The American Association of Immunologists
Oral History Project

Transcript

Dan R. Littman, M.D., Ph.D.
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Interview conducted by
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Williams: This is an interview with Dr. Dan R. Littman for the American Association of Immunologists (AAI) Oral History Project. Dr. Littman is the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Department of Pathology and Microbiology at the Skirball Institute of Biomolecular Medicine of New York University (NYU) School of Medicine. He is also Coordinator of the Molecular Pathogenesis Program at the Skirball Institute and a Howard Hughes Medical Institute (HHMI) Investigator.

Dr. Littman was the President of the American Association of Immunologists from 2015 to 2016, and he was awarded the AAI Meritorious Career Award in 2010. We are at IMMUNOLOGY 2017™ in Washington, D.C. Today is Saturday, May 13th [2017], and I am Brien Williams.

Dr. Littman, I'd like us to start with you telling me a little bit about your background, your family background. You go back as far as you want.

Littman: As far as I want. Okay. Well, I was born in Bucharest, Romania, in 1952, and that was a difficult time there postwar after Romania had fallen into the Soviet camp. My father had been trained as a physician, my mom was working in publishing early on as an editor, but they had been very fortunate to survive the war because they were in the southern part of Romania where Jewish citizens weren't deported. At least the war ran out before they could be deported, fortunately.

So it was in that climate that I was born during the Soviet times, and growing up as a kid there, I was exposed to what the Soviet kind of news wanted us to know about. And, of course, Sputnik in 1957 was a huge event for me as a five-year-old child, but I developed an early interest in science. I think in some parts it was fueled by the space race that was really brewing up during the 1950s. Growing up in Bucharest, I used to ask my parents to take me out, for example, to see anything that had any technological aspect to it. I used to ask my mother to take me to the train station so I could watch locomotives, steam locomotives, and I could sit there for hours and just *[laughs]* watch the locomotives and ask her why does it do this, why does it do that, you know. Not that she could answer it. So I had an early interest in how things worked, more mechanically than anything else.

Funny enough, we had the opportunity finally to emigrate in 1963, and we went through Rome for six months and then decided to move to the United States. But I had never really heard about any universities in the United States except for Princeton University, and that's because [Albert] Einstein had been at Princeton, not necessarily at the university, he was at the Institute for Advanced Study there, but I didn't know that. I'd never heard of Harvard or Yale or Stanford or any place like that. So from very early on, I sort of had my mind set on wanting to go to Princeton and wanting to do aerospace engineering. I was really interested in the engineering sciences in general, and I was interested in math and physics as a kid. So that's what I really kind of headed towards as we arrived in this country.

We lived initially in Providence, Rhode Island, for a couple of years and then outside Philadelphia before I went to college. So when I finally got the opportunity to apply for colleges, I was fortunate to get into Princeton into the engineering program and began to study aerospace engineering, and it was really during that period that I realized what I really wanted to do during the subsequent couple of years. Very early on, I realized that engineering was a little too constricting for me as a discipline. A lot of that, I think, had to do with the kinds of people that I met when I went to college who were in many different areas, in the humanities, in the natural sciences, and I decided within the first year, actually, to switch out of engineering into a bachelor of arts program, which eventually led me into biology.

Williams: So I want to pick up on that, but just go back for a moment. Was it difficult for your family to get out of Romania?

Littman: It was not easy. They tried multiple times. My relatives, my grandparents on my father's side, emigrated to Israel in 1949, along with one of my father's sisters and her family, and then in the 1950s they tried to obtain visas to be able to leave the country several times. Each time that happened, my father was basically fired from the hospital job that he had. He was working as an internist in infectious diseases in Romania, and he had to hop from one hospital to another because he would be fired whenever that happened.

Finally in 1962 at some point, the Romanian government used to allow emigration, particularly of Jewish citizens whenever it was politically convenient, and there was a window that appeared in 1962 and somehow we were able to get a visa. It involved payment from my grandparents through an intermediary in London through a semi-official kind of channel for my parents and my brother and I to be able to leave the country. So it was a long, protracted period. It was difficult.

Williams: And did your father have—did he lay plans for working in this country after he got here or before?

Littman: Well, he applied. He wanted to continue being a physician, of course. Coming to this country requires going through the exam system and then going again through training and internship and residency, and he did that. He passed the exam, the ECFMG [Educational Commission for Foreign Medical Graduates] exam, while we were for six months in Italy, in Rome, waiting for approval from the U.S. for the immigration.

We came to this country through an agency called HIAS, the Hebrew Immigrant Aid Society, which is a really phenomenal group of people who were very much involved in helping, initially, Jewish immigration, starting I think probably in the 1960s or maybe late fifties. Eventually it became an agency that helped people of

many origins, probably even Muslims like Syrian émigrés who need to escape the horror that goes on in their country. So it's a really wonderful organization, and they helped us initially to settle in Providence because we came here essentially with no assets whatsoever.

Williams: Tricky. Just while you mentioned your brother, tell me just a little bit about him. What was his career path?

Littman: My brother's five years younger than me. He became a physician here. He actually still, even though he's younger than me, felt a real affinity to the country where we came from, and when he was in college, he read that there were children of Romanian emigrants who were going to medical school in Romania, so he decided to drop out after two years in college and applied to go to medical school in Bucharest, and did six years of medical school in Bucharest in the late 1970s, early eighties. Came back to the U.S., did a typical residency, and became a general internist, and he's been working in the Philadelphia area since then.

Williams: Interesting. Bucharest really had a hold on him.

Littman: It did. I guess he was much more interested in pursuing a career path early on. I was not at all sure what I really wanted to do. I wanted to explore things, and, like I said, I started out thinking about designing rockets and then moved on from there until I finally found what I really liked doing.

Williams: So talk a little bit more about that process of focusing your interest into a certain area.

Littman: I think after I decided that engineering was too narrow for me, I wasn't quite sure what I really wanted to do. I did a lot of reading over the summer, I love chemistry, and I was very good at math and physics when I was young, or so I thought. When I went to Princeton, I realized that there was nothing exceptional about my abilities in math and physics. There were people there who were really absolutely brilliant doing that kind of work and working at conceptual levels that I could not even approach, and it wasn't something that really bothered me that much. I was just looking for what I would like doing.

