The American Association of Immunologists
Oral History Project

Transcript

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Williams: This is an interview with Dr. Thomas A. Waldmann for the American Association of Immunologists (AAI) Oral History Project. Dr. Waldmann is Chief of the Metabolism branch of the National Cancer Institute, National Institutes of Health (NIH). He was awarded the AAI Steinman Award for Human Immunology Research Award in 2007. We are in the Lymphoid Malignancies branch of the National Cancer Institute on the NIH campus. Today is Thursday, December 3rd, 2015, and I'm Brien Williams.

Thank you, Dr. Waldmann, very much for doing this today.

Waldmann: It's a delight.

Williams: Good. Let's start with you telling me about your family background, who your parents were and where they came from and so forth.

Waldmann: Well, my father, Charles, and my mother, Elizabeth, are immigrants. They came from the old Austro-Hungarian Empire, my father from Czechoslovakia, my mother from Budapest. But my father went to engineering school in Budapest and met my mother's brother, and so after my father had been in the United States for six years, 1922 to '28, he said, "Is Elizabeth married?" And the answer was, "No," and that was resolved by their getting married, and in 1930, eighty-five years ago, I was born. I'm an only child, and I was born September 21, 1930.

Williams: In?

Waldmann: New York City. And we lived in New York City during the onset of the [Great] Depression when things were really tough. My father had worked with a major construction company [Comstock Industrial Construction Company] as chief engineer. They did the airplane plant in Baltimore or the initial white-bread conveyor belt segments. But when Comstock, my father's boss, became bankrupt twice because he bid on the margins, he committed suicide, Comstock, and this left my father without a job in a very tough era.

But the New Deal was opening, and in 1936, we moved to Washington, and the vast majority of my life has been in Washington. He worked in the Resettlement Administration, Greenbelt, a community that still exists in Prince George's County [Maryland]. He was critically involved. And we stayed there in Washington, but during the war went to Detroit, where the bomber plant was being built on the old Ford factory to make housing for the workers there. Then, ultimately, when the war was over, we moved to Illinois, and I graduated from Evanston Township High School and went to the University of Chicago, an unbelievably formative experience for me. I was, like everyone, a philosophy major.

Williams: Like everyone?

Waldmann: Well, you had to take fourteen courses, and I passed out of the science and math ones by exam, leaving the second philosophy course of Plato, Aristotle, John Stuart Mill. So I was always through the night arguing with my friend, and he was interested in mystical, almost religious aspect. So we would agree that the questions that I was asking were answerable by science, but to him irrelevant, and to me, the questions he was asking were cosmic and global but unanswerable. So he, Flick Loeb, Sherm [Sherman M.] Weissman, who I met there, we were best men at each other's wedding.

I was an only child. My father died of a heart attack as I completed University of Chicago, and we all decided it would be good to leave home, and I went to Harvard Medical School.

Williams: What was your father doing in Chicago? What took him to Chicago?

Waldmann: He went with his previous boss to make Park Forest, Illinois. Park Forest is a community of about 30,000 people in the south of Chicago, so everything from churches to—it has been written up in many sort of sociological texts as one of the very early totally designed communities, although community design was much older. My uncle, who died before I was born, he was in Europe, was a designer of communities. He was an architect.

Williams: So you then must have moved a little bit from philosophy over to science. Is that right? How did that happen?

Waldmann: Of course, one has to take premedical courses, but one of the first efforts at science—science, by that I mean laboratory science—Sherm Weissman and I received a $50 grant, five-oh, and a niche at Harvard Medical School to study what was going on then, the erythropoiesis-stimulating factor by Allan [J.] Erslev. But if you wish anecdotes, I had a little medical condition of no relevance, but it brought me into Peter Bent Brigham Hospital [now Brigham and Women's Hospital], but we still needed to do the experiments. So at midnight each night, Sherm would bring my blue coat to the Peter Bent Brigham, I would sneak out of the hospital, and at dawn I would sneak back in, we having done the experiments in our rabbits overnight.

Williams: That displays a great dedication to your work.

