



The American Association of Immunologists Oral History Project

Transcript

Arthur Weiss, M.D., Ph.D.
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Williams: This is an interview for The American Association of Immunologists Centennial Oral History Project with Dr. Arthur, “Art,” Weiss, who is the [Ephraim P.] Engelman Distinguished Professor at the University of California at San Francisco and a past president of the AAI. We’re at the 99th annual [ed. 96th annual] meeting of the AAI at the Sheraton Boston Hotel in Boston, Mass[achusetts]. Today is Saturday, May 5, 2012. I’m Brien Williams.

Let’s start with a little bit of your family background.

Weiss: Okay. My mom and dad were Hungarian and they were Holocaust survivors. They immigrated to the U.S. in 1954. I was born in Sweden in 1952. They have an interesting history in that they were childhood sweethearts separated by the war. My mom went to Auschwitz, and my dad went to a Hungarian labor camp. They had a tough time, but after the war, my dad heard my mother was still alive and in Sweden, perhaps the result of efforts by Raoul Wallenberg, who was trying to save Hungarian Jews. So he heard she was alive through a relative that had walked into his shop after the war, I think in ’47, said she was still alive.

He got smuggled into Sweden on a fishing boat. He hid between the hull and the hold of the boat. After the war you didn’t have identification papers, so the only way to do this was through this sort of effort. They were united in Sweden, they got married in ’48, and lived there till ’54. So then they immigrated to Chicago, where I grew up, and they ran a small dry-cleaning business. So that’s pretty much early life.

Williams: I was asking you whether you had siblings.

Weiss: No, I don’t. I’m an only child.

Williams: And what then? So you went to school in public schools in Chicago?

Weiss: I did. I did. I had a great high-school biology teacher, actually who was my A.P. [Advanced Placement] teacher. I started working as a teacher’s aide for him, helping out in doing labs and everything, and I think he really kindled my interest in science. He told me about NSF [National Science Foundation] summer research programs, so I applied to summer research programs between my sophomore and junior year in high school. I went to Grand Forks, North Dakota. It was one of the only programs that would take students that young. I worked in the public health lab, and that was a lot of fun. I got exposed to medical problems like rabies. We did tests for rabies in the lab, in fact using fluorescent antibodies, which introduced me a little bit to immunology.

Then the following summer I went to the Jackson Laboratory in Bar Harbor, Maine, which was wonderful. That was a fantastic program. There were twenty-nine students, whereas the Grand Forks program had only, I think, six or eight. So there was a critical mass in the Jackson lab, and the Jackson lab is a place that

a lot of immunologists know because they make recombinant inbred mice that we all use. That was a fantastic summer, a great experience, and I guess I realized that not all students interested in science were nerds. So we had a lot of fun.

Williams: You mean all you nerds had fun together. [laughter]

Weiss: That's right. That's right.

Williams: So that led eventually then to going to university. What choices did you make there?

Weiss: So I applied to [Johns] Hopkins [University] because on my way to the Jackson lab, I traveled with a friend who also wound up going to the same place from Chicago, and he had a cousin in Baltimore that he wanted to visit, so we stopped there and I saw Hopkins and I fell in love with it. So I applied. My high-school guidance counselor thought I was crazy. She didn't think people from public schools got into East Coast schools, and I surprised her.

Williams: What was it that instantly attracted you to Hopkins?

Weiss: I don't know. The red brick and white marble maybe, and I did hear about the ability to do independent study there, work in labs. So I worked in a lab at Hopkins for four years with a guy named Mike Edidin, who introduced me to immunology and fluorescence microscopy.

Williams: Did you choose him and his work and interests, or did he choose you?

Weiss: You know, I heard a little bit about him when I was at the Jackson lab, so I think that's how I found him. He took me in and we had a great time.

Williams: So you did a four-year program there?

Weiss: Four years, and choosing my courses to some degree by how much free time I'd have for the lab. I completed my course requirements early and actually worked with him as a technician for six months during my senior year, and spent a couple summers there. I loved the lab.

Williams: What kind of work were you doing?

Weiss: I was doing a lot of fluorescence microscopy, really focused on cell biology more than immunology, but using immunologic tools, and Lededin was interested in immunology.

Williams: So then your next step was back to Chicago, right?

Weiss: Yes. I loved the lab, but I didn't really get a good sense of the relevance of what I was doing. I saw medicine as perhaps a more relevant science or more relevant outlet for my scientific interests. I got into the University of Chicago, which was a mecca back in the days when I was growing up in Chicago, had a fantastic reputation, and so I went there really just to do medicine, but once we started all the rote memorization of medical school, I started missing the lab, and I looked around for something that might be a little bit more relevant to medicine and perhaps related to immunology also.

I found a lab that was studying transplant immunology and found my future research mentor, Frank Fitch. Now, at that time I was just doing an elective in the lab, and during my spring, the spring of my first year, funds for the MSTP [Medical Science Training Program] program, M.D./Ph.D. program, became available.

That's an interesting story in that HEW, [Department of] Health, Education and Welfare, which was a department at that time, had decided that despite the fact that Congress had started the MSTP program, HEW felt that there was no need for physician scientists for M.D./Ph.D.'s, so they weren't going to fund the program. Then AAMC [Association of American Medical Colleges] took them to court and got the funds released. So in the spring of my first year in medical school, the funds became available and they opened up funding to our class.

I was having a great time in the Fitch lab, beginning to learn about transplant immunology, and he asked me if I'd apply and he was going to support me, and so I did. So I had a free education for six and a half years at the University of Chicago working with Frank Fitch. Now, it was interesting, his first full year that started during the summer between my first and second years, he went on sabbatical. He went to Switzerland, so I was on my own for about a year. There were other people in the lab, but I was pretty much on my own, and it was a frustrating year. I couldn't reproduce any of the results of the person who preceded me in the lab.