I just happened upon reading some biochemistry books and biology books because I hadn't studied any biology when I was in K through twelve, for reasons I don't really understand, but I was never really exposed to that. And I used to work as a lifeguard in Philadelphia during the summers in high school and then after my first year in college, and during that time I picked up a couple of books, including Jim [James D.] Watson's *Molecular Biology of the Gene*, which was in its first edition, and I also read his book *The Double Helix*, and I really latched on to it. I remember to this day seeing for the first time in the book electron micrographs of DNA and DNA replicating, and the whole idea that you could see the entire—you know, the information of life visually at the molecular level

through a microscope, that really, in a way, just blew my mind. [laughs] So I became very interested in how the process works, and I began to take biology courses at Princeton, and biochemistry, and I realized that I really loved it. So I felt fairly well set in that direction after my sophomore year.

Then something really wonderful happened, which was that—well, two things happened. At Princeton during your junior year, you're encouraged to find an advisor to do a thesis, and at that time there was a young new faculty hire at Princeton whose name is Marc Kirschner, who's now a very well-known scientist up at Harvard University, at Harvard Medical School. Marc had just arrived there, just was opening his lab, and somebody recommended him to me that I should go and talk to him. So I did so, and he got me very excited about some biological problems he was working on, which were very much cell biological problems of how the long, polymerized molecules that are involved in cell division and in cell migration, the so-called microtubules, how they are assembled and disassembled, how they polymerize and how they depolymerize.

So I decided to start working in his laboratory and perform some biophysical studies to try to understand the nature of microtubule assembly, and that involved a combination of biochemistry and biophysics. It was really a lot of fun. There was some mathematics involved in studying the properties of polymerization of the microtubules.

But then around the same time in my junior year, Princeton put on a course in immunology, and there was very little immunology being taught at any universities at that time in the early 1970s, but it was a time when there was a lot of excitement occurring because some new tools had become available to begin opening up the field. The whole idea of how adaptive immunity works and how is it possible for our immune system to recognize so many different types of threats, so many different kinds of microbial antigens, that's something that had been a question for some time, but it became possible in the early 1970s to begin to dissect that at a molecular level.

Because Princeton didn't have any immunologists, one of the virologists there, Arnie [Arnold J.] Levine, organized a course with a friend of his who was at the University of Pennsylvania, Norman Klinman. Norman was an immunologist and he basically enlisted about twenty of the top immunologists working in the field in the world at that time. So they each came and gave one or two lectures, and I just sat through that course and I was just totally captivated. It was really an inspirational time for me, and after that, I thought, "Boy, this is an area I really could see myself wanting to work in."

Williams: That's so interesting that you really were in the first cusp of immunology. I mean, Watson's book had just come out and so on and so forth. How dependent in those early development days was the science on technology? What's—

Littman: Well, the science is always dependent on technology, and at the time, the technology was fairly primitive, but what happened just during the next one to two years was a time when molecular biology and cloning came to the fore. It was really the time when Paul Berg at Stanford and a few other people who had discovered so-called restriction endonucleases that allow cutting of DNA at very precise locations, allowed these to now be cloned into bacterial plasmids so that one could propagate DNA of one's choice.

The technology that was developing in the early 1970s allowed for characterization of sequences that were identical to each other or complementary to each other through so-called hybridization approaches so that one could now detect changes in the DNA of the cell by looking at hybridization after cutting with the appropriate types of restriction enzymes. So that was the key technology that developed at that time, and that's what allowed then Susumu Tonegawa, who was at the time in Basel in Switzerland, to for the first time show that when an antibody-producing cell acquires the ability to make one particular antibody, which it was known at that time that each cell, each B lymphocyte makes a particular antibody, what he found was that there's a rearrangement of the DNA that makes that particular antibody.

So this was really a huge advance at the time. When I was taking this course, we didn't really know this. It was one of the hypotheses, but within I think a year or year and a half after that, I think it was 1974, '75, he published a paper showing that there is the arrangement in the somatic B lymphocytes of the segments that eventually were shown to be variable regions, basically becoming approximated to the constant region, which then can be read by the machinery in the cell to make the RNA and the protein for an antibody.

So technology at every step has been really critical for this. The technologies that followed after that that really pushed the field of immunology forward were monoclonal antibody generation, which also happened in the 1970s, mid-1970s, and then in the late 1970s and early 1980s led to a transformation of being able to identify all the different types of cells of the immune system by use of these kinds of monoclonal antibodies.

The ability to clone T lymphocytes, another huge advance in the late 1970s, early 1980s, that allowed for understanding of how individual T lymphocytes recognize their targets, the generation of hybridomas, of making T lymphocyte, T cell hybridomas. B cell hybridomas were used to make monoclonal antibodies, but T cell hybridomas only came to the fore in the early 1980s and, again, allowed for analysis of individual clones and what their specificities might be. So all of these were very important technological advances that allowed now the field to move forward.

Williams: So what year in college were you in Princeton when you took this course?

Littman: I was a junior. It was my spring semester in junior year.

Williams: So how did you funnel your enthusiasm into your senior year?

Littman: In my senior year, I continued to work on microtubules, and I was really very excited about that work, but I think more than anything the way this was channeled was in my decision of what I wanted to do after college. My parents were hoping that I would go to medical school. With my dad having become a physician in Romania, then being able to make a successful transition when we completely changed our lives by moving to this country, he obviously felt this was a safe kind of profession in a changing world, in a world that never gives you any—it's so totally unpredictable. For them I think it was important because they felt like this country was a safe haven for them.

I was kind of resistant to it. I wasn't sure. I was interested in the idea of the biomedical sciences, but more from the research point of view and from a very basic research point of view. At that time, I really wasn't thinking about human health, how is studying immunology going to affect human health. It was the furthest thing from my mind. There were really interesting questions there. So I kind of struck a balance. My advisor, Marc Kirschner, I think was a bit disappointed that I was applying to medical schools. He thought I should really be a pure scientist like he is and has been, and so the balance that I struck was to apply to M.D.-Ph.D. programs and to do both.

The nice thing about that is I discovered that actually the study of medicine was fascinating, and I actually found that I was very lucky that I went to Washington University in St. Louis, which had a tremendous curriculum for medical students, something that I don't think exists anymore, but that curriculum really has stuck with me for all these decades because I learned about so much human physiology but just physiology in general that helps me, in my mind, integrate different aspects of biology.

For example, I was just discussing this with some colleagues here at this meeting. We had an entire year's course in neuroscience, in which the first half of the year was neuroanatomy and the second half of the year was neurophysiology, taught by some of the top neuroscientists in the world at Washington University at that time. And even though I became an immunologist, I've always had a love for neuroscience and an appreciation of neuroscience after being exposed to it in that context. And here, forty years later now, we're beginning to look at how the immune system interacts with the nervous system, so it's finally my opportunity to maybe apply some of that excitement that I had for the nervous system.

