted Pauling, because that's what he had been saying.

But the literature was small. We knew only antibodies and how to make them in a sort of primitive way. It had only become firmly established a few years before that antibodies were proteins. Some people disputed the idea.

Williams: So part of this period of your career was in some very basic discoveries.

Eisen: Yes, you could say that.

Williams: Then, I would suppose, an increasing number of refinements and leading to more particular types of discoveries.

Eisen: I think, looking back, I could see the theme, being always interested in what's called antigen recognition, molecular recognition. That's what's always intrigued me about the immune system. How was this ability to recognize any foreign substance? What is the molecular basis for that recognition? So using small molecules was a very happy choice because you had something very tangible to which antibodies were directed against.

But as I've continued to work in the field, people have lost sight, lost interest in those small molecules. In fact, there was a very well-known paper by Charlie Janeway a few years ago, widely cited, which I've never forgiven him for, because he refers to the Landsteiner fallacy. He was dead wrong. It was not a fallacy. [laughs] He called it the Landsteiner fallacy. By that he meant Landsteiner was focused on chemical structures as the objects for the immune system to recognize, whereas it's really, according to Charlie Janeway, it's really infectious agents, bacteria and viruses and pathogens. Well, Charlie is right in a way, but Landsteiner was right in a more profound way, I think.

So antigen recognition is what's always driven me and still does. I'll tell you what's really odd about it. Immunologists don't know that. They think they know it, structures, antigens, antibodies, human receptors, T cell receptors recognize. They don't really. They really don't. [laughs] They think they do. They know in a very vague way.

See, as a whole, immunology has grown very effectively some of the best immunology using as antigens things I despise as antigens: red blood cells, chicken gammaglobulin, diphtheria toxin. These are big complex structures. You don't know what you're looking at. Antibodies are seeing little discrete patches on them. They're given a name: epitopes. But giving them a name doesn't mean you know what they are. It's very complicated. So I just published a paper, which I'm delighted by, on the epitopes that are recognized by the antibody-like receptor on T cells, or they're called the CD8 variety of T cells. They see small

peptides presented by a protein called the MHC proteins. I'm sure you heard about those from Bill Paul. Did you, do you think?

So MHC molecules present peptides. So the paper just published says how could MHC molecules bind so many different peptides? How many different peptides can it bind? It turns out this one small group in the MHC molecule can bind literally millions of different peptides, and the T cell receptors can see those receptors in a discriminating way, but they also see part of the MHC. They see a composite. The peptide part of it is clean chemically. The MHC container is vague, but critical. So even that it leaves open to question. But then that's about the molecules that are recognized by T cells, by CD8 T cells.

The other type of T cells that are important in the adaptive immune system are CD4 cells. They see larger peptides, not the short ones like CD8 T cells see. They see peptides twice as big or three times as big, and those are not very well defined at all. They're much harder to define. But then if you go to antibodies, they see proteins. They see patches on proteins. What those are are largely unknown. In fact, I would say I'm not satisfied any are known.

Williams: You're describing an approach to discovery of how things are and how they work. Have there been significant medical results in this science, or is it still in a period of just discovering how things work and what works on what?

Eisen: There have been practical spinoffs.

Williams: Many?

Eisen: Depends on what you mean by many, whether you mean many individual steps or many individual bucks, dollars—in terms of dollars, big dollars. [laughs] Conceptually I'd say the biggest conceptually spinoff for which I personally feel definitely responsible, though not everybody might agree, is in what's called the affinity maturation of antibodies.

Williams: Explain.

Eisen: When we first measured affinity of antibody, antibody affinity for molecules at NYU back in 1949, affinity was very low. When I got to Washington U and I measured them in a different way with different antibodies, they were extremely high. Then by doing it more systematically with a postdoc named Greg Siskind, we were able to show that antibodies on the average antibody molecule in serum changes progressively with time from low affinity, when they're first produced, and then the antibody molecules that populate the serum later on can be a hundred, a thousand, ten thousand times higher affinity.