Waldmann: Since you wish elements that are science and not science that give you a sense of the era, this was the era of the McCarthy era of investigation, and the Velde House Un-American Activities Committee came to Harvard to find communists and whatever they found. But there was a reaction in Vanderbilt Hall, which is where I was, and somebody painted all the toilet seats red. And I got up to urinate in the middle of the night, and my tennis shoe ticked the edge of the red-paint toilet seat. So the next thing I knew, I was brought back from the Mass General [Massachusetts General Hospital], and the whole panoply of the people in the

Dean's Office were there, and their first comments were, "You are financially and morally responsible for this." So I thought my scientific career was over.

But one of our classmates, who was, in fact, a newspaper person, thirty-five, entering medical school, and working in the Dean's Office, said, "Tom is too much of a grind to have done such a thing." [laughs]

I did not get into trouble, but my friend Sherm Weissman, I'm sure, was involved in the next. In my mail lockers every day, a little red jelly bean, every day, every day, every day, until finally I came to Washington, where my mother was, and at a party, a little girl of about two came up to me and said, "Mr. Waldmann, here's your red jelly bean." And that ended the story.

So medical school, otherwise, is like medical school, right? You work hard, but it has not quite the challenge at that time that undergraduate did. The next step was that I went to the Mass General Hospital, and what I have not written was we have the last of the polio epidemics, 300 patients with polio, seventy in these tank respirators. And since I was on rotation through dermatology, I and K. Frank Austen were assigned to the polio service, and it was really devastating. Every other tank, we had someone watching, a divinity student, someone from here or there to make sure that no one left the ports, the doors open.

The next year, the Salk vaccine. That was 1955, '56, and so that's the last polio epidemic that we've seen. I was so impressed that the Salk vaccine, that the immune system, that there was a way of preventing this catastrophic disease. That was one of the elements in my choosing immunology. Certainly, if we fast-forward to now, it is the hope that one will eliminate polio from the world, right? Polio [type] 1 and 2 are gone. But we had in [John F.] Enders, [Thomas H.] Weller, and [Frederick C.] Robbins at Harvard Medical School, the people that made the really leap. They cultured the viruses, and then it was sort of obvious, but this, again, reveals prevention as a way of going.

Williams: Did you have some very important mentors at Harvard?

Waldmann: Throughout my career, which you'll see, it has not been people who are above me that are the mentors. I have inverted throughout the normal experience in having my postdoctoral fellows, my fellow interns, one of which is Kathy Spreng Waldmann, who I married. So that the key often was people like technicians and others.

You will hear that I never had training in research. I came to the NIH because the doctors' draft was there. My boss, Jesse Steinfeld, resigned, and I became de facto, with a $50 grant as my only research experience, a tenured investigator at the NIH. And I learned from the corridors. My mentor was walking with someone to the lunchroom.

Let me give you a sense. Let me give you a sense of how little was known. I have it written there. Maxwell Wintrobe had the classical hematology textbook, and in it said the role of the lymphocyte is totally obscure. It has been denied that it carries lipids from the endothelium to the lacteals. How can you—could you visualize that now? So what it says is if AIDS had appeared at that time, it infects a T cell, but the T cell had not been discovered. It enters through a cell surface receptor that had not been envisioned, caused by a retrovirus that also had not been discovered. So what it means is that the techniques of the day, the things that everyone feels have been known since Egyptian times, were, in fact, not known, and that although cardiology, endocrinology were far advanced, immunology was not. [Byron H.] Waksman, the son of the Nobel laureate [Selman A. Waksman], gave the total knowledge of immunology in one lecture of an hour to the Harvard Medical School class. We had no immunologist at the Mass General. We had one hematology oncologist, a single person. So it is telling us that even the tools—you couldn't clone a lymphocyte. You didn't have a gene.

So our approach, my approach, was to study what was called the experiments of nature. In other words, the lymphocytes in the circulation were like a Tower of Babel. In other words, you had this as a suppressor cell, an infector cell, all of them in a mix. Now we know how to separate them, we know how to do the assays, but we had no—so Sam [Samuel] Broder and I studied the leukemias of mature lymphocytes that had a function. So this one had a helper function. This other one caused, we now know by the retrovirus human T cell lymphotropic virus-1, not HIV, but HTLV-1, it is a suppressor cell. We showed that it inhibited the immune system. It was a $CD4^{+}CD25^{+}$, which we discovered, Treg [regulatory T cell] leukemia. And so we used that.