Williams: Why do you think it is that the Washington model was not more widely adopted?

Littman: I don't think it was necessarily a Washington University model. I think it's the way that medical education has changed over the decades in this country. I think

there's much more of a utilitarian approach to studying medicine, in which there is an impetus to just shove a lot of information at students and basically have them complete medical school as quickly as possible, get exposure to the clinic as early as possible. And to some degree it's understandable, but I think it also makes it less likely that those people who have a real aptitude for doing experimental science are going to discover that aptitude during their first couple of years in medical school. So that is a trend that's really been throughout the U.S. medical school system.

Williams: So talk a little bit about your medical versus Ph.D. side and your clinical experiences.

Littman: Well, my clinical experience was very limited. When you do an M.D.-Ph.D., at least in those times, you do two years of classroom work, with very little exposure to the clinic. Maybe with the M.D.-Ph.D. students they'd occasionally have us don a white coat and go and follow a physician around for one afternoon to see some example of some disease, but there was really very little exposure. And that's one area where I think now there's much more attention to getting the M.D.-Ph.D. students to be more involved in the clinical side of things.

But after two years, I went straight into the laboratory for three full years of research, and then coming back into medical school, you feel scared and unprepared. I felt just the way I think everybody feels in that regard. What we don't realize often is that during those three years of working in the laboratory, we really learn how to think about problems, so when you go back to the wards and now are thrown in the midst of medical students who have been studying all along the medicine, and residents and attending physicians who are basically querying us all the time about pathophysiology of the patients that we see, you don't necessarily need to have all that information at your fingertips, which I maybe had forgotten, because it's enough to actually apply the thought process and the problem-solving process to participating in that educational environment. So the fear that I had and I think that all of us have when we do this was somewhat misplaced, because there were other skills and other tools that we learned along the way that made it not so difficult really to adapt to going back into the clinical rotations.

But after my clinical rotations, which I enjoyed, despite the terrible hours and all the work, I remember I had a neurology resident during my rotation who didn't like doing spinal taps, and she found that I was very good at doing lumbar punctures, you know, to be able to get to the cerebrospinal fluid in patients. So she would wake me up at 4:00 in the morning and say, "Dan, we need you to do a lumbar puncture." So I happened to be good at doing that, so I became the go-to person as a medical student for doing that. But it made for very little sleep during that time.

So at that time you could get away with doing only one year of rotations, of the clinical training rotations. During the time, I was trying to decide whether I wanted to do a residency in medicine, and most of my friends and colleagues were already doing that, and I considered it seriously, but then I got very excited about some new technologies that were coming around that I learned about in molecular biology, and that led me to apply to do a postdoctoral fellowship in an area that was really outside of doing clinical medicine. So I can go into telling you a bit about that. I happened to be at the end of my Ph.D. studies. I went to a conference, a molecular biology conference, and there was a young molecular biologist there by the name of Richard Axel, whose group had just recently figured out how to transfer genes between different eukaryotic, between different mammalian cell types. Prior to that, there was a lot of work that had been going on in being able to transfer genes between bacteria, and that's what made a lot of the molecular cloning revolution possible.

But very soon thereafter, Axel and his colleagues figured out how they could transfer entire chunks of mammalian DNA, for example, from a human cell to a mouse cell and, in that way, look for the properties of the human cell that are now manifested in the mouse cell. And that opened up, at least in my mind, all these possibilities of how to expand studies of the immune system to the level of cell biology and molecular biology and genetics. So I decided that I wanted to work in that area, so while I was doing my medical rotations, I began to think about doing a postdoctoral fellowship with him. I was lucky that Richard accepted me into his laboratory. So I was writing fellowship, basically, while delivering babies on the OB/GYN rotation, and I was writing a fellowship for the Jane Coffin Childs Foundation [ed. Jane Coffin Childs Memorial Fund for Medical Research] to do cloning of genes involved in the immune system.

Williams: So this was still at Washington U?

Littman: That was still was Wash U while I was finishing up that I decided to do this, and Richard convinced me. First of all, he said, "Well, I'd love to take you in the lab, but we're very crowded. Why don't you take a year before you come. You might do what I did and maybe do a pathology residency."

So I applied to the pathology program at Columbia University, where Richard was and still is, and I got accepted there, and I did a little bit of pathology during my first year in New York. But the truth is that if you really are dedicated to being in a laboratory, it's very difficult for somebody to keep you out of a lab. So even though I was ostensibly doing a pathology residency, I was spending 90 percent of my time in the Axel laboratory, where I made space for myself and I could do experiments there.

Williams: [laughs] So that was a good experience? And how long were you at Columbia?

Littman: I was there for five years. I tell my students and postdocs that the time you're a postdoctoral fellow should be the most fun time in your life, and I keep on telling people that, even though it's very stressful for people to do this and then find a job and go out in the job market and figure out what they want to do, whether they can do it. Maybe I was lucky that it was an easier time back then. It wasn't as competitive for jobs, maybe. The funding wasn't something that one thought about so much.

But for me it was the most exciting time in my professional career, because I was there with some really fantastic young people in a very free-wheeling time in which we were allowed to just go out on a limb with any idea that we had and really explore that. Richard gave us tremendous freedom to try out things. If we could come up with crazy ideas, he'd allow us to try them out sometimes without even knowing it. Frankly, that's how Richard's laboratory discovered the odorant receptor genes, because he gave tremendous freedom to Linda Buck, who was in the lab with me at the same time for several years, and Linda discovered the odorant receptor genes, for which she and Richard then won the Nobel Prize. And it was that kind of free-wheeling atmosphere that made that possible. I was sort of the one person in the lab at that time working on the immune system, so I could do anything I wanted with the immune system. [laughs]

Williams: And did you make some important discoveries there?

Littman: I'd like to think so. I mean, when initially I went there, I had some questions on my mind that were very much related to what I studied as a graduate student in St. Louis at Washington University. So stepping back just a moment, at Washington University I decided to work with a young couple who had just arrived there, Ben [Benjamin D.] Schwartz and Susan Cullen, and they had just come to Washington University from the NIH [National Institutes of Health], where they had both been postdocs. They were biochemists working on so-called major histocompatibility complex molecules, MHC molecules. MHC molecules are the molecules that are seen by the T cell receptor and that basically define how the T lymphocyte recognizes antigen because MHC molecules present antigenic peptides typically to a T cell receptor on the other side, on the T cell side, and that's what makes for the specificity of the T cell receptor.