So when all the antibodies that are now made for commercial purposes, especially monoclonal antibodies, and used as drugs are high-affinity antibodies. We knew

how you make high-affinity antibodies. You can't use too much antigen. You have to wait. You have to boost and so on. So then it all came out of the affinity measurements. Affinity maturation is a process by which antibodies in their first phase are rather ineffective, but then by going through progressive changes, which we never knew about, they end up by being selecting very high affinity and being very highly selective and able to work in very low concentrations. So they can be used for treating cancer, for treating rheumatoid arthritis, and so on. But it's the high-affinity molecules.

Williams: Does that progression occur naturally in the human body, or are you talking about an industrial production process?

Eisen: It occurs naturally, but you have to promote it.

Williams: So some of the medicines that are derived from all this research are promoters?

Eisen: They are derived by immunizing and then waiting till you get high-affinity antibodies produced. Nowadays you make monoclonal antibodies and use them as drugs, although sometimes just serum, purified antibodies, or the heterogeneous antibodies are used also in experimental work and diagnostic work. Most diagnostic works that's done in hospitals is based on immunological assays, antibody-based assays, high-affinity antibody-based assays also in diagnostic work. So high-affinity antibodies are pretty important.

Williams: What else would you have to say about your work in the period of time you've been at MIT?

Eisen: When I got to MIT, I sort of left the antibodies behind me, although let me make one other point about that. There are proteins called myeloma proteins. I don't know if you've heard of those. They're like forerunners to monoclonal antibodies. We were able to show using these small molecules—gave really convincing first evidence—that myeloma proteins are antibodies. We were able to take some of these dinitrophenyl compounds, for example, which we knew underwent what's called a spectral shift when they were bound. In the binding site of an antibody they change their physical properties so that when they absorb light, they change, the wavelength of light they absorb. I was able to exploit that to screen rapidly through a lot of myeloma proteins, human myeloma proteins. I could show that we found one that bound this small molecule and bound it precisely the way an antibody would. So that opened up the way in which people could show that myeloma proteins were now antibody molecules.

So we then took advantage of that and showed that you could immunize mice with an inbred strain with a myeloma protein that was made by one of these mice and make the mice resistant to the myeloma tumor. So that's why I ended up at MIT in the Cancer Center, because this seemed to be a way in which you could use basic immunology to develop a therapy for some kinds of cancer.

Indeed, people picked that up and used it for another form of B cell cancer. Myeloma tumors secrete a lot of the protein, the myeloma protein, but a precursor to the myeloma tumors or B cell lymphomas, they have the antibody in their surface, but they release very little. So if you take an antibody or myeloma protein from an animal and purify it and then reinject it back into them under with the right conditions using an adjuvant, you can raise antibodies, but you raise antibodies against that unique part of the myeloma protein where it differs from other molecules of the same type, against what's called the ideotype, the distinctive part.

That's what we did with the myeloma protein. Now, we knew it had bound anti-DNP. We took that, injected it to mice of the same strain from which the tumor had come, and when those mice had been then challenged with the tumor which would ordinarily grow in them, they rejected it. They rejected it presumably because they made an anti-ideotype response. So people did that with human B cells. They would make anti-ideotypes against the immunoglobulin from the tumor cells and treat people, and the treatment was very successful in some cases, expensive, but it worked in many cases, but not always, because it's not always you might get a good anti-ideotype response. And a company was formed. IDEC was formed by—and then merged with Biogen as Biogen Idec.

Williams: Was that one of the very first immunological responses to cancer?

Eisen: Probably not. It was the first clear-cut one with an antibody immunoglobulin, yes. Myeloma protein antibody, yes, absolutely. But I think when you ask the question you have, I think people had shown you could take tumors raised against a chemical carcinogen from one animal and use it to immunize others and make them resistant to the tumor. But they didn't know the mechanism.

Williams: So are you still an active scientist?

Eisen: Yes, but I'm a scientist who just operates without a lab now, which is the way a lot of science is going to be operating. I collaborate with colleagues who have functioning labs and postdocs and so on. I do a lot of computer work. I just do it at my desk. With the computer, I could do a lot of things.

