# The American Association of Immunologists
# Oral History Project

## Transcript

Susan L. Swain, Ph.D.
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Interview conducted by
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**Williams**: This is an interview with Dr. Susan Swain for The American Association of Immunologists Centennial Oral History Project. Dr. Swain is professor of pathology at the University of Massachusetts Medical School, and she was president of the American Association of Immunologists from 2004 to 2005 and served as an AAI Council member from 1999 to 2004. She was awarded the AAI Lifetime Achievement Award in 2010. We are in a conference room at the University of Massachusetts Medical School in Worcester, Massachusetts. Today is Friday, November 2, 2012, and I'm Brien Williams.

Dr. Swain, let's start with your talking a little bit about your own family background, maybe before you, where did you grow up, and where did your parents and so on.

**Swain**: So my father was a professor of mathematics and my mother was a journalist, and I was born in Columbus, Ohio. We were there, but it was during the time when professors moved around a lot. So I think in my early years we moved around, but then we settled in a very nice little Dutch Huguenot village, New Paltz, New York, when he was at State University of New York in New Paltz, so that's where I grew up. It was very attractive, right by the woods, and I always had a love of nature and being outdoors and catching insects and salamanders and roaming in the woods. [laughs]

**Williams**: You mentioned your mother being a journalist. Was she a practicing journalist?

**Swain**: Not really. She was in college when she married my father, and then she did a little work in journalism. I think she worked in the New Orleans *Picayune* for a short period of time early on, and then she was home. My father died sort of very early. He was in his late forties, and I was only about thirteen, and my mother had never had a job, so she had to go back to school. I used to help her with math. [laughs] Go back to school and get a degree, and she had a career in social work after that.

**Williams**: Do you have siblings?

**Swain**: I do. I had a sister, a younger sister, who also died of cancer, like my father, when she was in her forties.

My father moved to Rutgers at New Brunswick, New Jersey, so I spent my junior high and high school years in New Jersey, and then I went to college at Oberlin College in Ohio, and then I went to graduate school at Harvard Medical School.

**Williams**: When did science loom large in your life?

**Swain**: Well, like I said, I was always interested in bugs and natural things, and I'd say it was always in my life. When I was in high school, I had a very charismatic physics teacher, and also I had close friends who were physicists, including

someone you've probably heard of, Alan Guth, who started the Big Bang Theory. He was a colleague of mine. So at first I thought physics was the thing to do, so I was going to be a physicist when I went to college, but I soon realized that I actually liked biology better.

**Williams**: You made that discovery at Oberlin?

**Swain**: Yes, after about a year. I had gone in as a sophomore, so I didn't have much time to readjust, but I did.

**Williams**: How come you went in as a sophomore? Because of AP in high school?

**Swain**: Yes.

**Williams**: What was your time in Oberlin like?

**Swain**: Well, it was very good. It's a very liberal college, and that's very fine, had very fine teachers. I have very close friends from Oberlin, so it was good. But despite the fact that it's extraordinarily liberal, it's not a very diverse college. It doesn't have people of different ages. It's sort of a small liberal arts college, and I think that actually I would have enjoyed a larger place, although I hadn't thought that when I chose. But, anyway, so moving to Harvard Medical School, I really enjoyed Boston. That was really fun.

**Williams**: That was part of your decision to apply to and get into Harvard, correct?

**Swain**: Yes. Again, I had a very influential advisor when I was at Oberlin, who gave three lectures on immunology, and I was totally fascinated by the idea of memory, of the ability of vaccination to protect us from reinfection in the future. I remember that lecture, and that's ultimately what I went into.

**Williams**: It's amazing that something at that stage in your life triggered the basis of a career, almost, right?

**Swain**: No, I don't think it's amazing. It just struck me that this is really interesting and important.

**Williams**: But these two teachers in particular were really important in—

**Swain**: Yes. I think that's true of most people, that it's somebody who you admire that you feel that that's what you'd like to be.

**Williams**: Characterize your graduate work at Harvard. What was that like?

**Swain**: So I worked with Albert Coons, and he had originally developed fluorescent antibodies. So these were incredible tools that, of course, we still use extensively

in FACS analysis now. He just used them in immunohistochemistry. He was known for his studies of immunoresponse. In his lab there was another junior professor, and I worked with him for a while. They were very obsessed with trying to generate in vitro antibody responses because they felt that that would provide a way to really analyze the immune system. So I worked on T cells when I was a graduate student, trying to look at whether there were T cells that bound antigen, but that actually didn't turn out to be particularly exciting work.

When I decided to go on to be a postdoctoral fellow, I went to work with Richard Dutton, who you will interview later, and he was known because he—I went to work with him because he and his colleague, Robert Mishell, had figured out how to achieve this end of growing cells in vitro and getting them to respond. So I sort of started out. I thought that was the most exciting thing in immunology at that time, to be able to start to really analyze what was happening with lymphocytes in vitro. So that's where I started out, literally doing the work that I now continue, or progression therefrom.

**Williams**: So you sort of surveyed the postdoc opportunities around the country, and San Diego was—

**Swain**: Yes, and, of course, I got advice from people, and people said, "Oh, yes, that would be a good place to go." [laughs]

**Williams**: Did you know Dick Dutton at that point?

**Swain**: No. No, I had never met him until I did meet him in the course of applying to his lab.

**Williams**: So what was it like as a postdoc at San Diego?

**Swain**: Oh, it was really very exciting. I think especially for a woman in science, it really matters who you work with and whether you work with someone who's open-minded, and Dick is certainly that.

We had quite a large lab, and we had lots of discussions about what was important, what did we want to do. We had a wonderful journal club that many people over the years, many famous immunologists, have attended: Rolf Zinkernagel, Mike Bevan, of course Pippa Marrack, whom you will interview. She was his postdoctoral fellow, actually before me, so she was in the lab when I was there. We would discuss the most interesting papers of the day, and there was a lot of excitement at the time, because immunology was just starting a sort of explosive growth and analysis of how things worked. So it was really a wonderful time to be a postdoc, to be in science, and it was really exciting.

**Williams**: Where was UCSD in the sort of firmament of that kind of research at that point?

**Swain**: Well, I'd say the whole La Jolla area, so there was UCSD, there was Salk Institute, there was Scripps, what used to be Scripps Clinic but is now Scripps Research Institute. There were leading people at all of these institutions, and so it was really, like, I think, you always need, it was sort of a hotbed of ideas.