Back in those days there was a lot of interest in the immunologic network and everybody was working on it. The competing lab or the lab whose work was closest to ours published about twenty-three papers on this in this area while I was working with Fitch, and I just couldn't reproduce any of the results. So that was an interesting experience and a stressful one. I thought about dropping out, actually, after about a year.

Williams: So that was a reflection on your capacities, not on the theories that they were working with, or what?

Weiss: Well, knowing what we know now, that science couldn't have been right.

Williams: So you were proving something.

Weiss: I was proving something, but the whole world was working on the network, and there were a lot of people engaged on what might have been artifact back in those days. So I got some other things working.

Fitch had an interesting philosophy in that he wanted students, and mainly students because he didn't have many postdocs, to solve their problems themselves, really do troubleshooting. He gave us a lot of independence and freedom. Finances weren't much of an issue. Just to give you an idea, the NIH [National Institutes of Health] pay line back then was 43 percentile, so almost everything got funded, all of our animals were paid by the Atomic Energy Commission, so the only limitation was space.

So I was allowed to really explore a lot of things, and the first thing I did was work out a lot of techniques that were relevant to the rat that were already working in the mouse. So the model we were studying was a rat transplant model, and nobody had been able to generate antibodies in vitro or generate CTLs in vitro, and I worked out techniques to do that, largely because there were suppressor macrophages present in the rats' spleen.

So I got that to work, and then I was able to apply that system to a model of specific immunologic tolerance that they had in the rat kidney transplants. It was a way of treating a rat prior to transplantation with donor antigen, antibody against donor antigen, wait ten days specifically, and then the surgeons we collaborated with did a transplant, and the transplant survived indefinitely. My goal was to figure out why. So I had developed these in vitro techniques to do that. What I found out was that the rats never made memory responses; that is, more aggressive responses. It is as though they had never seen antigen. That's about as far as I got.

I published about eight papers as a student, so I had a pretty successful thesis, but at the end of it I was a little bit frustrated in that I thought I could spend the rest of my life studying this system and never figure it out. Still don't know how it works, but we have more tools today.

So I spent three years in the lab, went back to medical school, and at that point I wasn't really sure what I was going to do. I thought about pathology or internal medicine, wrestled with that a little bit, ultimately decided on medicine because I didn't think I would enjoy pathology if I really had to do it for a living.

Then I learned towards the beginning of my senior year that they had made sort of a tactical error in using the funds for our education, in that the University of Chicago used it all up up front, and we didn't have money for our last year in medical school. They didn't realize most people would take seven or eight years to finish their thesis and medical school, and so they used up the money in six years.

So they suggested that one way that I could potentially pay for the last year of my education is to do a postdoc with my thesis advisor, Frank Fitch, who, by the way, was a wonderful person. He was a former president of the AAI and editor of *The JI* [*The Journal of Immunology*] and really a fantastic person.

One day I was walking out of the building with him, and I said almost in jest, “Instead of working for you, why don’t I go to Switzerland and work in that lab you did your sabbatical in?”

I couldn’t back out of that, so he captured that idea and arranged for it to happen. My wife wouldn’t let me out of it, so I was the only student to graduate from medical school in December with the business majors, the guys getting the MBAs. I went to Lausanne, Switzerland, for six months, waiting to find out where I was going to go to do my internship in internal medicine. So I spent six months in Lausanne taking a lot of the techniques that were up and running in the Fitch lab to the lab in Lausanne, where I had a great time.

It was an interesting place. When I arrived, this was a place where cytolytic T cells were studied all the time. They had invented the assays, chromium release assay, to study this. They didn’t believe helper cells existed, which is what I’d say half of immunology studies now, and so I had to prove it to them. I also brought some of the other techniques there. We had a great time. It was a great cultural and learning experience, living experience.

Then in April or so, I found out I matched for my internship at UCSF [University of California, San Francisco] and wound up going there as a medical intern.

Williams: Why did you say you couldn’t get out of going to Lausanne?

Weiss: I think Fitch thought this was just going to be a great idea for my career. He always talked about doing sabbaticals, getting away, having a different cultural experience, and he was right. My wife just loved the idea of going to Switzerland for a limited period of time. She had been working for nine years as a special-ed teacher, and she thought this would be a great respite, and it was.

Williams: So what’s the verb you used for getting in touch with UCSF?

Weiss: I matched.

Williams: Explain what that means.

Weiss: Medical students do internships and residencies, and the way they sort out where they’re going to wind up, and given how many people are applying, thousands of people applying for a position and several hundred or maybe a thousand institutions who have positions, so they set up a match. It’s all computer-run so

that there's no bargaining and cheating underneath the tables or that sort of thing. So, really, I had no idea where I was going to wind up because when I applied for internship and residency in the fourth year of medical school, I flip-flopped coasts in terms of my choices, but I got my first choice.

Williams: So you were a happy man then.

Weiss: I was.

Williams: And your wife was as happy to go to San Francisco as she was to go to Switzerland?

Weiss: She was. She was. We fell in love with the city, and that's why we stayed.

Williams: So your role there initially was?

Weiss: Well, so I spent a little bit of time training in internal medicine, so did an internship and one year of a residency. Then because I was an M.D./Ph.D., I was able to short track, which meant that I was considered an exceptional candidate for specialty training, and the American Board of Internal Medicine then lets you move into a specialty a year faster, and you use that first year of specialty training to count towards your internal-medicine boards, and then you train for a couple more years to train for your specialty.

But one of the reasons I went to UCSF was because of my transplant immunology connection, and it was kidney transplants in rats, so I thought I wanted to be a transplant nephrologist. My second month there as an intern, I was on the kidney transplant unit, and I hated it. I just absolutely—UCSF had the largest kidney transplant program in the country, but I couldn't stand it, and the reason for it was the patients were lined up in the transplant service like an assembly line, and the same thing was being done to every patient. Maybe there were rejection episode that differed from patient to patient, but it just wasn't that intellectually interesting. My whole life I've enjoyed solving puzzles, and there were no puzzles to really solve here. Also, there wasn't a lot of academic interest in what I had done, and they weren't doing a lot of interesting research themselves.