Williams: So you're not in your lab coat much these days. [laughs]

Eisen: Not in a lab coat.

Williams: Let's talk a little bit about the American Association of Immunologists. You joined in 1951, which was sixty-one years ago. What was the organization like at that time?

Eisen: Well, the first meeting I'd been to, though, was a couple years before that. It was very small, as I said, I think about 250 members. They would meet in Atlantic City once a year, one room, one session. We'd go on for a couple of days, but always in the same room. I remember some of the folks who were there. They're no longer alive, of course. Once I started going in '49, I went faithfully every year for maybe twenty, thirty years.

Williams: Why Atlantic City?

Eisen: That's where the Federation met, the Federation of American Societies for Experimental Biology. They all met. The biochemists, the physiologists, the anatomists, the immunologists, the pharmacologists, each of those societies met jointly.

Williams: Jointly but in separate sessions?

Eisen: Separate sessions, and then there'd be an occasional overlapping session. But you could go to one to the other if you were interested, if you wanted to go to something in biochemistry or pharmacology or immunology.

Williams: Were these well attended by West Coast folks?

Eisen: Oh, couldn't have been very many. I remember there were some, yes. Dan Campbell would come from Pasadena. There's a guy whose name I don't remember from Seattle. Yes, people came from California, Chicago, Midwest, St. Louis.

Williams: So at one point you served as secretary/treasurer, is that correct?

Eisen: I was president. I don't think I was ever secretary/treasurer. I was a councilor, so called.

Williams: What did that entail?

Eisen: Nothing. [laughs] Literally or virtually nothing.

Williams: Was there a mission on paper?

Eisen: Probably. It was pretty damn informal. The council met at the time of the meeting, one meeting a year. The only business on hand was *The Journal of Immunology*. It was run by the editor out of his back pocket, a guy named—he was at Cornell Medical School. He was the editor many, many years.

Williams: Was the journal highly respected?

Eisen: Yes, very well. Small.

Williams: Peer-reviewed and all?

Eisen: Peer-reviewed, well respected. The finances were such that it could be dealt with an hour or two. If they took in enough money, the publisher paid them whatever they paid them.

Williams: You were president in ’68-’69. At that point were there quite a number of other organizations that you felt as a responsible member of the profession to be a member of?

Eisen: The only other thing was there was something called the American Society for Clinical Investigation, young Turks, they called them. That was sort of the very elite group of academic young biomedical researchers. So getting elected to that was a very big deal.

Williams: Does that still exist?

Eisen: I guess so. I don’t know. I’ve lost touch with it. I think when you passed forty or forty-five you became emeritus for that, and you could get elected to the American Association of Physicians, which I got elected to, but I don’t think I ever went to a meeting. But I was vice president of the young Turks.

Williams: You were?

Eisen: Yes. I went to those meetings. They also met in Atlantic City.

Williams: At the same time? Maybe not.

Eisen: I’m not sure, you know.

Williams: Describe your year of presidency. Were there some issues you dealt with, or was it just honorific?

Eisen: Honorific.

Williams: Really?

Eisen: Yes, honorific. I think there’s no issues I remember dealing with specifically. We elected people who were nominated, some of them. The journal ran itself. I made a speech as the president, but I never published it, although I could have published it in a peer-review sense, but I didn’t bother.

Some years later, there was a presidential symposium organized by a later president and previous presidents gave talks, and I did, and so I went back to give a talk, and I did. I really gave a talk of what I was doing at MIT, and it was really

good. The stuff was great. At this point, I was growing out of my amateur status. You see, I'm really an amateur scientist. I've had no training, no mentor, but I've gotten to be pretty professional, I must say.

Williams: Your speech that year was about your science?

Eisen: Yes. So I thought I would give *The Journal of Immunology* a break and submit it there. So it got peer-review and it got trashed. [laughs] But the reviews were so bad that I had no respect for the reviewers, and I wouldn't answer them, and I published in the *Proceedings of the National Academy of Science*. [laughs]

Williams: Was there any legitimacy to their objections?