One of the things, we would organize little mini conferences, one-day retreats, where the people got together and discussed the issues of the time, especially how T cells see antigen, which was unknown at that time, whether they—why is there MHC restriction? What does that tell us? What does it mean? So it was a very stimulating, exciting environment, and we were finding all sorts of things. We were one of the first labs to look at cytokines and to appreciate that once they were made by the T cells, they carried out many of the functions of the immune system. I think we were the first to show that they actually synergized with one another.

**Williams**: Then as it turned out, you were there for quite a few more years.

**Swain**: Yes, I was there for twenty years.

**Williams**: So how did your career evolve?

**Swain**: Well, I became a research biologist, and then I got on the research faculty track, and so I was there for, like I said, a long, long time, many, many interesting, fun years.

Then I felt that immunology was not growing at UCSD at that time, by the end of that time, and so it was a little frustrating. The biology department was an excellent department, highly diverse, but they didn't really have a deep interest in immunology anymore, so they weren't expanding the faculty. Also I had come to feel that the kind of in vitro studies that we had been doing and had taught us a lot had their limitations, and they weren't going to continue to teach us very much.

So when I got a letter trying to recruit me to the Trudeau Institute as its director, I thought it was a wonderful opportunity on a number of fronts; first, to start studying infectious disease. So it's my belief and, I think, many other people's, that infectious disease has really driven the evolution of the immune system. The immune system is amazingly complicated because it has to deal with this plethora of all sorts of different infectious diseases, and without the immune system, you would die of infectious diseases. Kids who have, for instance, combined immunodeficiency, severe combined immunodeficiency syndrome, they have to live in a bubble, and if you open that bubble, they get infected with something and they die.

So the immune system is very effective, very sophisticated, and I believed that we were sort of at the end of what we could find out pursuing mostly in vitro studies, and we really needed to expand into the animal, but not only into the animal, but

into infectious diseases. I thought that the Trudeau, because it was so well known for its studies in tuberculosis and infectious disease, that we could do that, and that I could recruit really talented immunologists who had shared my feeling that using their skills in infectious disease would teach us a lot. And I think that's what happened.

I think the other attraction was that at a small institute like that where you recruit everybody, you can create the kind of environment that you think is ideal for science. So you can create a highly collaborative environment and you can make sure that the resources go completely to support the science. So that was a wonderful opportunity.

**Williams**: Just to backtrack a little bit, explain a little bit more thoroughly why immunology had sort of run its course at UCSD.

**Swain**: I just think that there were competing things and that not enough of the faculty was interested in immunology. It hadn't run its course. Actually, right now they have very fine immunologists, and they had some that stayed, like Steve Hedrick, who's extremely well known, but they just were not interested in building immunology.

**Williams**: Were they moving in some other—

**Swain**: They were moving into more molecular areas, virology, yes, and certainly not infectious disease.

**Williams**: Did you know much about Trudeau before that sort of came on your radar?

**Swain**: No, no. All I knew is that a fellow who had been a technician when I was at Harvard had gone there to work as a technician, David Kirstein [phonetic], and then he went to work with Robert North, who was the director, who was director there for a very long time. I took over when Bob North stepped down.

**Williams**: And you brought along Dr. Dutton as well, is that correct? Or how did that work?

**Swain**: Oh, yes, that was great. [laughs]

**Williams**: That was part of the negotiation?

**Swain**: Oh, absolutely, and we brought thirteen people up from California. So despite the fact that we moved from one of the most clement climates in San Diego to Saranac Lake, which is gorgeous, but I'd say it's a challenging climate, yes, a lot of people came with us, and, of course, that helped ensure that we had a smooth transition and remained productive.

**Williams**: From various institutions in La Jolla, or did they all come from the university?

**Swain**: No, they were from our lab.

**Williams**: How many? Thirteen?

**Swain**: Thirteen, yes. Almost everybody in the lab came with us.

**Williams**: Is that unusual for such a migration?

**Swain**: I think people were surprised, yes. So we must have done a good job convincing them. [laughs]

**Williams**: It's a tribute to your magnetism, I would say.

**Swain**: Well, I hope so. [laughs]

**Williams**: So how did you find things at the Institute when you arrived?

**Swain**: Well, I guess Bob had been sort of scaling down, so there weren't very many faculty. I think there were six faculty, and it needed to be brought into the new world of science, and so that was very exciting. I had the resources to do that. We recruited wonderful people, and that was very good.

We did create, I think, an unusual environment in which we stressed collaboration. We had a fairly limited physical space, so we told people that, you know, you cannot have a lab of twenty-five people. You're sort of limited, and so what we would like is for the different people who have different attitudes and skills to collaborate that, and that was sort of part of the principle on which we recruited people. So by doing that, we recruited people who liked that idea.

I think there's a huge strength in science in collaboration, and not the sort of forced collaboration where you are told you have to collaborate for some grant for a particular purpose, but sort of the collaboration that comes from learning about what somebody's doing and realizing that there's something you could do together that you couldn't do apart. And because we were isolated and then because our welfare really was clearly interdependent on how all of us did, I think it was easy to forge very strong scientific collaborations.

**Williams**: So collaboration is how you all operated together, but what lines of direction did you take scientifically?

**Swain**: I had several things I wanted to do, several sort of scientific concepts when I moved in. The first was to sort of take the reductionist analytic approaches that we had used in vitro and apply them to in vivo studies of infectious disease using transgenic mice, using genetically manipulated mice, and other tools, high

throughput analysis of FACS, fluorescent activated flow cytometry, and other approaches such as that.

I was extremely lucky that we recruited really, really talented people. We recruited Fran Lund and Troy Randall, David Woodland and Marcy Blackman, Markus Mohrs, Laura Haynes, Andrea Cooper from TB, Steve Smiley. We had a diverse group of people, but they were all talented, highly talented, and with different approaches, but all of us interested in how the immune system can deal with infectious disease. So we had a real focus.

That was a time when people were very concerned about influenza, very concerned about bioterrorism, so we could be quite successful at gathering the funding necessary to conduct high-quality research, and I think the Institute became really very well known for that research. I mean, there had been very fine scientists there before, but perhaps it didn't have quite the outside recognition that it gained over the next decade.