In the mid to late 1970s, it was not really known how the so-called MHC restriction of T cell receptor works. At the time, there were hypotheses that there might be two receptors, one for the antigen, another for the MHC, or that they could be seen together. The subject of my Ph.D. thesis was to try to distinguish between these, but using very naïve kinds of approaches because at that time we didn't have the tools and we didn't have the foresight that the antigen that is actually seen by the T cell, by the T cell receptor, is not an intact antigen but rather just a piece of a protein that interacts with the MHC. That was a discovery made by laboratories in the early 1980s, so my Ph.D. work was before that. So

the Ph.D. was not terribly successful from that point of view, although I learned a lot and I did what I could, given the tools at the time.

But going to Axel's lab, I wanted to clone the genes for the MHC molecules, because those were not yet identified, and use this method that he had developed of transferring genes from one cell to another, in this case human MHC molecules expressed on mouse fibroblasts now to be able to identify the genes that were encoding the MHC molecules. Well, when I started in 1980 in Axel's lab was just when Jack Strominger's lab discovered the first gene for an MHC-type molecule, an MHC-class I molecule, which his graduate student at the time, Hidde Ploegh, did this work. So at that point I said, "Well, it doesn't make sense for me to work on MHC class I." I tried to think of some other directions to go, including cloning MHC class II, but there were internal lab politics with some adjacent laboratories that made it difficult for me to really embark in that direction due to there was a postdoctoral fellow there locally in the lab who wanted to work on this and move to another laboratory to work on that. So Richard, just to not have any conflict, said, "Oh, why don't you think of something else."

And at that point, I was lucky that I met another faculty member at Columbia at that time, an immunologist named Len [Leonard] Chess, and Len urged me to look at a number of molecules that weren't yet known as CD molecules, but were molecules that were known to exist on T cells based on the generation of monoclonal antibodies against them. Like I said, this was very early days in the monoclonal antibody field, so at that time they were called T1, T2, T3, T4, etc., which now we call CD, CD1, 2, 3, etc.

So I began to do gene transferring to look with these antibodies, and in that way I was able to identify initially the transfer of the CD8 molecule, what we called T8 at that time, from human cells into mouse cells, and I spent the next three years trying to pull out, trying to clone the human CD8 that had been transferred into the mouse cell. We had very primitive techniques at that time for doing gene identification. You basically had to take blocks of DNA that were cloned into replicating vectors and try to kind of walk your way to the gene of interest based on overlapping regions of the DNA that you are looking at.

I worked on this for, like I said, almost three years, with no luck, because it turned out that adjacent to this gene that we were looking at, there weren't any of the identifying landmarks that people can use to say that a region is actually mouse or human or porcine or whatever. So there were no identifying human regions adjacent to the CD8 gene that had been transferred. My ability to actually clone the gene eventually required—was fortunate that I was trying some different types of approaches, and Mark Davis at the time was working on cloning the receptor for the T cell, the T cell receptor, and Mark shared with me the method he was using for a technique called subtractive hybridization, which allows for enrichment of the DNA that can be used to probe the human sequences. So as

soon as Mark gave me his protocol, within two weeks I was able to clone the CD8 gene from the mouse cells.

So this was in the spring of 1984, and after that, it was very easy to do the same thing with the CD4 gene, so within just a few months after that, I was able to also clone the CD4 gene. So these genes were important because they defined the two major types of T lymphocytes. There are CD4 cells—they are the cells we typically call the helper cells, and they express this CD4 molecule. The $CD8^+$ cells are the cells we call cytotoxic or killer cells. So that's really what I began to focus on at that point and what led us forward after I started on my own laboratory.

Williams: Right. And where did that occur?

Littman: The first job I had was in San Francisco at the University of California, UCSF, and I was—

Williams: Talk about the transition from Columbia to UCSF. Were you considering a lot of places to go or—

Littman: I was hesitant to move that far away, and with my family still on the East Coast and my loving New York, I looked at a few other opportunities. I had offers at [Memorial] Sloan-Kettering [Cancer Center] and also at NYU. They weren't nearly as attractive as the offer that I got at UCSF, and by attractive I mean in terms of the environment that was offered there. At UCSF at that time, even though there wasn't yet that much immunology, they had begun to hire some younger scientists there whose work I knew of. For example, there was a fellow by the name of Tony [Anthony L.] DeFranco, who had just been hired, and there was evidence that they were really pushing forward to try to bring molecular approaches to studying the immune system.

The other thing that made UCSF very attractive to me was that Mark Kirschner and the person who had been the chair of our department at Princeton, Bruce Alberts, had both moved to UCSF during the time that I was in graduate school in San Francisco, and the biochemistry department at UCSF was really a vibrant department that had attracted some really spectacular people working doing genetics, doing more biochemical kind of work, doing molecular biology. So I could see myself being in that mix and being able to interact with these people, and it turned out to be a great decision for me.

Williams: I want to interrupt here with this question. What did your father finally do in Philadelphia? How did he settle out his professional career?

Littman: Yes, well, my father, when we went initially to Providence, had to go through an internship initially, and he did a rotating internship, and he discovered that he liked psychiatry during his rotating internship. So he decided to do a psychiatry

residency, and that's why we moved to Philadelphia, because at that time there was a city hospital there called Philadelphia General Hospital, PGH, and PGH offered him a residency in psychiatry. So then eventually he became a child psychiatrist, and he worked at a number of hospitals in the Philadelphia area and some institutions for juveniles with psychiatric problems.

Williams: So he retired from that career.

Littman: He retired fairly late. My dad is still with us; he's ninety-six years old. He's still sharp as a tack, and he doesn't see patients anymore, but he definitely advises my brother on everything that he thinks he should advise him on. [laughs]

Williams: How do you escape such scrutiny?

Littman: I escaped both by delving into the science and also by running off to San Francisco. [laughs]

Williams: What about your mother?

Littman: My mom, she went into library science, so she got a master's degree in library science when we moved to Philadelphia. She went to Drexel University to take courses in that, and then she worked at the Free Library in Philadelphia for a few years and eventually at the law library at Villanova University where she spent, I think, probably more than twenty years working at Villanova in the law library there.

Williams: Were you all English-speaking folks before you got here?

Littman: No, I was the only one in the family who spoke English.