So I decided I was going to do something else, and over the next eight months or so I thought about it, and I was exposed to a lot of patients, and what I found out is I liked zebras. That is, I liked unusual patients with difficult problems to solve. I learned that basically when patients had a difficult problem, they called two subspecialists. They called infectious disease subspecialists to figure out whether there was an infection, or they called rheumatologists to figure out whether this might be an unusual case of lupus or vasculitis or one of the other very unusual diseases we study.

So I talked to people about rheumatology, and that appealed to me a little bit more than infectious diseases. I interviewed with a couple of people at UCSF and at Stanford [University] and at the Brigham [and Women's Hospital], and I wound up choosing to work with a guy named Jack Stobo and stayed at UCSF. He was chief of rheumatology at the Parnassus campus, and I chose him because he was very open-minded and he basically told me I could study whatever I wanted, and I liked that. He had a very engaging personality, very easy to talk to, so I wound up working with him. It was a great decision, actually. I didn't know a lot about science at UCSF in detail, but it was a great institution to stay at because the molecular biology revolution was just starting, oncogenes were being discovered, an exciting place. I worked in the Stobo lab.

The other thing that happened, that I neglected to mention, during my graduate career was I became allergic to all rodents. So first rats, then I realized I was allergic to guinea pigs, and then rabbits. I thought mice were okay until I went to Switzerland and developed allergies there. Allergies were pretty bad. I developed hives and I wheezed quite a bit after I went into a mouse room.

So I decided that since I went into medicine, I was going to be a human immunologist. So I set out to try to tackle a very difficult problem during my postdoc, which was to try to identify the T cell receptor, but I was going to do it on human cells. Two months into my postdoc, the receptor was identified, but not by me, so I had to change gears a little bit. But as I began to work on this problem, I started working with a human T cell leukemic line which produced a growth factor that I was going to need to grow human T cell clones. We didn't know what that growth factor was. It turned out to be one that everybody knows about now; it's called interleukin-2. The T cell line was called Jurkat after the family name of a kid in Germany who had the leukemia. And I've worked with that leukemic line for the rest of my career as a model system to study signal transduction by the T cell receptor.

So that's how I got started there. It was a great experience. We wound up making antibodies against the T cell receptor on this leukemic line, learned a lot about signal transduction, and that was very satisfying to me because, remember, I was stymied by this complex cellular system of transplant immunology in the rat when I was a graduate student, and studying signal transduction allowed me to become a bit of a reductionist and really focus on molecular mechanisms rather than cellular mechanisms, which I've done most of the rest of my career.

Williams: I've talked to two of your colleagues now who had some medical condition on their own and therefore used their own experiences for themselves, literally, as their experimental instrument. So I'm surprised you weren't immediately driven to allergies.

Weiss: [laughs] No, I really wasn't, and nobody in my family has had rheumatoid arthritis or anything like that.

Williams: I'm referring to the reaction to the rodents and so forth.

Weiss: Yes.

Williams: So in your work in rheumatology, what have been the highlights and the discoveries?

Weiss: Well, so one of the reasons I chose rheumatology was not only the zebras, but I thought that during my career we'd make some inroads in rheumatology, because you have to remember, back in the eighties, we were treating people with injectable gold salts, steroids, and penicillin, all of which were very toxic, and other than the steroids, the others didn't work very well.

We didn't know anything about pathogenesis of any of the diseases, so I thought that during my career there'd be an opportunity for discovery. When I thought more about the rheumatic diseases, however, I also realized that in order to study disease, you've got to understand the fundamental ways the normal system works, and we knew nothing. Almost none of the molecules in the immune system had been cloned at that point or definitively identified. So I thought that I was going to take a pretty basic approach towards understanding how T cells got activated. And the reason for focusing on T cells is they had been implicated in rheumatoid arthritis and so many other diseases. Basically I focused on how the T cell receptor signaled, and I never departed very far away from that, even now.

So I think the high point of my career is really understanding the molecular mechanisms by which the T cell receptor signals. What I think we know now is the molecules involved in who's communicating to who, I don't think we know the detailed molecular regulatory mechanisms and how thresholds are set and that sort of thing, so there's still a lot to learn. So I think my greatest achievement is the work I did to help figure out how the T cell receptor communicated with cytoplasmic tyrosine kinases, which were regulated by tyrosine phosphatases.

In particular, I'm probably best known, and I think one of the best accomplishments, is identifying an enzyme called ZAP-70. This was identified by Andy Chan, who was then a postdoctoral fellow in the lab. He's now head of research at Genentech, head of basic research at Genentech. We still work on ZAP-70. So I think most people would acknowledge that ZAP-70 is a great therapeutic target. There's an immunodeficiency syndrome due to ZAP-70 mutations, so that sort of validates that it's very important. We recently solved the structure of ZAP-70. We've also made an experimental model system in which we can inhibit ZAP-70, so we can show that inhibitors, if we had good inhibitors to ZAP-70 would pretty much turn off most T cell functions. So that would be useful in most autoimmune diseases and in transplantation.

So we have a nice experimental model that we're using to do academic research, but three years ago we got a grant through the [Barack] Obama stimulus package to the NIH in which we were able to actually screen for inhibitors to ZAP-70, taking an approach that hadn't yet been taken by big pharma, looking for allosteric inhibitors, inhibitors that will block the ability of the enzyme to change shape. We know that it does so when it binds to the T cell receptor, so we want to prevent it from changing shape and prevent it from being activated.