**Williams**: These people you just named, were they in addition to the folks who came with you from California?

**Swain**: Yes. So the folks who came with me were people in our labs. They weren't other faculty.

**Williams**: They were not other faculty?

**Swain**: No, by and large, they weren't. I think one was, but, yes.

**Williams**: Did you have problems attracting postdocs to Trudeau or techs, even?

**Swain**: So there was certainly a challenge. The challenge was the spousal challenge. It's a very small town, and somebody comes with a spouse and the spouse needs to work, and so we had many couples. [laughs] Either you hire the spouse or they find a job, and, obviously, depends on what their line of work is whether that's possible. But we did what we could to make it an attractive environment aside from what I've mentioned. We had lots of seminars. We had faculty housing and postdoc housing right on campus, a beautiful campus overlooking the lake and the mountains, and that was very attractive. We built an extension and we were able, with a generous donation, to put in a daycare center that operated at the same hours as the Institute was open. So all these things were draws, and we actually got exceptional postdocs and we also got very highly skilled technical staff because there were people who wanted to live in the area. So we were very lucky to have—so I would say it was actually a positive, not a negative.

**Williams**: I imagine some of that housing was in former TB cottages. Was that correct?

**Swain**: No.

**Williams**: Oh, really?

**Swain**: No. But we did have right across from the entrance something called Little Red, which was the first TB cottage. So they had these very small little cottages, and it sort of sits there as a little museum piece across from the entrance to the Institute.

**Williams**: Was there any—it's hard to ask this question—but sort of leftover esteem or whatever for Trudeau himself? I mean, how did that figure in?

**Swain**: Certainly, certainly. Unfortunately, before I got there, Frank Trudeau, who was the grandfather of Edward Livingston Trudeau, who started the Institute, Frank was highly involved in the Institute. He had an office in the front, and he had shepherded its change from a sanitarium into a research institute, and he was very excited about it, very involved. His wife, Ursula Trudeau, she still lives in Saranac Lake; she's on the board. And Garry Trudeau, the cartoonist, was a member of the board for many years, and at one time he was the president of the board for a couple of years. So there's still the patina of the TB era. Of course, it's now long enough in the past that there aren't many patients who are still alive.

**Williams**: Did Garry Trudeau do any of your illustrations for you, diagrams and such?

**Swain**: No, but he does make a wonderful pin every year for the Winter Carnival in Saranac Lake. I have quite a nice collection of pins.

**Williams**: So during your time there, can you sort of break down what happened in terms of stages or try to explain that?

**Swain**: No, I mean, we continually built by recruiting faculty, and about five years in, we were able to build an extension and bring in, actually, David Woodland and Marcy Blackman. They needed a BL3. Then we built another BL3 facility for Andrea Cooper. So we were trying to broaden our base in infectious disease while keeping a very strong analytical basic science approach, and I think that was the strength, using that.

I also developed a program in aging, which I think is very extremely important and difficult to study, expensive to study, and so it needed institutional support. We got an Aging Program Project grant, which at that time, I think, it was one of two in basic immunobiology of aging. So we also developed a good reputation in that area, and, again, understanding how aging impacts your ability to combat infectious disease is extremely important.

**Williams**: So did you receive multiple grants over that time? I would expect quite a few.

**Swain**: Oh, yes. So when we started at Trudeau, we had about 2.3 million in grants. I think Bob North had the idea, you know, let the new director have room to

expand. But at its peak, we had about 13 million in grant support. Most of the principal investigators had three or four or more grants, and I think that was also a problem, because we could never convince our potential donors that we needed money, that we needed money to continue to build the endowment, because we were so successful at raising grant money. Even though those of us who've been around for a very long time know that grant funding has its limitations and it was going to go through a bad patch, or likely to go through bad patches in the future, it was difficult to convince people of that. So what had happened, people lost some of their grant funding. It became really difficult to support the kind of institution that we really wanted to have.

**Williams**: Who would you go to for endowment funding?

**Swain**: Well, usually that's a function that's spearheaded by your board of directors. It's a nonprofit institution, and we did get some generous, generous donations from some, and we got some money from the state, which was very helpful. But there aren't any grateful patients, there's not alumni, so it's a big challenge for a nonprofit research institution to raise donations. A couple have done it, most haven't been able to do it, so it's a big challenge. With the federal funding for research falling, it's just a tremendous problem.

**Williams**: Would it be likely that pharmaceuticals would be targets for endowment funding or not?

**Swain**: Now, that's an interesting question, and one might think that, but when asked directly, they have a very poor history of supporting research, they are concerned with making products and making money, and unless they can see a tangible way that the research at that moment supports that, it doesn't fit with their goals. So when I approached pharmaceutical companies, there was no indication that they had any interest in supporting anything other than something directly that they wanted to have done. I think that's a shame. I think it's shortsighted, because I think you have to have basic research to support the pharmaceutical industry, but they didn't see it as in their interest to take on that. I mean, I don't know about the future. You would think that they would be concerned about the erosion of basic research.

**Williams**: So then the targets would be other foundations and such? Would that be—

**Swain**: Yes, and there's not so many. There's not that big a pool of money. NIH [National Institutes of Health] has the biggest pool of money, so foundations make up a much smaller fraction.

**Williams**: So what opportunities did you have to continue to be a research scientist, or did you become strictly an administrator?

**Swain**: So I was very lucky. I had very good people who worked with me, and I had quite a productive time while I was there. I did switch over to studying infectious disease and how we deal with it, and we had a lot of interesting things that we discovered.

**Williams**: I'm having trouble honing in on this in general. As a senior person, what involvement do you have in—you don't do bench work, for example, anymore?

**Swain**: No, no.

**Williams**: So it's more directing?

**Swain**: Exactly, yes. So the model that one has is that the principal investigator, their job is to fund the lab and to decide what the lab is going to study, and then you hire what you hope are talented people, postdocs, technicians, graduate students, and senior postdocs to actually do the experiments. But the fun of science, I mean, I would not have wanted to be director of the Trudeau if I couldn't continue to do science, because that's what I like to do. So, as I said, I was lucky that we could recruit so many people to come with us, because that allowed us to keep going, and as long as you're doing interesting things, then you can recruit new people, and that worked very well.