Williams: How did that—

Littman: That happened because my father knew a bit of English, but it was more professional English to be able to understand medical terms more than anything else, but not so much conversational English. When we were in Rome, in transit, I was very lucky that I had my cousin, my mother's first cousin, who knew a person who was the headmistress of the overseas American School in Rome, and this was a school mostly for American expats, kids of diplomats and what have you or of businesspeople. And somehow he was able to slip me into that school. So it was a terrific school, and I learned English there, and so it was only six months, but at the end of six months, I was pretty fluent in English. I had actually an English woman who taught me, who was married to an Italian, Signora Ogialvo, I'll never forget her, and I learned English being in her class.

Williams: And then was it a struggle for your parents to learn English?

Littman: It wasn't that easy, and I used to do a lot of translation for them, and I would come home from school every day and watch game shows with my mother and explain to her what the English—what was being said, and eventually she began to pick that up, and, obviously, if she went into studying library science, she had to be fairly proficient in the English language. So it was a slower process than for me, but I was eleven years old, which is a time of great plasticity still in our brains. [laughs]

Williams: So I'm curious, what prompted you after a certain number of years in San Francisco to return to New York?

Littman: I think there are a number of factors. I loved UCSF, I had fantastic colleagues there, and I was able to attract really good people to work in my laboratory, but there were a couple of things that attracted me to going back. One was I felt that I could maybe help to do something on a somewhat larger scale to build something, and when the opportunity at NYU came up with a new institute, the Skirball Institute, that was certainly something that was different from what I could do in San Francisco. In San Francisco there were more senior people who had done a fantastic job of really bringing UCSF to the highest level, and I felt I'd learned from them and I could maybe try to apply some of that where I was going next.

There was certainly the draw of New York, I had loved living in New York before, having my family not very far from there, so these were all important issues. Frankly, at that time, immunology at UCSF hadn't developed quite to where I had hoped that it would. It was still early days there. Now it's one of the top immunology programs in the world, but this was twenty-three, twenty-four years ago, and even though there had been some improvements there, it hadn't moved that far forward.

I was also working on HIV, and even though there was a lot of work on HIV at UCSF, a lot of it was more on the identification of the virus and on more clinically related sorts of aspects of the AIDS problem. Coming to NYU, there was the promise of having the ability to do more molecular work with HIV in an environment where we wouldn't have to worry about containment, because it took a long time at UCSF to be able to do that kind of work. At that time we still a little bit concerned about working with HIV in an open laboratory environment. Now we know that you can get away with doing a lot of that without having to worry about infections.

So a lot of my laboratory's work at that time was still HIV-based, so we thought that it might be easier to do this work in New York, particularly with the Aaron Diamond Institute [ed. Aaron Diamond AIDS Research Center], which was initially founded as an AIDS research institute as part of NYU at that time.

Williams: What was the mission and the sort of initial concept for the Skirball?

Littman: The Skirball was an interesting experiment at NYU. I'm not sure NYU quite knew what to do with it initially, but when they hired [Carl] Lennart Philipson to become the director, it gained a focus. So Lennart Philipson had been the director general of the European Molecular Biology Laboratories (EMBL) in Heidelberg, and he really was the person who helped build EMBL into a world-renowned institution. So he brought a lot of his philosophy for how to do science from Heidelberg to NYU. It was interesting because he left Heidelberg because he got frustrated of having to deal with too many interested parties from different countries in the European Union, because EMBL was really to encompass the interests of all the different countries in the EC [European Commission]. So when he came to NYU, it turned out that he thought it would be simpler, but it turned out there were a lot of competing interests as well at NYU that he had to deal with. But what he wanted to do was to start from scratch and hire people who would be able to build programs in areas that he saw as evolving rapidly.

So one of the areas was, for example, the genetics of development. Another was the molecular aspects of neuroscience. Another was applying new approaches to the structure of molecules. I was lucky because he was looking for somebody who might be interested in building a program in the molecular biology of disease of pathogenesis involving microorganisms but also involving other disease processes in the body. So it was really a wide-open kind of environment, and the idea was to really hire young people and give them as much freedom as possible to develop the programs. It turned out to be a great philosophy. Again, as I said, there were competing interests from the university that made it very difficult for him to actually achieve what he was trying to achieve, but eventually I think he did, with help from many of us that bought into this model.

Williams: So you and he must have had a good deal of discussion before you decided to come to Skirball.

Littman: We did, but he was very persuasive. He was a very large, imposing man from Sweden who used to always have a pipe, an unsmoked pipe, in his mouth, and whenever you met with Lennart, in his deep bass voice, he would tell you that something needed to be done, you felt like, "Yeah, that needs to be done." [laughs] Now, what I loved about Lennart, and many of us did, was that he came across as a very authoritative figure, but he would always listen to a good argument, and eventually you could sway him that his way of looking at things may not be the best way of looking at things. That, I think, made for a really great environment at the Skirball Institute.

I must say a lot of what I saw in terms of collegiality at UCSF in terms of the quality of science there, I could see applying that to the new environment at NYU and at the Skirball Institute, and we were fortunate that several people who got recruited around the same time as myself, including Ruth Lehmann, who is now the director of the Institute, who came from the Whitehead Institute at MIT, we all

had very similar philosophies about how to do this, and we bought in with Lennart of how to build a really quality, exciting kind of environment.

Williams: Did you bring people with you from San Francisco, or did you collect people on the East Coast?

Littman: Yeah, I tried to convince people in my lab at UCSF to come with me. At the end, I could only convince four people, a technician and three postdoctoral fellows, and they really helped out in making the move, although they didn't stay around all that long, but it was long enough to be able to really get things off the ground.

Also around the same time there was a postdoc, a person who applied to my lab for a postdoctoral fellowship, and most people to whom I said that I would be moving to New York decided to look elsewhere at the time, but this fellow's name is Hongkui Deng, and he was a student at UCLA at the time in immunology. He said, "Oh, sure, wherever you want to go, I'll come." [laughs] That turned out to be very important because he's the guy who figured out what is now we call the co-receptor for the AIDS virus, the molecule CCR5. He was really a phenomenal guy, and now he's the head of the Stem Cell Institute at Peking University in Beijing. So even though he didn't come with me, he started immediately after we moved, so he contributed to the success of this move.

Williams: Over the years, I'm curious, how large a lab have you run in terms of—

Littman: The lab's been fairly consistent in size for over twenty years now. It's typically fifteen to eighteen people. That includes a mix of usually only a couple of graduate students, mostly postdoctoral fellows, and maybe about three technicians.

Williams: And where do you feature yourself in that mix? How do you operate?