So we did a small molecule screen, which we wouldn't have been able to do with our regular, with our normal funding, but the stimulus package enabled this. So together with a colleague at Berkeley, John Kuriyan, we did a screen, screened 150,000 compounds, and came up with a small panel of hits.

About a month ago, we started a small biotech company, and one of its major goals will be to develop real inhibitors to ZAP-70. So I think the work I've done on ZAP-70 is probably the most important work of my career, but it interfaces with other work that relates to how the T cell receptor signals.

Williams: Fascinating. What about dead ends and big disappointments so far? Have you exerted a lot of energy to something that just proved to be a waste of time?

Weiss: You know, I don't think anything we do that fails is a waste of time. We can always learn something from that, and I think those tough times in the Fitch lab that first year taught me that things would get better, that we would gain insights, and I learned a lot about methodologies and techniques during those years.

I think if there's one thing I'm disappointed in, it's still not having had a fantastic impact on therapeutics in rheumatic diseases. I think some of the most exciting things I've done in my career is to sit on scientific advisory boards of a couple of companies that developed therapeutics that are now FDA-approved, and one in particular, which is pretty well known—it was on the front page of *The New York Times* recently—is a drug that treats melanoma, and it targets a signaling enzyme a little bit like ZAP-70. It's a kinase. Turns out in about 50 percent of melanoma cases, a mutation in this kinase activates this kinase, and it plays a major role in driving disease.

So a small biotech company that I was on the SAB [Scientific Advisory Board] of, called Plexxikon, developed an inhibitor against this kinase. When we saw the results of the Phase I trial, we all had shivers up our spine, I think, because we were looking at penicillin for cancer. These people had hundreds of lesions on their PET scans, and within two weeks of therapy, the lesions were gone.

That drug went from initial beginning of work on that as a target at Plexxikon to FDA approval in five years, which has to be almost a record. It's approved now, helps about 50 percent of patients with melanoma. It's not a cure, but it prolongs survival two to three years, or two- to threefold, anyhow. Sometimes that

amounts to two or three years. But it was only used as a single agent, and their resistance develops to the therapy, and we're hoping that combination therapies will result in cures. But it was so dramatic, and to have that experience in a setting of malignancy was just really awesome, and I'd love to be able to do that with autoimmunity, and maybe we'll get somewhere with the ZAP-70 inhibitor.

Williams: I want to go back just a little bit. When you advise students, what do you say about the Ph.D. versus the M.D.? Do you have a philosophy along those lines?

Weiss: I do. I did both, and I tell them they should choose one or the other. It's only the rare person who says they can't, that I encourage to try to do both. It's tough to really do both. I think it's tough to live up to your expectations of yourself. You can't be as good in both as you could be in one or the other. You have to make compromises in life if you choose both, in that you're not going to have as much time for your family, not going to have as much time for hobbies. You're competing, at least as a scientist, with Ph.D.'s who are spending all of their time doing research, and they're not taking care of patients and trying to keep up with clinical literature and talking to their family. So it's a tough road to take. I think the people who do do M.D./Ph.D.'s who are really happy and successful wind up focusing on one or the other, but you benefit from having training in either one.

Williams: So if you had it to do over again, you'd do the same thing?

Weiss: In a heartbeat.

Williams: In your particular case, what was the advantage of the double?

Weiss: Well, I think it's given me perspective on disease, which has had a big impact in thinking about pathogenic mechanisms. I think I have a much more realistic view of disease. Over my career, I've been on about a dozen or so scientific advisory boards, and I think my perspective on both has been very valuable to the companies, and it's been very satisfying to me because I can get vicarious thrills a little bit through the companies. They do the translational science that I can't do in my lab. So I think having the perspective on both gives me a more rational sense of what human disease is, the heterogeneity of human disease, the difficulty in doing research in humans on human problems.

We define lupus, for instance, as a disease, but no two lupus patients are alike. It's so heterogeneous, we define the disease by describing eleven different symptoms or findings, and if you have four of them, you can qualify for a study. That doesn't sound like a disease to me. It's a syndrome. It may be a collection of many different diseases that have some common features.

So I think it's that perspective that's lost sometimes by the Ph.D. doing hardcore research on animals or their animal models, and physicians just don't have the time or the patience or perhaps the rigor that they need to approach scientific

problems. So I think the M.D./Ph.D. has the advantage of offering people the opportunity to get a perspective in both fields, but you wind up being a little schizophrenic doing both.

Williams: Have you maintained a clinical presence up to today?

Weiss: Up until five years ago. Five years ago we had a major retooling of our Rheumatology Division because our two clinical gurus both turned sixty-five and decided to retire. So we brought in a lot of young people and they needed their own patients. They also wanted to teach more. At that point in my career, I was more of a preceptor than having my own patients. I'd go to clinic and I'd supervise the residents and fellows. I took clinical. I took responsibility for the patients, but largely I was managing them through the trainees. The new young clinical faculty wanted to have more of a role in that, and I couldn't blame them. At the same time, I've taken on a lot of administrative responsibilities, traveling a lot, and I thought it would actually be good for my patients. [laughs]

Williams: What about your research work? You still very active directly in research?

Weiss: I am. I have about eighteen people in my lab, a couple of graduate students, mainly postdocs, one wonderful technician who's been with me for twenty years, and my lab manager who's been with me—gosh, I was a fellow and she was in the lab at that point, so it's been about thirty years that we've worked together. Both of them are really equal colleagues and friends, and I can't imagine doing science without them. We have lab meetings every week.

I'm still a Howard Hughes [Medical Institute] investigator. Perhaps we ought to talk about that as well. So I've been fortunate to have Howard Hughes funding since I started. Stobo was a Howard Hughes investigator, and he was able to appoint people at that point as assistant investigators, and that was one of the carrots he held out to me when he tried to recruit me to stay on the faculty instead of going elsewhere.