**Williams**: Did you spend a lot of time in Bethesda at the NIH over this period or not?

**Swain**: You can't go lobby NIH to get money. You just have to write grants. I mean, I do do things with the NIH. I was on the Council of the National Institute of Aging and various advisory councils and so forth, but I didn't go to NIH to raise money, because that's not how it's done. You do it by applying for grants. You don't negotiate it.

**Williams**: So the growth that you were directing at the Institute, NIH became aware of basically by passing paper through, grant proposals and so forth?

**Swain**: Yes, that's right, and seeing what was done by the scientists, so the scientists made major contributions to the field.

**Williams**: Comparing your work in the academic setting, Harvard and San Diego, what differences were there then in working at an institute?

**Swain**: I guess the biggest is the bureaucracy, that at this small institute there was no bureaucracy. There were people in the same building you could go to who would help you, and it was clear to them that their job was to help you and they did help you, and they were very helpful. But I think in a huge bureaucracy, I think the biggest shock is to go from Trudeau to UMass, which is not only an educational institution, but it's a state educational institution, it's also a medical school, so it has several layers, many several layers of bureaucracy. There's a lot of

bureaucracy and it's a little bit of a shock to deal with it. So that's a big difference. Also, of course, we didn't do formal teaching. So the scientists really could focus on their research, and I think that's what attracted the good scientists who came.

**Williams**: You feel that an institute, in the eyes of the NIH and elsewhere, is fully competitive with the academic programs?

**Swain**: Oh, yes. Oh, yes. They always encouraged us very much. I think everybody appreciated that having a place where the scientists could really focus on their research, not be distracted by bureaucracy, and that everybody could appreciate what a strong thing they are, but the current structure of funding can't really support nonprofit private institutes.

**Williams**: So what do you see as the future for [nonprofit private institutes]?

**Swain**: I think that they will disappear over time.

**Williams**: I notice both you and your husband took adjunct positions in Vermont and New York, Burlington and Albany, so I thought that that was probably a way that you could continue to function as a teacher. Was that right, or why did you choose adjunct positions?

**Swain**: You might think that, but actually I have to say the number of times we went to teach was fairly limited, but we did have excellent collaborations with scientists at those institutions, so it was more for pulling together and scientific collaborations. Usually at academic institutions the faculty at those institutions need to teach in order to advance their careers, so your faculty shouldn't be competing with them. So I think some of the people at the Trudeau did miss the opportunity to teach.

**Williams**: Did you and your husband? Because you—

**Swain**: We had taught a lot, so I would say I did not particularly miss it. I had done my teaching, and I think my husband the same, so we'd had a lot of opportunities to be educators.

**Williams**: So talk about the transition from Trudeau to University of Massachusetts.

**Swain**: So I was lucky enough to be able to move here. The University of Massachusetts has a lot to offer, and, again, I think with every new challenge, if you take advantage of the new opportunities, you can sort of enhance your research and build on what you've been doing. UMass has a highly diverse group of immunologists in several departments. There's the Department of Pathology I'm in, where there are excellent people in T cell recognition, antigen processing, signaling pathways, also in the kind of thing that we actually do, virology. So it's wonderful to collaborate with them.

Then there's the Department of Medicine that has an awful lot of people working—really amazing group—on pattern recognition, receptors that see pathogens, so pathogen recognition pathways separate from the adaptive immune system receptors that influence the innate system. So that's a wonderful opportunity to work with them. Then there are also more immunologists in a program that's molecular. Now it's what is called MAPS, molecular genetics and physiology. So there's really a wonderful group of people.

Then there are people in metabolism, which is very relevant to immune function, and in molecular approaches, such as Craig Mello, who, of course, won the Nobel Prize. So there's really a lot of opportunity for collaborations in areas that are new, and I think to keep interested in the research and to keep your approach fresh and to really move forward, you need to take on new approaches.

**Williams**: You still have a connection there or—

**Swain**: I'm adjunct faculty. I'm on two program projects with people at Trudeau, so one of them is a project that I'm the principal investigator of, and Andrea Cooper, who is still there, is on, and another one is an aging project that I was the original instigator of, and before I left, Laura Haynes took that over, and she's still there, and I'm on that. So, yes, I have a lot.

In fact, I was there two weeks ago. I was honored to give an introduction to the Steinman Memorial Lecture. So Ralph Steinman had been on the board of Trudeau, I think since 1981, and he was a huge supporter. It was because of him that I went to the Trudeau, and he was a fabulous supporter all the time I was there. H was a wonderful, wonderful fellow. We owed him a huge, huge gratitude, a charismatic, enthusiastic fellow, who was totally dedicated to the Trudeau. So I was very honored to do that.

**Williams**: Expand a little bit on his role in drawing you there.

**Swain**: Well, he was relentless.

**Williams**: He was there.

**Swain**: No, he was not there. He has always been at Rockefeller, but he was on the board, and he was part of the recruiting team. Ralph could convince anybody of anything.

**Williams**: What do you imagine was his thinking about how that would be such a good fit for you?

**Swain**: I don't know. I don't know. I don't know why he thought that. It's interesting, yes.

**Williams**: Did he start that campaign because he knew that you were looking to leave San Diego?

**Swain**: No, I don't think so.

**Williams**: Or would you have stayed there if—

**Swain**: Dick and I had always fantasized about having our own institute, so that's an important thing to know. And I love all bodies of water. So when I got this letter—I got a letter, cold, you know—asking if I would be interested in applying for this position, I said, "Ah, Saranac Lake, Trudeau Institute. Sounds like it's on a lake." But I didn't really believe it. But, anyway, so that's how it started, and we were very charmed and excited about the possibility of creating a really fine research environment and moving into infectious disease, as I had said.

**Williams**: What was your husband's role over the period of time you were there?

**Swain**: He helped with everything, so he was my collaborator and co-administrator, and so that was very, very good. Two minds are always better than one.

**Williams**: And you had plenty of pillow talk, I guess, over that period of time.

**Swain**: I don't know. By that time of the day, we didn't need to do pillow talk.

**Williams**: Great. Looking over your career to date, sort of in laymen's terms, talk about what you consider to be your major accomplishments and how they might affect the public at some point.