Littman: I operate in a fairly free-wheeling manner. I think one of the things I learned being a postdoctoral fellow in the Axel lab during a time when anything went, was that the best thing to do is for those people who have their own ideas and are excited about pursuing them, is to just give them a little nudge every now and then, but otherwise let them go with that particular interest. But it really depends on the person. Some people need a lot more guidance, and occasionally there are projects that really require that we focus on a particular goal, because, for example, I told the NIH we're going to work on this, and I want to deliver what I told the NIH I was going to do. So those kinds of projects typically require a bit more focus and my sort of guiding people more in the direction of a particular problem. So it really depends on the people, but, by and large, I allow people a lot of leeway to sort of develop their own direction to come up with some of their own ideas, pursue observations that they make.

The observation, the cloning of CD4 that I did as a postdoctoral fellow, I did pretty much without Richard Axel really necessarily even knowing what I was doing at any particular moment, because he was skeptical about some of the things along the way. I like it when people in my lab sometimes do an experiment without even telling me that they did and then show me some crazy result that's very interesting, that it now changes the way we think about things. I have a graduate student right now who is an M.D.-Ph.D. student in my lab, who did an experiment on his own that I didn't even know he was doing and has a result that we don't yet understand but that may change the way we think about how different regions of chromosomes that regulate a gene, how they interact with each other. So it's sort of—that can lead us in new directions. I can give you other examples of that as we go through our discussion.

Williams: What about funding your work? Has that been a complicating thing or not? I'm amazed that you've had the HHMI grants for so many years.

Littman: Yeah, I've been very lucky there. When I started my own laboratory, it was remarkably easy for me for two reasons. One, I came out of a great laboratory in Richard Axel's lab. Two, it was a time when the AIDS epidemic was really upon us in 1985, and the virus had just been discovered, and I happened to be working on the molecule that turned out to be the receptor for the virus, the CD4 molecule. So that made it remarkably easy to get funding, so I actually had funding from the NIH and from a California agency for AIDS research that had been established before even setting foot in my laboratory in San Francisco, something that doesn't happen these days. It was very easy also to get an ACS [American Cancer Society] grant very soon thereafter. So early on, it was fairly easy to get funding.

I was then very, very fortunate in 1987 to get HHMI funding, which I've now had for thirty years, and that came through a very fortuitous route. I had been an HHMI fellow previously in Richard Axel's lab as a postdoctoral fellow, but at that time the position I took at UCSF didn't have the opportunity to have HHMI. I was hired around the same time as another junior investigator who became a very close friend and colleague, Rudy [Rudolf] Grosschedl. We had adjacent laboratories. So we were hired and told that space was going to be renovated for us, but for the time being, we needed to go into somewhat restricted space that we would share across the hall from Harold Varmus and another junior investigator there, and that within a year we'd get new space.

So what happened—this was California politics that came in the way—was that it was decided to develop another campus for UCSF in an area called Laurel Heights in San Francisco. So the money that was going to be available for our laboratory renovation was diverted to pay for Laurel Heights, which eventually didn't work out that well because of neighborhood opposition. There were all kinds of politics going on in San Francisco. But the money kind of disappeared. So Mike [J. Michael] Bishop, who at the time was the head of our graduate program but was also very much involved with the Howard Hughes Medical

Institute, he was on their advisory board, was able to somehow convince the then-head of the Howard Hughes Medical Institute to look at the CVs of Rudy Grosschedl and myself and see whether they might be able to fund us. So it was really a backroom deal, because that's the way Howard Hughes operated in those days. It's completely, totally different now. It's a really a fantastically well-run organization. But back then, the history of the Howard Hughes Institute was that initially it was sort of a tax dodge for Howard Hughes. Then after he died, it ended up that it owned the Hughes Aircraft Company, and then the trustees sold this to General Motors and started with a $5 billion investment. That happened in the late 1980s, I believe, I think after I was appointed, and the entire culture of Howard Hughes began to change.

But at that time, it was this backroom deal that allowed Rudy and myself to get renovation money for a new laboratory and also funding from the Howard Hughes Institute. Rudy kept it until he decided to move back to Europe and became a director of an institute in Munich, and I continue to have it after thirty years.

Williams: Now, were you with Laurel Heights or were you on the hill?

Littman: No, no, very few people moved. Nobody really moved to Laurel Heights. I think it was one laboratory that was allowed to operate there, and they had a lot of restrictions on what kinds of experiments they could do there. [laughter]

Williams: So you were at the main campus.

Littman: I stayed. I stayed at the Parnassus Heights campus of UCSF.

Williams: Let's see. How can I ask this question? Because I always have to ask it at some point. You've had a distinguished career, which is, of course, continuing. What do you want the layperson to know about the significance of your science?

Littman: There are two ways of answering that question. One is what a layperson could perhaps learn about how having sort of unfettered access to the resources that allow you to continue to investigate ideas that come across, that come in front of you, how that kind of an approach can really foster novelty and creativity and new discoveries. The other way to answer it is to actually describe the kinds of things that we do work on that we have discovered.

But just to start with the first, by not being constrained in so many ways, it's possible to allow people in the lab to make observations and then help them follow ideas in a creative way. That's how we kind of make the shift in my laboratory from studying T helper cells and cytotoxic cells to studying how the microbiota, the bacteria that inhabit various surfaces of our body, influence the immune system, because that all came through a combination of serendipity and some good decisions along the way, but it all really had to do with asking questions that were directly related to what we were trying to answer, but then

when we saw something unusual show up, something interesting, following that lead and then discovering something new. So I think that's a great way of being able to do science. That's kind of the way we do it. There are other people who do science very differently, who really have one problem that they focus on and then really dig deeper and deeper and deeper until they really understand it at its most fundamental level. It's very important to be able to do that kind of science as well.

So what we have done, for example, we started studying how is it that you make CD4 cells versus CD8 cells, and we've continued to do this, but in the process, we identified a molecule that is a transcription factor that regulates expression of genes in the thymus in those T cells prior to their making that decision to go to branch one way or the other. But it turned out when we started looking at that molecule that it did something very different than what we initially set out to look for. It wasn't involved in this decision-making process; it was involved in survival of cells during development in the thymus, but then we found that it's also involved in development of lymphoid organs like lymph nodes, patches along the length of the intestine, so-called Peyers patches.

So we began to look in more detail at this, and in the process, we discovered that it's expressed also on T lymphocytes that exist in the intestine that we now call T helper 17 (Th17) cells, and the timing of this really coincided beautifully with the realization of others in the field that these Th17 cells are critical in most autoimmune diseases. So it was just a very nice timing of our finding this transcription factor and the field discovering the importance of Th17 cells.