I was a little bit worried about that, worried about staying, because it's not a great thing to stay at the same institution that you trained, in terms of developing a sense of independence and your own reputation, but we worked out a deal, a bargain, in terms of carving up the project I was working on, which seemed reasonable, and I thought getting the Howard Hughes position would be something that, if it worked out, I could take with me if things weren't working out at UCSF.

Well, the day I become a faculty member, he left to become Chair of Medicine at Hopkins, so that, I think, was perhaps the best and perhaps the worst thing that could have happened, the best in that independence was no longer an issue, or wouldn't have been; the worst because my scientific mentor and faculty mentor was gone. People don't didn't know me as well as he did, so I didn't know who

was going to help me learn the academic ropes. Lots of people did, so I'm very grateful to a number of people.

But HHMI also said that I could keep the funding, and so I've been an HHMI investigator for twenty-seven years, which is a long time. It's allowed me to take a lot of chances during my career, which I otherwise probably couldn't have done with NIH funding. NIH funding tends to be risk-averse, whereas HHMI really wants people to take chances.

Williams: That's very interesting. I'm just curious about how you and your postdocs work together. Are you the originator of a lot of thought, or are you a manager of it? What's your role?

Weiss: So my role, I think, is to help them get started on a project and, if they're struggling, to really work with them hard to get them out of the doldrums and get them into a project that works well.

So usually when someone starts in my lab, we meet a couple times a week sometimes to find a project that they can begin on. I think, quite honestly, that the people who do best in the lab are the people who think more independently and come up with the ideas themselves. Fitch was that kind of person. He let me sort of struggle on my own and find answers myself, and I think I've tried to do that a little bit with the people in my lab. I get pretty eager to know the answers and anxious, but eventually they have to become colleagues rather than trainees. I mean, that's what we aim for in the end. So I spend more time with people when they get started in the lab and when they're struggling, but less so later.

We have weekly lab meetings. I meet with the people who are struggling outside of the lab meetings. Usually the people who are doing really well either don't want to talk to me or are so excited that they come knocking on my door. Actually, the door is always open, but they come to my door to show me results spontaneously. That's actually the best part of the day, when people do that.

Williams: Where are you in terms of being creative yourself?

Weiss: Well, I like to think that I come up with some original ideas that I suggest to them. I don't do experiments, although I mentioned Terri Kadlecsek, who's worked with me for twenty or so years. She works for me and she largely gets instructions from me, so her successes have largely been inspired through my ideas, although she has a lot of input into the projects too.

I think a lot of my ideas fail, as they do for any scientist that takes risks, but I like to come up with ideas, and I think—I hope I still inspire people. If I'm not doing that, I probably shouldn't do this anymore.

Williams: You received the Junior Investigator Award from the AAI, I guess in 1993. Was that for something in particular?

Weiss: I think that was about the time we were beginning to learn how the T cell receptors signaled, so we had just discovered ZAP-70 and began to understand how the antigen receptor regulated tyrosine phosphorylation. So that award is really for a body of work. It's not for one discovery.

Williams: Let's talk a little bit about AAI. You became a member in '81. It's been an important part of your professional life?

Weiss: It has been. When I was a student, even before '81, I would go to the AAI meeting to see the big-shots, the names that were in the literature in *Nature*, *Science*, *Cell*, *The JI*, wherever, and it was rare for a student to get to see the real stars of immunology, and the AAI really provided me with that opportunity, because it was the only national meeting I went to.

As I transitioned to my postdoctoral training in the eighties, it offered me the same opportunities. Then early in my faculty career, I started participating in program committees and things like that. It was interesting to see how a meeting was organized and how you chose abstracts and how decisions were made. So it gives you a little bit of an opportunity not only to go to a meeting and hear science, but begin to understand how a meeting's structured.

I've also met friends and colleagues here. I think one of the greatest things about going to meetings, whether it's the AAI meetings or other meetings, is you get to see the same people in your field over and over again. You develop personal relationships. It's a way to meet prospective postdoctoral fellows and maybe even colleagues that you're going to recruit to the faculty. So it provides an important function in that regard. I've taught in the courses a couple times and gotten a few postdoctoral applications from doing that as well, and it's very gratifying and rewarding to have the opportunity to represent the AAI at courses.

Williams: Then you were president in—

Weiss: 2009, '08-'09.

Williams: What was that like?

Weiss: I think that I saw enough from being on the council to know that I wouldn't be making decisions alone, that the council was there to participate in those decisions, that I had the backing of an incredible staff, especially led by Michelle Hogan. She's really made this organization an incredibly strong one from many regards, not only financially, and she had a big role in turning the organization around, but working with very talented people.

I knew I could rely on them as president, because you're only president for a year. You don't have much time to learn about the job. So they help you teach you what you need to do. But still it represented a real honor because of the responsibility that was being entrusted in you to run the organization of several thousand people and being their representative when we gave out some congressional awards and met with some staff members. So it was a real honor and a privilege, and it was made easy by the folks at the AAI.

Williams: Were there any major issues that you dealt with during that year?

Weiss: I don't think there was anything unusual.

Williams: Or any particular memories, vivid memories of something that occurred, fire drills during speeches or something? [laughs]

Weiss: No, and I didn't faint during my presidential address either. You know, I think I just enjoyed presenting awards to people who deserved those awards, and I remember just being so busy at the annual meeting and not knowing what I was going to be doing next, but knowing that someone was going to be telling me what to do next. [laughs] But I don't think we had any particular challenges that year. *The II*, I think, was perhaps just taken over by Jeremy Boss, and he was doing a great job.

Williams: So even though that was the beginning of the recession, you were not feeling it yet, perhaps. Is that correct?

Weiss: I don't think so. We anticipated investment issues, but we had already sort of taken on a more responsible investment policy, a more conservative one for the organization. So although we knew we might be stressed by the economy, I think we were more concerned about our membership than the AAI itself and how we might help.