Eisen: Stupidity. They didn't understand it.

Williams: That's quite an episode. Sixty-eight, '69, that would have been the Great Society, [Lyndon B.] Johnson.

Eisen: You mean the world at large then?

Williams: Right. What impact on the study of immunology, and then with [Richard M.] Nixon and the War on Cancer coming just a few years later?

Eisen: Right, '68-'69. See, after World War II, the government, the federal government, the establishment, were so impressed, for good reasons, about the importance of science for national defenses that they continued to support biomedical research very well. Not only that, the armed forces also had a series of commissions called the Armed Forces Epidemiological Board, because infectious diseases had been such a big problem for the military over the years. So I was on the Armed Forces Epidemiological Board and on the Commission of Immunization. And you got a grant out of that to entice you to be on that. You got a small grant by just writing a one-page request. I was on that, and it was a one-day meeting. It was usually pretty good, pretty interesting. But then they asked me to be chairman of it, and that I didn't want to be. I didn't want to do administrative things, I didn't want that responsibility, so I didn't do it.

At that point, '68, '69, the military was coming under a lot of criticism because the Vietnam War is on. There was a tremendous amount of social unrest in the sixties. I became very embarrassed by being on the Armed Forces Epidemiological Board, although what they were doing, you couldn't really object to, because they were concerned about tropical diseases and rightly so, but I think I must have not renewed my membership in that and left it. But there was a lot of civil rest about all that, and that was one of the reasons why I wanted to get out of the medical school.

Because also when I started to teach immunology at Washington U in '55, in the late fifties, I could teach immunology the way I wanted to. I could teach hapten binding to antibodies. Even though immunology was taught in two weeks, I could teach it the way I wanted to. It was what interested me. I could teach the Scatchard equation and the medical students would sit quietly through it, absorb it, and not complain. But you got to the sixties, they didn't want to hear this basic science. They wanted to hear more translationally important, clinically important stuff. There was a rebellion against too much science in medical education. They were polite with me, but they were not so polite with some of my young colleagues who tried to talk to them about molecular genetics, microbial disease.

Williams: Now, these were students who were focused on becoming clinicians. Did that same period of unrest have an impact on immunology students? Were they demanding things differently or—

Eisen: I don't think so. There weren't very many immunology graduate students. When I was at Washington Medical School, I think I may have had only a couple.

Williams: So I'm asking you to talk about some of the big changes in the field over the period of your time.

Eisen: Oh, it's enormous. I mean, there are now virtual Departments of Immunology with many graduate students, although not at MIT. MIT has never had departments. It's only one Biology Department, thankfully.

Williams: Why is that so?

Eisen: Well, you avoid all those turf battles and the warlord conflicts.

Williams: So talk for a moment about the growth of the field and the number of people.

Eisen: In immunology?

Williams: Yes.

Eisen: Well, the growth had been obviously explosive, from meeting one meeting once a year with 50 people, you could hear all the current immunology to it's now, how many come, 5,000, 10,000, I don't know, 7,000 people come to the meeting? That's been proven in all the other fields too.

I recently visited the websites of some of my colleagues at MIT who have these very elaborate websites. However, there's a lot of PR now in science that didn't exist at every level, and the websites list their interests. There are about a dozen people who say they are doing immunology. Everybody wants to do some immunology, protein chemists, geneticists, because as some whiff of being politically or medically significant doing translational medicine if they're doing

immunology. So many people are doing immunology because it's only tangentially related to what their interests really are, but that's okay because a lot of immunology has benefited from those tangential interactions.

Williams: There's also been a proliferation of departments around the country, right?

Eisen: Proliferation of different departments, which I've always opposed to, incidentally. I don't like Departments of Immunology. I think they get too inbred. Immunology has always flourished best by having new ideas of instrumentation come out from the periphery. What immunology has really benefited from all the time is the changes in technology, and hardly any of those and most of those were not started originally in immunology.

Williams: Give me a couple of examples of what you're talking about.

