The American Association of Immunologists
Oral History Project

Transcript

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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 Feldman, 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 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 sp3 lt krp2(unol)-2(0

that there's no bargaining and cheating underneath the table 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 flipped 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 pro

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, 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. 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.

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 focusingon 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:

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? 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. [illegible]

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.

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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 JI*, 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 educate, 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

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-

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

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 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 Herzenbergs 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 Randy Schekman, who are no longer there. Then I inspired two former AAI presidents—the three of us inspired two former AAI presidents, Lewis