I think one of the things I tried to do in particular during the AAI when I was AAI president was talk to Tony Fauci about how many people we were training and what we were doing about that, because I am concerned that we're training too many people, given the economy right now. Pharma and biotech is contracting their R&D programs, and so a lot of jobs that would have been available to our trainees aren't there anymore. I was trying to think about that even then, we need to contract our training and think about other kinds of positions.

I think one thing we don't have enough of in the U.S. is professional scientists working in academic settings. We have principal investigators. We have professors who are training a lot of students and postdocs, but everybody in our labs turns over every three to five year. It's not a very efficient way to do science, and we're not offering people opportunities to stay in that setting unless they become PIs, unless they become professors.

Some people just want to work at the bench and participate in a collaborative group, and I think we don't have enough people in that kind of position in the U.S. If we did do that, it would make science more efficient and perhaps give people opportunities for a different kind of job. Right now it's either you become a teacher, you become a principal investigator as a professor in an academic setting, or you go to industry. Those are all wonderful jobs, but they don't suit everybody's needs and there aren't enough of those positions.

Williams: Have you had success advocating for that, or are some people experimenting with that role?

Weiss: I think more people are talking about it, but I don't see anything happening at the NIH yet. I think the concern about this is there's tremendous abuse potential, in that people who go into these positions might be taken advantage of in terms of getting credit for the research and that sort of thing, maybe not being treated well.

So I thought that actually the NIH ought to fund the individual taking this kind of position, rather than that individual getting funding through someone's RO1. So if you had a career scientist path where perhaps the individual would have 75 percent of their own funding and the institution would provide 25 percent, it would give them a lot of flexibility to take their money and go elsewhere if things weren't working out, and yet it would take enough of an institutional commitment so the institution would pay attention to how these people were treated and that sort of thing.

Williams: You said something a moment ago that surprised me a little bit, and that is that you found council work substantial. Because several people I've asked about their time as councilors, and they've sort of said, "Oh, well, yeah, it's sort of honorific," or, "We didn't do very much." Did you have a sense of that?

Weiss: I think that over the years we've made important decisions for the AAI. It's not a lot of time commitment, but I think the decisions that we've made have been important. I think the other thing that happens on the council is you share responsibility with the president, and over the years you learn the job and learn that it doesn't take a huge amount of time, but there is a lot of responsibility for an organization that has twenty to thirty million dollars in investments and is running a business and a journal, both at the same time. So it's not a lot of time, but it's significant responsibility that I think people take seriously.

Williams: You mentioned turnaround in the organization a little while ago. Talk about that.

Weiss: I think I was referring to the time when Michelle Hogan was hired. Prior to that, the AAI was not doing well financially. Its funds weren't perhaps being managed as conservatively as they should be. So I think Michelle did a great job and continues to do a great job in running the organization as a business but also an

academic enterprise. So I think she in particular deserves a lot of credit for the turnaround in the AAI.

Williams: I'm going to ask you something here that's a little bit off the track. Several of the people that I've interviewed who are at least one generation before you, if not more, have talked about the quota for Jews in universities, like Columbia University was cited in one instance, that they only would take a certain number. You have never experienced that at all?

Weiss: Not at all. In fact, if anybody would be on the lookout for it, I would have been, given my parents' background. No, not at all. If anything, I think Jews are overrepresented in medical schools, anyhow. I've never experienced any sort of discrimination.

Williams: I think it's important for someone of your generation to say that for the record. Talk about the development of the Asthma Foundation.

Weiss: Oh, that's terrific. So I never did research in asthma, and there was a very wealthy family that owned a banking business in San Francisco, the Sandlers, who owned Golden West Financial, which basically survived the housing and loan calamity, the only one that did, I think. They became interested in asthma because Mrs. Sandler has asthma, and they were a little frustrated with asthma research at the time. This was in the mid-1990s, late 1990s. They wanted to change asthma research, and they felt they had the power to do so financially. They started talking to physicians at UCSF involved in asthma care and research, and UCSF came up with proposals to establish a center, and they got me involved. I'm not sure why, except that I was prominently involved in immunology and they thought that that might help.

The Sandlers weren't happy with the proposals. They kept traveling around the country and heard that UCSF was okay but it wasn't a powerhouse in asthma at the time. They didn't know what to do. After about three iterations of proposals, they finally wanted a meeting in my office. Herb Sandler was parking the car, and Marion was in my office, and I said, "What was wrong with the last proposal? What do you want?"

She said, "Well, we want to change the way asthma research is being done."

I said, "Well, the NIH funds a lot of asthma research."

She said, "Well, they've been at it for a long time and haven't gotten anywhere. We want to change what's being done."

So I suggested what they really were thinking about, maybe, was setting up an innovative grants program, because, in fact, the NIH is a conservative granting

agency. I said, “You know, what you really want to do is attract new people into the field who will think differently about the research because it’s going to be hard to change the ideas of people in the field. But in order to do that, you’re going to have to hold out large carrots and make it pretty easy.” So we talked about this a little bit, and they decided in the end to fund this innovative grants program, had a budget of about seven and a half million dollars a year. So over the past twelve years they’ve given out close to \$100 million.

They also set up a center at UCSF. They saw that there could be synergy. I introduced them to a colleague of mine who I thought would be a great director of the program, Bill Seaman. Bill was Chair of Medicine at the VA [Veterans Administration]. He’s an immunologist who was doing a sabbatical in my lab, and he was bemoaning the fact that he’d have to go back to being chairman, but he didn’t have something else. I suggested this, and he’s been just a spectacular director.

We have a fantastic board, a lot of people in the National Academy and Hughes investigators. We get about 350 applications a year for about twelve to fifteen awards. We have a meeting every year. The applications are easy. We basically say you don’t need preliminary data. What you need is a good idea and a good track record. We want innovation and creativity. We don’t want people doing the same experiments. It’s a five-page proposal, runs for three years, \$250,000 a year for senior investigators, and \$150,000 a year for three years for junior people. And if you get something close to being translational, we might fund you for another year or two if we see that potential.