And the other area was we studied the immunodeficiency diseases. In other words, here I am, not a molecular biologist, using the patients who could not make a B cell, could not make a T cell, but we also were studying the metabolism, the turnover of albumin and gamma globulins and could discover new diseases. We could discover that myotonic dystrophy has a short survival of IgG [immunoglobulin G], or we discovered—co-discovered loss of protein into the intestinal tract, just like nephrotic syndrome, and within that, a disorder of lymphatics where lymphatic development was such that the thoracic duct lymph went into the GI [gastrointestinal] tract. So you had lymphocytopenia, had low albumin, low gamma globulin, and it was with those patients that Warren Strober and I developed some of the techniques that one can use to study the immune system.

Williams: You have said that you came here thinking that you would be here for two years.

Waldmann: Yes.

Williams: So what happened?

Waldmann: So what happened? Life in science has an aspect like dominoes. You always have a project that's incomplete and where you have planted the seeds of an orange tree and you want to harvest it. So when this one is over, however, this one is now going on. And I've had many chances to leave and be professors at most places you could think of, but there are real advantages. First of all, as we discussed, due to the doctors' draft, it brought people like Phil [Philip] Leder and, into my group, Stan [Stanley J.] Korsmeyer, Warner Greene, Warren Leonard. So that at the time we were studying one of the critical questions: how, with a limited amount of genetic material, can you make an almost infinite number of antibody molecules with different—and, of course, [Susumu] Tonegawa, Leder, [Leroy E.] Hood showed that these are bits of genetic material, like letters of the alphabet, that can be used, and we showed immunoglobulin gene rearrangement in pre-leukemia, pre-T and B leukemia, we could define whether this was an early B cell or a T cell, or how mature was it, or what was the effect of therapy. So it was answering a critical question.

But one of the aspects of science is serendipity, right? Chance. And chance opened new fields, three new fields for me, and it is that area that led to my winning the awards. And in each case, there was an impediment. The first impediment, we wanted what was newly discovered antibodies, how to make monoclonal antibodies, and monoclonal antibodies to CD4, to helper cells, but for whatever competitive reasons, we were not given that anti[body], so we wanted to make our own antibody. But our antibody was not to CD4—by "our," I mean Takashi Uchiyama—and it was, in fact, to CD25, to the IL-2 receptor alpha. It was a blocking antibody to the IL-2 seeing its receptor, and we found that virtually none of the resting cells of the body, except what we now know as Tregs, 1 or 2 percent, reacted with this antibody. But the antibody reacted with the lymphocytes of patients with autoimmune disease, those rejecting an organ allograph or those with certain leukemias caused by HTLV-1, and we reasoned we could use this antibody in therapy.

That started in 1981, and in the intervening years, first we used the antibody in what has been for us an unbelievably heuristic teaching disease, this retrovirus, HTLV-1, adult T cell leukemia, and we treated that first and then organ transplantation. And in fact, our antibody was approved by the FDA [Food and Drug Administration] for use to prevent allograph, kidney graph rejection.

But in the intervening years up to now, its real star status is in certain autoimmune diseases. So T cell mediated uveitis, a major cause of blindness, but the most pivotal one now is multiple sclerosis. Our antibody to CD25, initially called anti-Tac, for T cell activation, then it became Zenapax when Hoffmann-La Roche, Frank Zena used it. But now it's daclizumab, and it was used first by us here and then more widely. And finally, three companies have joined together and studied 3,300 patients with multiple sclerosis, and there's been in all studies a 70 percent reduction in gadolinium-enhanced MRI lesions, new lesions, and all the aspects of

multiple sclerosis progression are prevented or reduced, and essentially no toxicity, no black box. In other words, there are other agents that work.

So the company has sent this—companies, Abbott [Pharmaceuticals], Idec Biogen [Ed. Biogen Idec]—have given this to the FDA, and presumably in the next quarter, it'll be approved by the FDA. So even though the [National] Cancer Institute with a really big "C," they're very oriented in cancer, still many times one's discovery as an immunologist affect transplant, affect autoimmune diseases. Being a clinician, that's very satisfying.