**Swain**: Oh, yes, this is the biggest challenge always, explaining it. I guess my first major accomplishment, so I was very interested always in T cells, which are the cells that regulate the immune response, especially CD4 T cells. So those are the cells that I've mostly studied, and we sort of started from the beginning studying what happens to—the T cells, the amazing thing, they have a very complex differentiation. They come out of the thymus, and in the thymus they've generated this diverse repertoire of receptors, and they come out of cells that are called naïve, meaning just that they have receptors, although they haven't encountered their antigens that they recognize.

So we sort of started at the beginning with the naïve cell and have sort of followed it all the way to the memory cell. So I always had the idea that the memory cell that is able to respond so much better in the secondary response when antigen is reencountered, that that's your goal, but you have to understand the first steps. So early on, I worked more on the first steps and have sort of evolved.

The first major thing that I did was to show that you had these two types of T cells, and they were just being described when we were doing this work in the mid-, late 1970s. There are CD4 cells and there are CD8 cells, which are surface markers. So that doesn't tell you anything about what they do, and people had thought that CD4 cells were helper cells and CD8 cells were killer cells. So that was the functional distinction. We realized from the studies we had been doing that there was something more fundamental that separated those two populations, and that was what they recognized.

So there was the discovery of major histocompatibility antigens, and it turns out that the way T cells recognize antigen is to recognize these major histocompatibility antigens that are binding the peptides, all the universe of peptides, which can come from bacteria, virus, whatever. So we fell on this discovery, as I think most major discoveries are not made with people thinking they're going to make a major discovery and planning it. There's something that you discover as you do something for some other purpose.

But we discovered that CD4 cells could, in fact, also be suppressors, which was thought to be a function of CD8 cells, but they still recognized this second class of MHC molecules, MHC Class II, whereas CD8 cells could have functions other than killing, but they would still recognize Class I MHC. This was before the nature of the T cell receptor was understood, that the T cell receptor recognized these MHCs, and it was sort of one of the basic facts about T cell recognition that contributed to the way people thought about how T cells recognize antigen.

We still work on that today, so many, many years later it's clear that these two populations of cells, CD4 and CD8, although they have differentiated to have a set of different functions, they also overlap in many things. In fact, right now we're studying how you generate CD4 T cells that have killer functions, which was thought to be the *sine qua non* of CD8 T cells. So we're still studying that years later.

**Williams**: By moderating the—

**Swain**: So by all the things, so the differentiating of the cells turns on and off various genetic programs, and it turns out that when you have, for instance, influenza infection, you actually generate a good population of CD4 T cells that are cytotoxic and that play an important role. They've been identified in humans, they've been identified in mouse in some diseases, but the spotlight has not really been shown on them, and we're finding out exactly what it is you need to generate those cells and what functions they have, and it's actually very interesting.

**Williams**: And there's no thought that you could modify this process.

**Swain**: Oh, yes. So the whole purpose of understanding the process is how you can make vaccines that can give you what you need. So there's a lot of steps. First you

have to know what are the processes that lead first to the generation of the effector response that deals with pathogens when they come in the first time, and then how do those cells go to memory, and then which kinds of memory do you need under different circumstances to combat a pathogen when it comes in again.

A tremendous amount has been learned, but there's still an awful lot to be learned. We're still looking at those fundamental questions. So we just published a couple of papers on what memory cells can do, I mean, new things that people didn't realize. So there's a huge amount, because people have tended to study the beginning of the process more. It's easy. It's much easier. It's harder to study memory. So there's still a tremendous amount to learn.

One of the things we found out is that memory T cells that you generate with a previous infection are incredibly multi-potential. They can turn into cells with all different functions, and they do. So under a circumstance of reinfection, they will turn into many, many, many different subsets that do very different things, that do very different things in different places, so in different sites. So, for instance, if you get infection in the lung, you have unique subsets of cells that have functions in the lung. You have different ones in the periphery that are helping B cells make antibody and doing other things. So there's tremendous multifunctionality that is just—many people have been studying this over the years, and it's just beginning to be apparent how diverse this is.

**Williams**: How different is the response to a vaccine as opposed to antigen itself?

**Swain**: That's a very good question. I think the real question is how different. So the immune system was evolved to deal with pathogens, and so a pathogen comes in, you mount a response to it. If you're lucky, that response is big enough and you survive. Then each component of your immune system has developed immunological memory and now is much, much better to work again. That happens extremely well when you encounter, when you actually are infected with something.

Vaccines, the original vaccine, the smallpox, actually cowpox, but to protect against smallpox, was a live vaccine, so it did the same kind of job that the infection would do. Many of the successful vaccines are attenuated vaccines, so they are the polio vaccine, for instance. They are live vaccines, but, of course, health concerns and so forth have now led to the development of lots of vaccines that are actually not live.

The real problem is that the immune response, that those non-live vaccines, non-pathogen-based vaccines often are not very good at engaging all the components of the immune response, because the way that they're engaged is based on the different pathogen properties that they respond to, but in order to convince people who make vaccines, we need to show why it is that the simpler vaccines, vaccines

just made out of proteins, perhaps, with an adjuvant, why they don't do a very good job of producing this really excellent state of protective memory.

**Williams**: What do you see as the current and potential implications of this for public health?

**Swain**: Well, I think one of the things that attracted me to immunology and certainly also many, many of my colleagues is that it's so relevant to human health, to really all aspects of human health, but especially to protection against infectious disease, to protection against cancer. So the immune system has the capacity, if properly harnessed, to protect us against the most terrible diseases, but in order to bring that to fruition, in some cases we've been lucky, some vaccines have been amazingly effective, but only against some things.

The immune system has the capacity to protect us against infectious diseases of all kinds, to protect us against cancer. It is the cause of the overactivity or the misplaced activity in the immune system is responsible for autoimmunity, for allergy. So the immune system, making sure it works properly could produce huge improvements in human health. As I said, this is why myself and many of my colleagues, actually we're fascinated by immunology. It's both an intellectually fascinating problem because it's so highly sophisticated, but it's also of tremendous importance. But in order to harness the immune system and to use it effectively, we need to understand how it works.