Eisen: Spectral photometry; immunofluorescence; chromatography; immunoassay analysis; genomics.

Williams: What do they have in common?

Eisen: Immunologists now use them to answer immunological questions, but the tools are coming from all over.

Williams: What input does the scientific community have on the technological industry?

Eisen: Immunology and the rest of biology and biomedical community, not just academic but industrial, has benefited enormously from immunology because immunological reagents and analytical procedures have penetrated to every part of biomedical enterprise. Diagnostic laboratories and hospitals use immunological assays all the time, antibody-based assays, for the most part, affinity-matured antibodies.

Williams: So in summing up, what do you consider your greatest achievements?

Eisen: Well, I'd say affinity maturation, making that clear, unambiguous, and definite so that it's accepted now as one of the standard ideas, I think came from that set of experiments done at Washington U with Greg Siskind and Lisa Steiner.

Williams: What about disappointments or dead ends over your career?

Eisen: Disappointments. I think my biggest disappointment was that I didn't pursue the genetic aspects, molecular genetic aspects of immunology, but instead always dealt with the protein side, which has been rewarding and I've been able to do it in a way that I always felt rewarded by, but I think I missed becoming really fluent in molecular genetics, being able to manipulate molecular genetics.

Williams: If you had it to do over again, would you do your career much as you have done it?

Eisen: No.

Williams: What would you do differently?

Eisen: I would have gone to graduate school, not medical school.

Williams: And how would that have advantaged you?

Eisen: Oh, I don't know. I think I would have gotten to live the kind of intellectual life that I enjoy, sooner, without a lot of distractions. The medicine is interesting. I must say my wife is a pediatrician, retired now, but I've always enjoyed seeing medicine as an outsider and following it, but I enjoy science more. I enjoy science. The kind of science I enjoy is dispelling ambiguities. I can't stand ambiguity. Getting insight to a problem can be pretty rewarding.

Williams: Has there ever been political influences on your work?

Eisen: Have there been political? No, not directly. On people I know, there have been. Elvin Kabat, who is an older colleague of mine and one of my heroes in immunology, couldn't get an NIH grant in the 1950s in the [Senator Joseph] McCarthy period because he got somehow tainted as being a communist, which was not true. He probably was a leftist of sorts in an unthinking way, but he was never a—[laughs] he was too self-centered to be communist or anything else. [laughs] A very selfish, self-centered—[laughs] but brilliant. But the Office of Naval Research supported him, so he was never short of money.

But, myself, I was never impacted by that in any way.

Williams: What would you say in general terms about the state of science in the United States today?

Eisen: Well, it's enormously productive. It's carried out in a way that is entirely foreign to the way I was able to operate. I was a coauthor on a paper recently with nineteen other people, so that if you look at the authorships of papers, you start out, you're the only author or there's two authors, maybe three. Now ten, nine, ten, fifteen, twenty. A paper I looked at the other day had thirty authors. It's becoming like particle physics, high-energy physics, which is almost necessary. But today the papers are more full of content. There's so much in them, they have to draw on a lot of people with a lot of different expertise to put it all together.

Williams: So that would suggest a high degree of collaboration.

Eisen: Yes, but collaboration in a curious way. You don't even know who your collaborators are, for the most part, most of them. This paper I was on, the lead author, who's like an orchestra conductor, Michel Nussenzweig at Rockefeller. He got me involved in it because he wanted something. He wanted to know if something was okay, basically, make suggestions about some experiments, but basically he was uncertain about some critical part of the paper, and I was able to clarify that and reassure him and suggest ways of validating it—pretty small contribution, I must say. But I know Michel very well. I'd only met him a couple times, maybe, but talked on the phone a lot. Email messages were flying back and forth for months. But other people on the paper I don't know; I never met them. So it was a curious kind of collaboration.

Williams: There's a lot of talk these days about the poor performance of American students pre-college in math and sciences, and the assumption being that we're becoming more dependent on foreign students and foreign practitioners, even. Do you agree with that and do you see that as a problem? Talk a little bit about that.