Williams: So that's where the serendipity comes in—

Waldmann: The serendipity was we were looking for an antibody to CD4, but discovered a totally new one that opened the field of CD25, that opened the field of IL—we have been dominated since that time by what are called the gamma cytokines, IL-2, -4, -7, -9, -15, that affect T cells, that control the leader of the orchestra, the T cell, that regulates what's going on. They all share a common gamma chain. But IL-2—and my next serendipity, we were treating patients with adult T cell leukemia with our antibody and found cells making what looked like IL-2 stimulating lymphocytes, but it did not react with the anti-IL-2 antibody. Thus, by chance we co-discovered IL-15. And so IL-15 shares with IL-2 the beta and gamma chain, but each has a unique alpha chain that's critical. And you would think both of them sharing the two signaling chains, JAK1, JAK3, STAT5, they'd be the same. IL-15 would be IL-2 light. But, in fact, although they do, in fact, share roles, IL-15 especially is good for NK cells, they are, in fact, in their unique roles different in ways that therapeutically is very important. IL-2, in its unique role, prevents an immune response to self, Tregs, antibody dependence, cellular—no—activation-induced cell death, so these two processes terminate immune responses. So you don't want excessive responses.

IL-15 has none of that. Its role is to have a long-term immune response to invading pathogens, to have immunological memory. So it, along with IL-7, is the big memory. And knowing these differences, we said, well, maybe IL-15 would be better than IL-2 in the treatment of cancer. It might be better than—IL-2 was approved by the FDA for the treatment of melanoma and renal cell—may be better in a vaccine. And so we studied IL-15 in mouse models of tumors, and it was effective. So we, in terms of real world, are often dominated by can you get the money, and with the company, is there a business plan. Right? So we did, in fact, get what ultimately turned out to be $2 million to make, under good manufacturing processes, IL-15.

So what you're hearing with IL-2, with IL-15, with anti-IL-15, is a sort of vertical study. We make a discovery. We would see how whatever we discovered differs between disease and normal. We would make an agent using a monoclonal antibody or a cytokine to take advantage of this, study it in mice, then, let's say, in monkeys for IL-15. If I give IL-15 to a monkey, it will increase the number of

effector memory cells a hundredfold to 80 to 100,000 per cubic millimeter, an unbelievable number of cells. So, given it wasn't very toxic to monkeys, we were given the money to make IL-15 for the clinic, so just as daclizumab went to the clinic.

So IL-15 is very much in the developmental phase. It has gotten interest elsewhere. Admune [Therapeutics], Altor [Bioscience], Novartis, others, Cancer Immunotherapy [Trials] Network have joined. But we have used IL-15 in bolus infusion for patients with cancer, we've used it continuous and subcutaneous, and what it shows is a dramatic increase in the number of natural killer cells [(NK cells)] and some CD8 cells.

Williams: Let me just—this is a remarkable history here you're sharing, but I wanted to shift your attention a little bit to talk about the NIH and the [National] Cancer Institute over the years. What kind of a home has it been for you? You described it when you came here in '56 as in its infancy.

Waldmann: One wondered how one would use all this space in this building. Of course, you know that changes. There are advantages. You are in the old clinical center, so there has always been 250 to 500 beds that the patients do not have to pay for, insurance companies don't have to pay for, so you can bring exceedingly rare diseases. Adult T cell leukemia appears in Japan, in the Caribbean, Sub-Saharan Africa, virtually not in the U.S., and yet we can amass 200 such patients, or a genetic disease in my early career, or a leukemia with a function.

So you do not have to take care of patients because that's how the hospital survives; you bring in patients because they are immediately related to the basic research. So that has always been there, and I cannot emphasize more that although basic science at Harvard, Stanford, you know, is everywhere, but clinical translation that is not dominated by industry, NIH—. A second area, I've told you [about] that we were able to have here at the NIH agents made: daclizumab, an antibody to the IL-15 receptor to block IL-15 for celiac disease, for neurological disease caused by—or IL-15 itself. So you have this capacity to follow from discovery to your own patients in the clinic that I think is very special.