Actually, there's a huge amount still to understand, so we have sort of a basic outline of how the T cells and B cells and innate system work, that they respond, that they differentiate, but over the last, I think, ten years, with the sort of improvement in analytic techniques and signaling pathways, in genome-wide analysis, in fluorescence-activated cell sorting, it's become clear that the immune system is much more diverse and powerful and complex than we appreciated. So there's a huge amount to discover about how we get effective immunological memory of the kinds that are protective without inducing deleterious things. It's a very carefully balanced system, so there's positive activities in immune system that kill, for instance, virally infected cells, and then there has to be something to shut those off, something to damp them down so they don't continue after the virus is gone. So it's a very complex system with many interacting parts that all have to work together, and so there's a huge amount to learn.

The ideas that once you've learned that, you should be able to design strategies to manipulate it, so that you have new kinds of vaccines that are really effective at engaging all the parts of the immune system, not just the B cell antibody response and that can ensure that they don't go too far, but this amazing complexity means that it will be a little while before we figure it all out. Actually, in immunology it's sort of ironic that with the loss of funding for basic research, basic research has over the last ten years, I'd say, exploded into finding new things at an amazing pace. In fact, it's very hard to keep up with it. All of us scientists feel

humbled and a little overwhelmed by the amazing pace of discovery, and it's at this time when things are going so extraordinarily well from a scientific perspective, that basic research funding has really dropped to a very low, very low level.

So when you sent in a grant ten years back, the chance of it being funded was about one in four. On the first go-round, one in four of the grants were funded. This year, in some instances they're predicting that less than one in ten, one in fifteen will be funded. So funding for basic research especially, there's been a lot of funding that's been going to more directed research. So this is really astounding, given the great success of basic research and the great potential for its application to human health. It's sort of quite unbelievable.

I think basic research may be moving to other countries. This last weekend I was visiting friends in La Jolla, and we discovered that several people we knew were moving to other countries, one to Singapore, one to Korea, because they couldn't get enough dependable funding to carry out their research.

**Williams**: You mentioned direct research just a moment ago. Just give me—

**Swain**: Directed research, yes. So if you look at the total funding of the NIH, it has not fallen very much, but not so much funding is in what's called investigator-initiated research, especially that where the investigator says, "This is what I'm going to study." So there's a substantial amount of funds that are being directed to mechanisms where you're sort of suggested what will be studied, and then you put in a proposal to study it. To me, that flies in the face of exciting, basic discoveries, because I think most really exciting discoveries almost happen by accident, by serendipity. You're studying something and you get some result that is unexpected, and that leads you down a path you had not planned to go down at all, but that turns out to be exciting and new and tells you something fundamentally different that nobody realized.

That, I feel, is true of the discoveries that I've made, that I wasn't looking for that discovery; I was looking for something else. And I try to tell my students that. It's a hard concept, because everybody is most comfortable, including those who fund us, with the concept that "I have this problem, these are my hypotheses, I'm going to test them, and we'll move forward in this very clear-cut way." But, in fact, that's not how you make most exciting discoveries. You made them because you're engaging in that kind of research but something comes up that was unexpected.

So these mechanisms where they have a place, they fill a need, but I think it's out of balance, and basic research is not being funded well enough. And I think if you don't have the basic research, eventually you can't translate it, and we're all interested in ultimately translating the research. That's what everybody's goal is.

But you need to understand things in order to translate them, and we're falling behind in funding that first step of understanding what's going on.

**Williams**: Give just briefly a couple of examples of directed research.

**Swain**: So directed research would be almost like a grant, except it would say look at the effect of a particular, for instance, adjuvant on a vaccine to a particular disease. And that's fine. I mean, that's something that is important to do, but that's not going to give you an unsurprising answer.

**Williams**: It's very directed. [laughs] And would that come mainly from NIH to investigators, or who would propose that?

**Swain**: Yes. So they're under a mechanism that's called U. I have no idea what U means, but there's a whole bunch of these U mechanisms. Actually, some of them, many of them, are cooperative grants among different institutions, different investigators. They take a big chunk of resources. They're very clear-cut. You say what you're going to do for seven years at a very high level of detail, with very clear milestones, and the NIH monitors that you reach those milestones. But it doesn't allow you the freedom and it doesn't encourage finding out bold, new things that we don't already have an inkling of yet.

**Williams**: You do a wonderful job of describing things in laymen's terms, and I just want you to do one other, and that is talk about the relationship between T and B cells.

**Swain**: So I talked a little bit before about the relationship between CD4 and CD8 T cells, how they were sort of overlapping but different. So B cells really are different because they are the only cells that make antibody. So the production of antibody, antibody is a very powerful protective mechanism, so it's extremely important to make antibody. There is a lot of fascinating things about B cells and how they make antibody, and they also have memory, and memory B cells respond much more quickly. The key thing about B cells, that is to make the best antibodies so they can make some antibodies sort of autonomously without the involvement of other cells, but in order to make the antibodies that are most effective, they need to be helped by CD4 T cells, our favorite cell. [laughs]

So the production of and actually the generation of B cell memory, long-term B cell memory, the kind we all hope to have, including long-term secreted antibody so that's in your system so you can pass it on to your baby if you're a mother, that is completely dependent on CD4 T cells. So, again, you need multiple arms of the immune response.

One of the things that I think is really important is that we studied which cells were involved, which arms of the immune response were necessary for a response against influenza. If you give a low dose of influenza, if you have any of those cells, a CD4 cell that's specific, a CD8, or a B cell, you're fine. All of them are

fine. But as soon as you start raising the dose, making it a more dangerous pathogen, then you need others, and what you find is that they cooperate with one another. So if you have CD4 T cells plus B cells, or CD4 T cells plus CD8 cells, they are very effective, much more effective than those individual cells on their own.

So the whole immune system together, if you can have everything, that's what you want. So you want your vaccine to induce all the different arms of the immune response, and that has not been the focus of vaccine makers. They have focused on antibody, easiest thing to measure, but they have not focused on generating these other kinds of immunity, and that's really important.

**Williams**: Let's turn to the Association of Immunologists. You became a member in 1977, I found.

**Swain**: At the beginning of my career, anyway.

**Williams**: What induced you to make that commitment?

**Swain**: It's sort of obvious. So the journal of the Association, *The Journal of Immunology*, is a fine journal and very sort of nonpartisan. It covers all aspects of immunology. That's one of its big strengths. It demands scientific rigor but it doesn't discriminate. It doesn't say, "Oh, well, this is interesting this week and something else is interesting next week."