So we’ve had a fantastic group of people, lots of new people drawn into the field. We’ve had some people from the NIH who have seen the program develop, Dan Rotrosen in particular. I think he really likes the program. He was a little skeptical in the beginning. But I think the program’s really attracted a lot of people to the field that wouldn’t be there otherwise, and it’s a very prestigious program.

Williams: And the Sandler are happy?

Weiss: The Sandler are happy, yes. I think they’re very happy with the national program.

Williams: Have there been some really important findings yet?

Weiss: There are a couple of projects that have gone into clinical trials. The trials aren’t funded by us; they’re funded by the NIH or by industry. There was a trial that we funded, Mick Croft’s project on Ox-40, and Genentech is now moving that forward. There’s someone who had something unrelated to immunology but an inverse beta antagonist. The beta blockers are contraindicated in patients with asthma because it will cause contraction of their smooth muscles.

There was a fellow, Bond is his last name, who proposed using an inverse beta agonist, which would have a slightly different effect, and he did some preliminary preclinical trials and now clinical trials. Now the NIH is sponsoring a larger trial on that. So there have been a few things like that, and a couple others that are maybe in earlier stages of development. But, yes, I think more than anything else, more than the projects, we've attracted a cadre of people, young people in particular, that I think will stay in the field.

Williams: You've mentioned the NIH quite a few times now over the course of this interview. Give me your general impression.

Weiss: Well, the NIH has been a great way to fund research in the U.S. I think immunology in particular has benefited a lot, but it tends to be rather conservative in the funding it provides. It provides project-related funding, which is very different from the way HHMI funds the investigator. We're in hard times now. I was on an NIH study section in the late nineties, and we had a pay line of about 20 to 25 percent. It was rare that I lost sleep over our funding decisions then, because I thought we were funding probably the projects that deserved to be funded. But now when we're at 8 to 10 percent, we're not doing very well. It's very frustrating for people applying and for the reviewers.

Part of the process of submitting grants has gotten a little bit better in that they've gotten shorter, but revisions are welcomed only once, and with an 8 to 10 percent pay line, you're not funding many grants. What do you tell a young person who submitted a grant twice and didn't get funded? You've got to start over and come up with something entirely new? Doesn't make much sense.

I think in part we're to blame ourselves, and when I say "ourselves," I also mean the NIH, in that we wanted all that doubling of the budget in the early 2000s to go into RO1 investigator-initiated research. Well, for the most part, that's what they did. We increased the number of investigators enormously by doing that. The doubling wasn't going to go on forever. I think we needed to come up with a better scheme by which we were going to use that money and use it in a way that doesn't just do the same thing.

Again, I think this professional scientist track would have been a better way to do it. I asked Tony Fauci how much of training is funded by RO1 grants, and he said about 85 percent. So that means that 85 percent of the funding that supports our student and postdoctoral training is coming off of RO1s. That just means the community is getting larger and larger, and it's driven by opportunity in the RO1s rather than some sort of strategic planning. So I think we need to be more strategic about how we're doing science in the U.S.

I'm not sure how to accomplish that with a Congress that's elected every two years and a new budget every year, but something has to change because I think

the scientific enterprise is in real dire straits right now. I know that there are a lot of young investigators that may not be able to make it because they can't get that second RO1.

Williams: The long-term consequence of this, what do you see for science and particularly immunology?

Weiss: Well, it's got to change. I think we'll go through a lot of pain first if no one really champions this. I think right now we have to turn to our institute directors to be champions for change and to initiate change. It's going to have to be fairly broad and painful change, something that might have to be fought politically because every state wants its share of the funding. Everybody wants their own immunology training program, but can we afford to have as many immunology training programs now as we do? I would argue the training programs have to be cut back. RO1s have to be thought of strategically in line with our training agendas. I think that's going to be difficult. It's going to have to be developed by a consortium of people at the NIH and the academic investigators, and it's going to be a battle.

It's a battle worth fighting, because we have more opportunities now than we ever have had before. If you look at all the therapies that have been developed in rheumatology and autoimmunity and transplantation over the last several years, it's amazing. When I started out as a rheumatologist, we had a lot of people with deformity coming to our clinic and getting joint replacements. Recently I called up my colleagues in orthopedics because I wanted to get some synovium for some experiments we were interested in, and they said, "We don't do that many joint replacements in patients with RA anymore," and largely it's because we have much more effective therapy.

So I think the evidence is there that basic research and clinical research can provide society with a lot of benefit, so it's worth engaging in it. There are a lot of opportunities now that weren't available twenty years ago. I think we also have to perhaps change the system now to take into account our economic situation and the opportunities.

Williams: So what advice do you give trainees who are looking at the possibility of going into the field?

Weiss: Be highly focused and be part of a team. Look to an institution that's going to be supportive, that will provide hard money. Consider the NIH as a career. Funding at the NIH is easier to get than it is in academia. It's an interesting place to work, I think, fantastic colleagues there, so I'm encouraging many more trainees to look at the NIH than I ever did before.

Williams: Does the NIH promote the kind of scientists that you want to see more of, the sort of single-focused bench worker, or not?

Weiss: Yes, they do. They do. They have small labs, and people are part of a team, but they have their own independent research project. I think they have more opportunities for staff scientists than we do in academia as well. So science will have to be done more collaboratively and in smaller groups. The NIH is already set up that way. It's a little bit top-heavy right now because NIH grew exponentially in the sixties and seventies, and I heard a quote that 65 percent of the tenured faculty at NIAID [National Institute of Allergies and Infectious Diseases] are retirement-eligible. So that means they're top-heavy. It also means that there's likely to be turnover in the next ten years or so.