Then we brought these together and found that the Th17 cells require this transcription factor which is called RORgammat. We found that this is a factor that can be targeted therapeutically, so that every pharmaceutical company now is making small molecules to try to target this to treat autoimmunity. We also in the process discovered—and by "we" I mean the postdoctoral fellow working on this, his name is Ivaylo Ivanov, who is now at Columbia University, he noticed that there were some unusual features of the Th17 cells in the colony of mice that we were keeping, and he figured out it had to do with the microbiota differences in these animals, and that led us to discover that you need particular microbes in the intestine for the Th17 cells to develop. So all of these came together from just being open to—we weren't interested in going after studying microbiota or after studying Th17 cells, we just kept our eyes open to what was coming across our viewfinder, in a way, and just followed those leads.

So at this point I'd say the things that are most interesting and most important in our laboratory are trying to understand how different microbes shape the immune system. These are microbes we all live with, what we call commensal microbiota, because it's now evident that depending on the composition of the microbes that we live with, one can be more or less susceptible to certain diseases, one can have better or worse responses to cancer therapies, and we're trying to understand what

is at the bottom of this, how is it that the particular microbes influence the immune system to render us healthier, to render us more able to fight off tumors.

Williams: So can you mention maybe one or two of the accomplishments you've already made? I mean, what you're talking about now is fairly future oriented. I mean, you're on the cusp, but—

Littman: Future, but in the very foreseeable future, I hope. [laughs]

Williams: Yeah, we all hope, I'm sure. What would you point to as super highlights of your career so far? AIDS?

Littman: I think our work on the AIDS virus has been quite—to me it was very rewarding and I think it was quite important. Initially, others pointed towards the CD4 molecule being the receptor for AIDS, for the AIDS virus. We were able to actually prove that using genetic approaches and then found that that was not sufficient through other cellular genetic studies, and that led to the characterization of the so-called what people called co-receptor, the molecule CCR5, which again is a target for the pharmaceutical industry to prevent the virus from getting into the cell. That discovery was made just after we moved to New York, but it was something that I'd been trying very hard to achieve at UCSF, and it was a little bit of a point of frustration there that I felt it was harder for me to get that done in San Francisco. So by the time we moved to New York, there were already multiple other groups working in this area, so I think there were four papers published at the same time, including our work on CCR5. So that work on AIDS I think was a highlight.

Related to AIDS, I think another highlight is that work that was done by a postdoctoral fellow in the lab who is now in Paris, Nicolas Manel, characterizing how the virus escapes detection by the immune system. This is really very much ongoing work, but the virus basically avoids turning on so-called innate immune responses very early after it infects cells, and in that way it can continue to replicate in the absence of such responses. So that's an exciting area that we don't really work much in anymore, but my former postdocs do. But I think in the field of AIDS, I think it's conceptually significant.

Then the other areas really are in understanding how T lymphocytes develop in the thymus, in terms of the decision making process. We identified some of the key components involved in that, but the most important thing really is the discovery of ROR-gamma, its relationship to T helper 17 cells and to what are now also known as innate lymphoid cells, and it's these innate lymphoid cells that are important in the development of lymphoid organs, lymph nodes, Peyers patches, etc. So that has a lot of current applicability to understanding autoimmunity and to coming up with therapeutic approaches to autoimmune disease, particularly in the context of how the microbiota regulate these cells.

Williams: Let's turn to the AAI for a moment.

Littman: Sure.

Williams: You have been a member since 1987, I believe. How important has the organization been to you?

Littman: It's been very important through its bringing me closer to many of the colleagues in this field, and that was its importance in the early days. The first talk I ever gave was as a graduate student when the AAI meeting was part of the larger Federation's [Federation of American Societies for Experimental Biology] meeting. So the first talk I ever gave was in a Federation meeting in—I'm trying to remember where it was. I think it may have been in Washington, so that was probably about 1978 or '79, something like that, when I was first talking about my project on the two receptors versus one receptor recognition. At that meeting, there was another postdoctoral fellow from Harvard from Jack Strominger's lab who, I realized, was working in a related area, and we became friends from that. We didn't know about each other's works, and that came through our involvement with the AAI at the AAI meeting. So that was a very early time, obviously, when I was a graduate student.

But I've participated in the society since then in many ways in terms of the many meetings, having people from my laboratory participate in the meetings, and then eventually, in the more recent years, it's been very important for me in terms of policy and in terms of having the AAI really have an important voice in science policy in this country. So for that reason, I was very happy when I was nominated to be on the council. It was a time when funding for the sciences was beginning to be a little tenuous after the increase in the NIH budget during the late 1990s and early 2000s. I thought that the AAI could have an important role in that, and indeed the organization has done a fantastic job in doing that. I mean, the public affairs group led by Lauren Gross has really been front and center in dealing with policy regarding NIH funding, regarding priorities, and it's very well organized as an advocacy organization, meeting with people on Capitol Hill to try to push forth the importance of basic research, of the kinds of funding that foster that.

Williams: You actually participated in—I think it was 2015—going to the Hill and talking to members of Congress—

Littman: Yes, I've done that on a few occasions, and I'd like to think that we can contribute in some way. I had a postdoctoral fellow in my laboratory who became an AAI public policy fellow [Gretchen Diehl]. She's gone to Capitol Hill multiple times. She's met with local representatives. She is now in Houston.

So I think that these are all important aspects of what the AAI does. In addition, in this very difficult time of funding during the last few years, AAI has really stepped up and helped people who have had difficulties by funding fellowships,

postdoctoral fellows in some laboratories that maybe had some gap in their funding, and that's really very important, and it's really gratifying that AAI could do that because the investment arm of AAI has been very successful. They've managed the growth of the society very well, so they have the resources to be able to help the members in the organization, including travel grants, for example, last year for going to the international immunology meeting in Melbourne [ed. International Congress of Immunology 2016], but also for national meetings. It basically fosters a lot of interactions through conferences as well as courses, and I think we're going to see more and better courses coming from the AAI in the future as science really is moving forward in different directions very rapidly and brings in the need to be conversant in new disciplines that we are normally not exposed to.

I think the AAI is cognizant of that and trying to create the kinds of courses to educate people in those directions. One example is something that I had suggested when I was president of the AAI which was to have some courses in how you deal with big data, and in the age of genomics that we're in now, we are confronted with just enormous amounts of data on genes, on how genes are regulated, which cells express which genes, and a lot of this requires computational talent. What's really special about immunology is that we in our field probably have more access to genomic data than researchers have in any other field, in large part because the cells of the immune system are readily obtained, sometimes just from a blood draw, and it is possible to really study this in experimental systems that, for example, the central nervous system, doesn't yet yield. Or even studying cancer, it's much harder to really do genomic analysis at a level where we can really understand what's going on. So the immune system is really *the* place where a lot of the large-data genomics revolution has occurred, and most of us are not really equipped with handling this. I think the AAI is now trying to create the opportunities for people to learn how to work with this.