Mostly, I think I appreciated the fact that the organization had a political role in trying to support immunology in a more broad way, and I think that's what the strongest role of the Association of Immunology is. It's not only to provide the sort of institutional support for immunology and hold the yearly meetings and run the journal, but to deal with the issues that come up and to try to support funding for immunology, and it's always hard to make the case for basic science. It's an obvious case, but the rewards aren't going to come for some time, so it's not an immediate reward, and it's a big investment.

**Williams**: I notice that the first committee you went on, I think, for the AAI was the Women's Committee.

**Swain**: Yes.

**Williams**: Why that and what—

**Swain**: When I graduated from Harvard Graduate School, half of my colleagues were women who were getting their degrees, but if you looked at the major faculties around the United States of scientists in immunology and other things, the representation of women, especially at the professor level, was very low. In fact, I think at UCSD it was about 10 percent when I went. Most of the big labs were

run by men, and it was a hard thing for a woman to forge her way in and be treated equally and become a scientist. I have to say that at Trudeau, not only did we have a woman director, but half our faculty were women. When we had seminars, half the seminar speakers were women. I suspect that may be unique and deliberate, although not necessarily stridently mentioned. It just happened because there were excellent women doing excellent science.

**Williams**: Was the AAI itself sort of a men's club at that time?

**Swain**: That's a good question. I think not as much as some things, not as much, and certainly by the time I was elected a councilmember, there were a number of women, and I think it's become highly, highly influenced by women. It's a very equal influence.

**Williams**: Is that due at all to some of the activities of the Committee on Women?

**Swain**: Certainly, partly. They worked very hard to make a list of speakers to try to especially promote visibility of women scientists, and they still work at that.

**Williams**: At what levels, in what places?

**Swain**: Well, I think they have a list of seminar speakers, so if people are looking for women. I think the climate has changed a lot, and people often are looking for women speakers, and so this helps facilitate that, but it hasn't changed totally yet. It's not an even playing field, but it's getting there. It's way, way better than it was when I was starting out in science, way less discrimination.

**Williams**: Do you recall some stratagems that the Committee on Women used over the years or not?

**Swain**: I think mostly they just lobbied within the things that the AAI had some control over, for instance, committees that the AAI promotes, editorial functions of the AAI. Actually, *The Journal of Immunology* is going to have its first woman editor. She was just chosen, Pamela Fink, a friend and a colleague of mine. So, over the years this kind of attention to making sure that there were women represented at every level has made a huge difference.

**Williams**: Have you had occasions in your own career where you really bumped against the glass ceiling?

**Swain**: Sure. [laughs] It's not something you particularly want to talk about, because, obviously, you can only do so specifically by inciting those who impose the ceiling on you, but certainly many times, and I think every woman in science has had those, just a lack of appreciation by some of your male colleagues that you could be a good scientist, just sort of an assumption that you were limited by the fact that you were a woman, many times.

**Williams**: Have you developed particular strategies to combat that?

**Swain**: There's not too much you can do except just do as good a job as possible, and sometimes a little prodding.

**Williams**: You then went on the Program Committee at the AAI. What was that like?

**Swain**: Oh, that was fun, because the Program Committee decides what areas should be covered in the meeting. It's a big committee that has many different people. It's all about the science, so it's lots of fun.

**Williams**: But the Program Committee's only function is the annual meeting?

**Swain**: Yes. Basically to develop the program for the meeting, yes.

**Williams**: Then you were invited to join or stand for the Council?

**Swain**: Yes. So the councilmembers and the nominating committee, they identify people they think would be good councilmembers, and then they're voted on by the Council and the three candidates that get the top votes are invited to stand for election.

**Williams**: What was your reaction to being nominated?

**Swain**: Oh, I was very pleased and honored.

**Williams**: And then you won, and so you were on for, I guess—

**Swain**: This is the standard thing. So you're on for seven years. You're a councilor, then you're vice president, president, and past president.

**Williams**: Were there particular issues while you were on the Council that you recall?

**Swain**: That's a good question. I know the things that I was concerned with, certainly when I was president, I was very worried about the funding situation, and I could see that there's some inherent challenges in funding, which is that it had been growing, and it can't grow forever. I think that the way that basic science has been structured in this country with people starting labs, having a lot of trainees, postdocs, graduate students, who then want to start labs, it has sort of an inflationary trajectory. It couldn't go on forever with that kind of—so I thought there was an inherent challenge that funding could not go up.

I did not, I guess, anticipate the very flat, actually declining funding that we've had in the last few years, which is a disaster, in my opinion, but I did realize that funding was going to have to level off, and that was going to make a problem for

the people coming up, because there were more of them at every level, many of the people above them. So there is a problem, and I think there's going to have to be major changes in the way labs are run, regardless of whether there's good research funding. If there's good research fundings, I think labs can adjust. They need to have fewer, probably, people at the training levels because there won't be jobs for them, basically, and so they have to run their lab in a somewhat different model. I think Leslie Berg talked about that in her presidential address, so we see eye-to-eye on that.

But I think at the moment with funding actually eroding, I think it's in danger of crippling basic research in the country at the moment, because I think the senior people—it's so uncertain whether you're going to have research funding, that people can't adjust to that. I mean, it's not acceptable, and so people, like I said, I think they're leaving, they're dropping out of science. Sometimes they're very excellent people. It isn't just choosing the most talented. So I think there's a serious problem. We have other serious problems, and it's not being addressed.

**Williams**: Be specific about what you see as the new model that needs to be.

**Swain**: So it's very hard to be specific, I think. People have to first accept the reality, and I think that hasn't quite happened. I think the size of graduate programs has to shrink. There's no point in training a huge cadre of people. People's research depends on those graduate students, so people have to have smaller groups. Success has to be measured not totally just by the volume of what you produce, but just more by the quality and what you find out.

So it's going to mean smaller labs, career employees, as opposed to trainees, because you can't be expanding the field. So I've trained and many people have trained—and I'm no exception—have trained maybe twenty postdoctoral fellows. That's a huge increase if they were all to aspire to your position. So some go into industry, but a lot of them try to go into academics. So it's clear there's a problem with the structure.