Eisen: It's true, I think. I think it's absolutely true. I agree with that general sentiment and it fits in with my experience. First of all, let me say, in general, immunologists are not happy with math, I mean with physical science, aspects of immunology. Immunology is a field, when I started, it was really pretty clearly divided into immunochemists with whom I identified, and sort of the cell biological immunologists, who have now become the dominant field so that immunochemistry no longer even exists as a term. It's a term that's even forgotten. But I think of myself still as an immunochemist. But in terms of immunologists, and American immunologists especially, see themselves, their work is very descriptive, phenomenological, and very interesting, thoughtful, penetrating, original in many ways, but not rigorous in the sense that a physicist would talk about rigor.

This most recent paper that I published, I buried the mathematics in it because I know that if you have equations in a paper, I've heard this before in general, that the cliché is that for every equation, you lose half the readership, which is true. Maybe not 50 percent, maybe it's10 percent, could be 90 percent, I don't know. People are put off by that. They don't like equations, especially several equations.

Williams: So are we likely to become more dependent on students from overseas?

Eisen: Well, you never know. No, not necessarily. Well, that's true to some extent. My most recent experience, the other graduates I've worked with at MIT who have been very good and very strong and better than I am in handling the physical science aspect and the mathematics of it are Chinese or Indian. They are clearly terrific at it. But I wouldn't want to jump to conclusions so much. One of my precursors at Washington U, Al Hershey, a Midwestern American, was a brilliant

science and mathematician. Al Hershey was terrific. So there are some guys out there in Indiana and Illinois.

Williams: I'd be curious of your observations about the NIH in the overall landscape, and since you, other than grants, probably quite a few grants, actually—

Eisen: They supported me very lavishly, I would say, up until I was about eighty-five. I had to retire officially at MIT at seventy, so I've been officially retired for the last twenty-three years, but I had grants until eighty-five. Now I don't have any grants anymore, so I live off of my colleagues' grants.

Williams: But you resisted the allure of going to Bethesda [Maryland]?

Eisen: Yes.

Williams: Why?

Eisen: They wanted to recruit me when Jules Freund died. Do you know Jules Freund's name? He's a friend who had multiple myeloma. Did you know that? He died of multiple myeloma. When he died, the NIH approached me about taking on that job, but I was then, I think, at Washington U and I was satisfied there and I didn't want to leave. But Benacerraf took that job and did very well with it.

Williams: What advice do you give to trainees that are considering a career in immunology?

Eisen: You know, no one has seriously asked me that question recently, so I haven't thought about it, but you're asking it, and I think it deserves a serious answer. What advice would I give? I would say do a postdoc in immunology, not a Ph.D. in immunology.

Williams: Why would you make that suggestion?

Eisen: Because I think immunology provides a limited framework for thinking about science. I think if you are well trained in other fields, chemistry, physics, computer science, mathematics, applied mathematics especially, you can then bring something to immunology that's potentially very useful. I think you've got to be in immunological training as a postdoc and learn what you have to do then, but not as a graduate student. That would be iconoclastic. That shouldn't get out. It's just between us. [laughs]

Williams: I want to ask you to be self-reflective here for a moment. How has your mind as a scientific mind worked? Have you gone a lot of intuition, more craftsmanship? Someone described to me the fox versus the hedgehog.

Eisen: The hedgehog and the fox? [laughs]

Williams: Yes.

Eisen: Well, looking back, I think people would say that I'm more of a hedgehog, but actually I feel myself more of a fox. [laughs]

Williams: So explain yourself.

Eisen: Well, I think when I pick up a journal, there's a lot of things I like to read. I don't just zero in on my immediate interest. I have a lot of interests in browsing through. That's one of the reasons I don't like very specialized technical journals. I like journals that are more broad-based, or I like *Nature*, *Science*, *PNAS*, *PLOS*. *The Journal of Immunology* is too limited.

Williams: That leads to one of my very last questions here, and that is I'm curious about outside pursuits. Do you have an interest in music?

Eisen: No. I wish I did. I have a big interest in gardening. I used to be very active in tennis. That was years ago. Gardening, and I'm a big reader.