Williams: I have a couple of questions for you about industry. One is, as a scientist over the years, how dependent have you been on developments in biotech?

Weiss: Not at all myself, and the reason for that is because I'm funded by HHMI, there's a wall between industry and me. I can't do industry-sponsored research in my lab. That has to do with the IRS and HHMI remaining a medical research organization under the tax code. I also can't consult at a company and do research with them. I can't collaborate with them and also be a consultant. So very little comes back from my interactions with industry to my lab. It's pretty hard to get reagents from industry as well, so I'd say I might be a little bit unusual, as would be other HHMI investigators, in that there's this barrier.

Williams: But you've created a company.

Weiss: HHMI allows us to create companies as long as we're not using our labs to collaborate with the company. So we transfer things out of our lab into the company and then we cut ties. This was an easy thing for me to, actually, because the money that we used for our screen for our ZAP inhibitor in particular was funded by the NIH. What really needs to be done with these chemicals now, these hits, is to optimize them. I'm not a chemist. I don't have a chemistry lab. I couldn't do it in my lab anyhow. The only way this is going to get translated into a therapeutic is through industry. We don't know how to do it very well in academia. We don't know how to make drugs in academia. There's so many things that people have to be skilled at, that we just don't have the expertise in academia with. So I think early discovery work can be done in academia but actual preclinical studies or clinical development really has to be done in industry.

Williams: What is the connection between your ability to practice your science and the equipment that you need to do it? In that sense, how are you dependent on industry, cell sorters and so on and so forth?

Weiss: So that kind of industry, cell sorters are developed, the technology is developed, and we take advantage of it, but the equipment isn't provided by industry. We have to buy it.

Williams: No, I just meant you couldn't be doing the things that you're doing without a tremendous development...

Weiss: No, absolutely. You're absolutely right, and some of the instrumentation is just remarkable. It's fantastic. We just were able to get a new cell analyzer that can do fifteen colors, and people in the lab were initially resistant to use it, and now they want to get another one. [laughs] It's just so booked up they can't get on it. It allows us to do so much now that we couldn't do, so it's enabling.

Williams: Do you ever go to industry and say, "We need to be able to do X, Y, Z"?

Weiss: I don't so much. I think that there are other people who do do that kind of thing. I know that the Hertenbergs had a big role in helping to develop the FACS, for instance. Occasionally people will come by or we'll be at a meeting and we'll say, "Gee, it would be really cool if we could do this," and maybe they take that back and work on it. I don't see a lot of that, but I'm sure it happens.

Williams: I'm sure the ingenuity and creativity at that end is generated by the industries.

Weiss: Yes, and I suspect that postdocs coming out of lab who have made connections, get jobs at those companies have a better sense of what's needed and bring that information to industry.

Williams: I think you've pretty well answered this already, but I'm going to ask it again. Where is immunology headed, in your view?

Weiss: Well, I think immunology is headed towards more human disease studies. I think it will be tough slogging. I think right now what we can do is largely descriptive work in the human. I think one of the things we'll be doing is dealing with a lot of systems biology and informatics in a way that we've never had to do before in immunology. I think we'll have datasets that are very, very large, all the parameters we can measure when we phenotype cells, all the information that will be available from microarrays or even from patient medical records as we learn how to interface with that a little bit better. So I think we're going to be dealing more with complex information, large databases, and I think our work will become more translationally relevant over the next decade or so.

It's also very hard to predict. I think microRNAs would be something that maybe you've heard of. I think in the nineties we would have never predicted they existed. Now they're revolutionizing the way they do some of our experiments and provide an entirely different understanding of how genes are regulated. So I think it's hard to anticipate exactly what will happen, because it's hard to anticipate the really important unanticipatable discoveries.

Williams: You mentioned the problem of balancing family and profession. Just talk about that a little bit.

Weiss: Sure. I married a wonderful woman when I was twenty-four and a student, Shirley, and we've been partners. She's played a much larger role than I have with the kids' education and care, but she tells me when I need to. I think she's made sacrifices because of my traveling. I travel maybe a week a month, and so she's alone at those times, but she's been extremely supportive and interested. She doesn't understand the science in depth, but she's interested in it and she's interested in the people that I interact with. So she's been great. She made a sacrifice. She left her family in Chicago when we went to San Francisco ultimately and has started a new home and friends and job there.

So I think my family has done exceptionally well because of her and because of the partnership we have. My kids are great. My daughter's now twenty-five, and she's just started a nonprofit job for a sustainable farming organization, directing their farming interns and doing some courses just north of New York City. My son is a graphic designer, and he's just quit his job and is starting his own business, and that's exciting. He's twenty-nine. They've been great. They've just been super. They're wonderful people. I'm very proud of both of them.

Williams: But they haven't followed in your footsteps exactly.

Weiss: No, they're not scientists. So both of them have a bit of an artsy tendency, and my wife is now still a special-ed teacher, but she has a very serious hobby in making jewelry. So I think her artistic genes have surfaced and both of my kids have more of a tendency towards the arts, I think.

Williams: What do you do recreationally?

Weiss: Not enough. [laughs] I love the Giants and sports in general. I like hiking. I took up sailing a little bit. I don't do it enough. But it's interesting, I took up sailing with two other immunologist at UCSF, Dan Littman and Rudi Grosschedl, who are no longer there. Then I inspired two former AAI presidents—the three of us inspired two former AAI presidents, Lewis Lanier and Jim Allison, to take up sailing. So once we were taking our sailing lessons, they've started sailing. We were all in the Bay Area together, all good friends. Lewis is the only one who really does sailing, sails seriously. He's racing every weekend, and I enjoy go out with him, but I can't commit myself to that quite as much.

Williams: Anything we're leaving unsaid in this?

Weiss: No. We've covered a lot of ground. [laughs]

Williams: Thank you very much.

[End of interview]