**Williams**: You say twenty postdocs at a time.

**Swain**: Altogether, over their career, over their lifetime.

**Williams**: No, you said *you* have been responsible for twenty postdocs.

**Swain**: Over my whole career. So if you train that many people who would like to have the job that you have, it's too many.

**Williams**: In your presidential message, you talked about some very specific things related to NIH. For example, cost for construction were being converted into contracts—I'm not terribly clear on that—and the NIH roadmap.

**Swain**: Right.

**Williams**: Were these issues that are still prevalent? And the diversion of funds to multidisciplinary and team research. So talk about those issues a little bit.

**Swain**: So the last of those is, in fact, what I was talking about with these U contract things. So the NIH, as I am, likes the idea of scientists collaborating together to reach a common goal, and I think that's a wonderful concept, and when it works, it's a very good thing. But it doesn't work when it's applied from above and they say, "Okay, everybody get together and achieve this particular goal, and this is the goal that you need to achieve."

I think some of the best work is done by scientists working with their group of people following where the science leads. I think it's where the science leads that's so important, because that's how really new discoveries are made. If you're following, if you have to adhere to a particular pathway, when those new things come up, you have to ignore them, because you're going to be on the phone to the NIH in a couple of weeks, and they're going to say, "Well, have you done this?"

And you said, "Oh, well, no." So that's the kind of thing that I worried about.

The roadmap included diversion of funds from basic research to initiatives from the director in areas that the director found interesting. So, again, I think it's not leaving it to the scientist to choose the science that's done, but having the NIH choose the science that's done, and I think that's one of the reasons why, as I said, although the budget has only gone down slowly, the budget for basic research has been much more severely impacted.

**Williams**: Would it be true to say that the director in this case and other cases is also responding to political pressures with their own funding consequences?

**Swain**: Oh, absolutely. Absolutely, absolutely, and that's a big challenge for them, but it would be wonderful if they and everyone else could articulate better to the granters of money how the really fundamental discoveries are made so that they don't cut off this wellspring from which the really fundamental things come. That's their job to do, and some of them do it extremely well. So they do do it, but still this change has occurred, and it is in response to political pressures, but also it's in response to sort of the desire for anybody who leads something to have an impact. They want to have their personal impact, things that they think are important. It's bad, not because that's not a perfectly reasonable desire, it's a very fundamental desire, but the scientists have to direct. If they are to find out really important, new, unanticipated things, they have to be in charge of where the research is going.

**Williams**: What do you see as the Association's role in this particularly turbulent time?

**Swain**: So I think it plays a tremendously important role because it has worked very hard. It has a Public Affairs Division. They do politic, they do have a lobbyist, and they are trying to articulate some of these. It's always very difficult to articulate these kinds of issues, and especially in hard times. It's easy for people to say, "Well, you haven't cured my son's cancer yet." And it's true, and it's horrible. So, as I said, my father and my sister both died of cancer in their forties, so unacceptable. So it's perfectly understandable that people want to see translation, want to see the cure, but the only way to get to many of the aspects of the cure is to understand what's going on, and that's a very, very hard job. But it will only happen if you understand the basics, and that is not achieved when you do the more applied research.

**Williams**: Looking back over your career to date, what would you say are your happiest moments in the field?

**Swain**: Well, I guess the happiest moments are when a postdoc comes in with a wonderful new finding and you realize that you've discovered something that nobody knew before that's really new and different and unexpected. Even at the beginning, you sort of start to say, "Well, how could this really fit in to how to build a better vaccine?" So those would probably be the best.

**Williams**: If you had your career to do over again, would there be things you would do differently?

**Swain**: I don't think so. I think I've been very lucky, very lucky to be a scientist when there was enough money and the field has been growing and moving into new areas. I had the opportunity to actually move into new areas myself, so I expanded and I still kept the focus on understanding memory, so, yes, I've been very lucky.

**Williams**: Any thoughts about the dynamics of a team such as you and your husband have had in research?

**Swain**: Yes. So a lot of our friends are scientific husband-and-wife teams that work together. I think a partnership makes it easier. You have someone to share your joys, triumphs, and miseries with, and there are plenty of miseries. So I think having somebody to talk to who understands is a wonderful help. So I know a lot of people sort of cringe at the idea of working with your spouse, it's a common response, but I think it's a very, very good synergy.

**Williams**: Mention a couple of miseries.

**Swain**: Lots of miseries. I mean, a lot of times when you find out something new, it's very hard to get published, and sometimes you get high levels of criticism, and, of course, now with grants, that's the biggest misery, not being able to get grants. And I think the other misery has been growing bureaucracy, dealing with all sorts

of things that distract you from getting your research done, dealing with animal protocols, and any scientist will share the difficulties one has now because of increasing bureaucratic demands, compliance issues.

It's much easier for the administrations to respond by putting all the onus on you to solve the problems, so it's clear there needs to be some regulation so that things aren't done, so that animals aren't abused, etc., but the way that these things are administered is they just make lots of hard and fast rules, because that's what it's easy to do. Then often they undermine your ability to do the research and they increase the cost. As the money is decreasing and the costs of compliance are increasing, it's very difficult to do biomedical research to study infectious disease. You can only do that in animals, and it's very, very consuming to have animals. You have to have somebody in your lab who spends most of their time dealing with the issues. When you work on humans, there's also a huge number of issues to deal with. The purpose of them is to protect, and that's wonderful, no question, but the way that they're imposed creates a huge burden and huge expense, and the results are you get less research done per dollar, and there's not much cost benefit analysis.

**Williams**: What recreational pursuits and outside interests have you had?

**Swain**: Outside?

**Williams**: I mean, one of the ways I ask this question is what does a scientist do for fun, but I know perfectly well that doing science is fun.

**Swain**: It is. It is. So I have children, and so they have always been extremely important to me. I've always loved to do things outside, hike, swim, canoe. And I love to travel, so I've been lucky that I've had more opportunities to travel than I might have, being a scientist, so that's been wonderful. And I love to garden, and as long as you live in some place that has soil, you can do that.

**Williams**: Are we leaving anything that you can—

**Swain**: No, I think I have said a lot. I worry about the future of basic science in the United States. I worry about it a lot. I have wonderful people in my lab who could make a great contribution, and I worry that they won't get the chance to do it.

**Williams**: On that happy note, thank you very much, Dr. Swain.

[End of interview]