The [National] Cancer Institute, there are always ups and downs, which are, in part, related to the budget from the Congress, and we no longer have the doctors' draft. We no longer have as many of the brilliant young people choosing research at all in our country, or certainly within the Cancer Institute here. Nevertheless, there are a number of people that have stayed here a long time. With me, Carolyn Goldman, Jean Decker stayed for thirty-eight years each. I suffer their retirement. How could they retire at sixty-two? [laughs] But Ira Pastan, Joe [Joost J.] Oppenheim, you know, there are many people that are in their eighties. So one of the aspects, having mentioned my age, is that one is not forced to retire. If you look at Australia, Japan, Germany, England, whether it be sixty-two, sixty-five, or

sixty-seven, they're forced to retire. Some are forced to leave their old university so that the young will not have the hand of the old. But some who are still very vigorous come to work at Harvard or whatever. But here, even my classmates were forced to retire from their posts. I'm, in fact, now co-chief of the Lymphoid Malignancy Branch. We just changed our branch from Metabolism to Lymphoid, as in your introduction.

So what you do have to do every four years, we get a very rigorous review from outside scientists. If you're listed as outstanding, if you're one of the NIH distinguished investigators, you can continue. If your rating was not that, you might lose your resources. So there's not as though you could continue.

So these are facets that are very special here, and the community of immunologists is magnificent. It started one module, four people. Everyone else is excluded. Therefore, it's desirable. Of course, if you exclude people, they want to be in. But soon you were in three modules, and a huge number of people draped on the floor around the speaker, you know, and the philosophy then was like the University of Chicago. "Good morning." "What do you mean by 'good'?" [laughs]

In other words, they were unbelievably interactive. We had outside speakers who pleaded for fifteen uninterrupted minutes. But the sharing, molecular biologists were more sensitive of their unique aspects, but the theme of sharing, that initial one now is at the Lipsett Auditorium, 160 people. You're far from the speaker. You don't interrupt. It's changed its character. But, nevertheless, if you look at the—we have a retreat of immunologists. It had to be restricted. I don't know how many hundreds and hundreds of people came to this that are all intramural scientists.

When I say I learned from the corridors, it's really true, or the talks. Of course, people will not do your work for you, but if you try and go to someone, you will see emails, two hundred every day, but among them is sort of a communication among immunologists, you know, "I'm having trouble with so-and-so. Do you know a good company about this?" Or, "Can you lend me this and so reagent?" So there's a great interaction.

Harvard, the doors were closed. There was a competition. There was an intensity. Maybe it's—for whatever reason. And the late Bill [William E.] Paul, he's unbelievably missed. But, you know, to have people in a benign way, would ask the question. So I feel that both within the [National] Cancer Institute, but certainly in the immunological community, there is this interactive environment. If you go give a lecture, some places there are very few immunologists, and I feel you really can learn not only from reading journals, but from talking to people.

Williams: You joined the AAI in 1971. What motivated you to do that?

Waldmann: Well, I had obviously entered the back door of immunology. You haven't heard me having a mentor who was an immunologist. So I started, as we discussed, with protein metabolism, and I found that the number of people asking for reprints for an albumin paper was much fewer than for an immunoglobulin paper. And so we gradually go from metabolism to the genetic era, so we did enter the AAI.

I must admit I'm very happy that the award [AAI-Steinman Award for Human Immunology Research] is for someone who has an impact on human disease diagnosis, prevention, and therapy, because there were eras where the basic immunologist and the clinical immunologist didn't really talk to one another. So to the great distress of AAI, we opened the Clinical Immunology Society and focus for the more clinical. In other words, we felt we were on the wrong part of *The Journal of Immunology*. We were on the half day at the end of meetings in the wrong hotel.

Now, of course, I was always treated well because we had a basic science aspect, but there was this—it has joined. In other words, there was, with the exception of antibody as an inhibitor of antibody synthesis for Rh, there was virtually no translation of basic immunology into the clinic. Clinic used cancer drugs, you know, instead of—but now cytokine. In other words, when we were finding antigen-non-specific things, cytokines, they were interested only in antigen-specific immune responses. But as time went on, the Bill Pauls became interested in the IL-4, and DNAX [Research, Inc.] became interested in IL-4, and Th1 and Th2 became clinically relevant. So with AIDS, the chasm between the two ended.