Williams: Are we leaving something important unsaid today? I know you came with some notes and whatnot.

Eisen: Yes, I think I do. That's a very good question. Yes, I think that the way science is practiced now is very impressive in one way, in that it's technically very effective. Information and insights are being generated at a faster pace than ever before, but it's also characterized by a lot of hype and public relations aspects that I find distasteful. Every organization has to have a more glitzy and fancy brochure advertising its wares so it can compete with its peers and compete for money.

When I started in science, this was just immediately as World War II was ending, but I was working part-time in a laboratory with Michael Heidelberger who was one of my great heroes and whose biographical memoir I wrote recently. You might want to look at that memoir. Michael Heidelberger was a very productive scientist, and he was supported by a philanthropic organization, the Hawkins Foundation, all his life. He never had to apply for a grant, worked private philanthropy-supported research, a little bit of industrial grants maybe here and there. NIH did practically nothing. Department of Agriculture, nothing. Department of Defense, maybe Aberdeen [Proving Grounds] supported ballistics research.

Then came all this explosion of support from the government after World War II, for very good reason, and now it's drying up. That support is drying up. The amount of money is still very large, enormous, but the pool of people competing for it has grown enormously. People unwisely but inescapably thought they could grow exponentially. Nothing grows exponentially. You can't have every

scientist training ten more scientists and each one of them ten more. You get to the point where you have too many scientists. In a way now, we're training too many people. We're certainly training too many people for the amount of resources available.

So we're going to go through a very painful period of contraction, and private philanthropy is going to become more and more important. That's why the public relations aspects of science are becoming more and more important, and I find that distasteful but inescapable, this cumbersome competition for money. I find my younger colleagues spending enormous amounts of time and energy applying for grants over and over again, many of them.

I didn't have that problem. I had to apply for grants, but it was a trivial matter. I'll give you one example. When I was at Washington U, I became chairman of the Department of Microbiology. The school gave us a budget. The budget was big enough to cover my salary completely, my secretary's salary, and the janitor's salary, and a little bit more for teaching. So when I started to recruit people in order to populate the department, to hire young faculty members, I expected them to get 50 percent or three-quarters of their salary from grants, and the rest we would supply. I said I should do the same thing. If I expect that of them, I should do the same thing. So I refused to take a salary, my complete salary, from Washington U. I said I'd take only 50 percent. I'll get the rest from my grant. I wasn't being noble. It was easy to do, and it set a good example. You'd be crazy to do that these days. [laughs] So I think the sciences can be great, but the conditions for doing science, I think, will be getting worse.

Williams: At Washington when you presented a grant, you were getting grants because you were applying for the grant, or did they rigorously review your proposal?

Eisen: There was peer review, the study section. In fact, I was chairman of the study section of the NIH for four years and honors study section for eight years. Yes, we used to review. Yes, it's peer-reviewed.

Williams: So the application was rigorous.

Eisen: The process was rigorous, although the bar was set not very high. In other words, they would approve maybe 30 percent of the grants, 25 percent of the grants.

Williams: What's the percentage today, do you imagine?

Eisen: Five percent. My daughter's applying. One of my daughter's is a professor at [University of California] Berkeley. A recent grant application, she was in the 2 percentile. That means she was in the upper 2 percent. I've got to ask. She's visiting now. I'm sure she got funded, but she was not sure if she was going to get funded. I think it must be about 10 percent, maybe.

Williams: So your legacy is being carried on by members of the family?

Eisen: Some of them.

Williams: Tell me.

Eisen: Well, my daughter is a professor of biostatistics in Berkeley, one daughter. The other daughter is a professor of psychiatry. I have two sons who are physicians, black sheep. [laughs] The one who's the real black sheep is the lawyer, a rich lawyer. [laughs] I have a grandson who's not going to go to graduate school.

Williams: You've done well.

Eisen: He wants to go to graduate school.

Williams: Great. Listen, if there's nothing else to say today, thank you very much for this opportunity to talk.

[End of interview]