Williams: What about the balance between basic science and more focused science, particularly like at the NIH?

Littman: By focused science, you mean translational science or—

Williams: Yeah.

Littman: Well, my philosophy is that if you do really interesting basic research, eventually you'll see the translation right in front of your eyes, and that's certainly what's happened with our work with my laboratory. Sometimes you do need to target it more and to focus it more, but I think although both are important, I think it's really important to always remember that the great discoveries almost always come from the basic research, and we can all cite one example after another. The most relevant for us these days, because of the age of cancer immunotherapy, is the discovery by Jim [James P.] Allison and others of how antibodies against inhibitory receptors can actually unleash the immune system against cancer. All

of that was done with cell biology, basic research with animal models, and eventually could be applied to human disease.

So I think focused research on particular diseases can be important, but it needs to be done in a way that does not really tread on the basic research that's done. I'm afraid in the last few years there's been a little bit too much of an emphasis in that direction without necessarily great outcomes, and I think we need to look at the outcome from those kinds of translational studies and discuss how to rebalance, particularly to foster the development of younger people who are getting into the field of basic research and allow them to have the joy of making these kinds of discoveries that eventually will lead to new therapies or new diagnostics.

Williams: How much of your work has resulted in translational applications?

Littman: I think a good deal of it has, and I would have never predicted it, but certainly the work that we did on HIV very early on led to the discovery of CCR5 as a potential target for therapy, for blocking the entry of the virus into cells. Although it's not one of the major therapies now, it is a therapy. Pfizer makes a drug that is used as a second-line therapy for HIV, how to target this. I think our work on the innate response to HIV opens up ways of looking at how to improve on vaccine development, so in the HIV area, I think it's clear that has translational potential.

In the other work that we have done, particularly on T helper 17 cells most recently, that is one of the most exciting areas these days for targeting of various molecular pathways to treat autoimmune diseases. Psoriasis is already being targeted broadly for using this pathway, not necessarily from our work, but there are applications of our work that are leading to exploration of new drug possibilities there.

And the microbiome is an area that's just exploding now, and I think we're realizing that there's going to be a lot of translational potential in exploiting the microbiome. Identifying individual bacteria that can be basically live types of drugs that would be really rational probiotics, I would call them, that can target particular pathways of the immune system, and eventually molecules that are either made by various bacteria or that are modified by bacterial enzymes that can also influence health. So I think there's a tremendous amount of translational potential there.

Williams: I get the sense that you feel like you're on the cusp of some really great—a wave, maybe, of new developments in immunology. Does that—

Littman: I think so. I've been very lucky, I would say, that we've been in a place where there's a lot of exciting development in immunology and a lot of potential in the future. So, like I mentioned, the microbiome interaction with components of the immune system, the interaction of the immune system and the nervous system, I

think that that is a fantastically exciting area. I tell incoming graduate students that I think that's going to be *the* most exciting area in immunology in the next decade, and I tell our administrators that they should be thinking about that. If they could develop some vision, that that's actually a place where science and medical science is going to, and I'm hoping that they will listen. [laughs]

Williams: You encourage your trainees and whatnot to pursue a career in science?

Littman: I'd say I certainly do encourage them, and most of the people who have come out of our laboratory have gone on to academic careers. Some have gone into industry. Some have become entrepreneurs. I have a former postdoctoral fellow [Yuelei Shen] who decided he wanted to start a business [ed. now Biocytogen] on making genetically modified mice and now has maybe the largest such enterprise in the world, with multiple plants and laboratories in China. It's run out of Massachusetts, but with laboratories in China making every imaginable type of gene-modified mouse. So people who have come out of the lab have been tremendously successful, by and large, and I certainly encourage that. That's really gratifying.

Williams: That's kind of hilarious that these mice are manufactured in China, along with everything else. [laughs]

Littman: Well, it's like everything else. It's a lot less expensive to make a mouse in China than to make a mouse in New Jersey.

Williams: I've asked everyone this question. What does a scientist like yourself do for fun?

Littman: I don't have as much fun as I'd like to have. [laughs] I like to travel. I am fortunate we have a place out in the end of Long Island, and I like to go out there and ride my bicycle and do road biking. But I can't say that I have any particular hobbies. What I try to do is stay physically active and go and visit really interesting places. I live in New York in large part because of the culture as well, which I didn't mention, but I love music, opera in particular, I love having the museums there, and being able to just walk over now to the Whitney [Museum of American Art], which is only two blocks or three blocks from where we live. So I manage to—the little bit of time that I have as free time is always occupied. [laughs]

Williams: You looked pretty happy on those boats in San Francisco Bay that your wife showed me. [laughs]

Littman: Well, I do like to sail. I'm not a particularly good sailor, but I have friends with boats. [laughs] Art [Arthur] Weiss and I and Rudy Grosschedl took a course in sailing in Sausalito when we were all assistant professors. None of us became a very proficient sailor, but they were very lax with us and allowed us to have sailing licenses so we could take those boats out into San Francisco Harbor, which

was not a very smart thing for them to do because we could have killed ourselves or other people, but somehow we managed to make it through. But those were exciting times going out on 35-foot boats that we were taking out ourselves in San Francisco Bay.

Williams: What about the balance between career and family life?

Littman: I have a partner who herself is a scientist. She has a son who is an adult in Seattle. So we manage to spend a lot of time together, we travel together, we do a lot of these cultural activities together, but in terms of my having a family, I have not. Not necessarily because there was a choice; it's just the way things happened. Maybe there was too much science to be done at all times so that the family aspect wasn't quite as high a priority for me. I think it was not necessarily a bad thing. I would have loved to have had more of a family, but on the other hand, I feel like I have an enormous family of scientists with whom I've grown up, and I continue to be very satisfied by that, and it's a very rewarding thing for me to see that.

Williams: Anything else you'd like to add to this interview today?

Littman: I'm not sure what else I can say. I'm very thankful to the entire immunology community for being so interactive and for giving me the opportunity to be part of it in such a visible way. I have so many friends I've made over the last few decades in this field, and the AAI has been really central to this. So I never knew that being president of the AAI would bring these kinds of benefits, but actually it's been a tremendously positive experience.

[End of interview]