So everyone wants to be able to translate their insights into the clinic, and that has been an evolution that this sort of separation—so I joined in part to learn, in part to give talks. Part of the reason you do research is to communicate it to others and to be shot down or to be revered and to get advice, you know. It was not only immunologists, but [Michael S.] Brown and [Joseph L.] Goldstein on surface receptors. We were starting with immunoreceptors. He was working with lipid. So this sort of communication was at a meeting, the setting up of collaborations. I mean, Congress at one time felt that one could send five people to an international AIDS conference and they could come back and teach everyone. This was a conference in Florence [Italy in 1991]. When that did not happen, Congress got very angry and cut the NIH budget by 5 percent when the year was seven months over and you couldn't fire people. So that meant your supplies and services were cut 30 percent, but they didn't sense why.

You asked why AAI, and the answer, as I say, to go to the meeting, to meet other people, to learn from them, and especially in the informal aspects, you know, over a meal, over the coffee break, and people come up to you and say, "Dr. Waldmann, I have a this or that or the other." It's good. So it's very exciting.

Williams: One of the points you're making is that the AAI was able to incorporate the clinical perspective as well as the—

Waldmann: Now, very much. I think AIDS, the wish to be part of the AIDS dollars but to be part of the AIDS pathogenesis, to be part of what it is doing to a lymphocyte, what receptor is it entering, the therapy, you know, the Tony [Anthony S.] Faucis, this bridged between the two communities because it was a recognition of an enormous need and the fact that this is in our world, right, that this is an aspect here, and that the public—you capture the excitement and demand. I mean, there was a vocal demand, right. "Why are scientists doing nothing about AIDS?" "Why is there so little about AIDS?" And you couldn't not feel—so just to give you a sense, the first patient with AIDS was one of my patients, and we were studying immunodeficiency, and here a patient in 1981, before the publication of the five patients from San Francisco, comes in with fungus of the retina, with pneumocystis, with a TB [tuberculosis] form, and what his family did not know was that he was gay. We were able to keep him alive for six months, but we did not really know what he had—this was in January—until in the middle of summer, the first—and so this disease, this "lifestyle" was so disturbing to his Connecticut exceedingly wealthy family that his chart disappeared when he died, and it was taken because they did not want this revealed. So I had an opportunity. "In Their Own Words," there is a document with that title to say something about this first patient.

Again, the techniques that I and Tony Fauci and others had developed, how to study, how to study T cell proliferation, how to study the levels of immunoglobulins or whatever, had been developed with genetic immunodeficiency diseases and now were available to be used in patients with AIDS. So I had to decide were we going to study AIDS, or the gamma cytokines, or adult T cells. So we studied the retrovirus HTLV-1 and IL-15 and disorders of IL-15, whereas I felt the virologists would play the biggest role, and ultimately they played a big role in HIV. But we have made vaccines with IL-15 and HIV. We have done so with the agents that are used for bioterrorism and with tumor antigens. So we have used IL-15 and its memory to help make better vaccines.

Williams: What do you see as AAI's role in today's world?

Waldmann: I think to maintain a stimulus for the young individuals to be captured by the enormous value of immunology. We all know that immunoprevention, whether it be human papilloma virus or whatever, from the era of, the late—over two centuries, vaccines, but other areas capture the attention, the brain, for example, or Wall Street. In my class, four of the eight summas of Harvard were in Harvard Medical School class with me. In other words, you did not have such a wide array of opportunities or demands or payments or whatever. And if you look at the researchers who are postdoctoral fellows, during the doctors' draft they were all people eligible for the draft, which meant they were all men, and it meant they were all U.S. citizens and probably born in the U.S. If you look at my medical school class, not only did everyone have a white coat, they probably had a white

face and, with the exception of two or three, were men. So we have seen, to our great benefit, the enormous expansion.

But if you look in the labs, they look like the United Nations or, in fairness, a predominance of individuals from China and Japan. In other words, the era where the NIH had 400 postdocs from Japan, they now have 500 from China. So you see coming to the U.S., some of our greatness is the way research is evaluated. It's not some huge professor who is given the money and doles it out. You have the grant system where you have meritocracy.—you compete for grants. And I think that aspect has been one of the great contributions to immunology, all biomedicine of the U.S., this approach to science, and with it real support. I mean, $30 billion is real money. Industry $50 [billion], whatever. So one can visualize real opportunities.

The concern I have, of the people in postdoctoral training, postdocs, one in six, at best, will get their own independent research effort, which means we are probably training too many people. And Harold Varmus and others felt we should have staff scientists; that is, people who are semi independent but who are not sort of in the training phase of their career. As I say, it is not easy for someone born in China getting a green card toward citizenship to get a job after finishing. One can stay at the NIH eight years in training and then one has to leave. And that is a challenge. So somehow, I think also to convey to the public, the AAI has that role, to convey to the public how valuable this is for the U.S. and to the Congress. I think one has very few enemies in biomedical science. But you're encompassed in [Department of] Health and Human Services with Obamacare, and so the Congress might like to support the NIH, but you are affected globally.

And things can be very difficult. Things can be very difficult for scientists on the outside as well as here, and I think the AAI is positioned with such respect for it, that it, like the National Academy of Sciences and Institute of Medicine, other places I've joined, to speak to the Congress, and I think the Congress listens, at least the younger people in the—so in terms of its role, teaching, making a place where people can give their talks to their peers and to talk to the Congress and the public.

Williams: What do you tell people in training about their future? What guidance do you give them? What direction do you point them in?

Waldmann: Well, of course, I write letters and talk to people about helping them get a job, but it is important to speak to people and have them recognize that beyond being a PI [principal investigator], there are other alternatives. Industry in my era had been for chemists. Now 650 or whatever biotech firms, there are the great major firms where one is—so if I was a consultant in an era where that was permitted, let's say to DNAX, I would see IL-4, IL-13, IL-10, Th1, Th2. So that this is an alternative. Working for the FDA and having your lab is an alternative. Working for each of the—that there are alternative directions to go, being a staff scientist.

But also, you know, finish your projects. Write up the paper. Be here. Don't send in the paper when you're leaving. Where the journals now demand more, they always demand more, good journals, more and more. So if you're gone, how does that get finished, right?

So partly it's ask important questions, ask questions people wanted an answer to, not just following some little—but keep your mind open to serendipity, right? I mean, in co-discovering IL-15, someone else had studied the same cell line, HuT-102, and said, "There's an odd IL-2 being made by this tumor cell." They didn't see it as this is a new cytokine. You don't want to try to wedge things where they won't go. Keep your mind that something new can be there. And that, as I said, happened with the IL-2, IL-2R beta, which is shared by -2 and -15. So you can target this and block both IL-2 and IL-15, as you need to do in refractory celiac disease, as you need to do in alopecia areata, as you need to do in Type I diabetes at the beginning.

Many people don't really feel in their bones for what they're doing, and to try to understand and to ask them to say, "Where is the story?" right? They will give you Phase 1, and you'll say, "But do you realize that you have something really new here?" that you're just sort of—because you ask the question to start with, Phase 1 trial, but you don't realize that you've discovered that this new cell is going way up when you give IL-15 or something like that.

Williams: Tell me about your wife. Has she pursued a science career or not?

Waldmann: So a bit of my wife. First of all, my wife, children, grandchildren, unbelievably important in all aspects of this. My wife's, certainly, grandfather was a physician. Her three uncles were physicians. Her mother was a physician. Her father was a physician. Her brother was a physician. So my wife was a philosophy major at Oberlin [College], graduated summa cum laude, was number one in her class at Case Western Reserve and therefore was one of the very few people from that institution, and exceedingly few women, accepted as an intern and then resident. She was my boss and she was my resident. I was an intern at the Mass General Hospital.

But she, like my daughter, who's a physician, one of my two sons who's a physician, desperately likes taking care of patients. She loves to talk and listen to patients, is enormously helpful in both my daughter was—well, we'll get to her in a moment. So my wife became the leading physician of the AIDS Clinic of Montgomery County [Maryland], and from the time of AIDS in 1981 till the time she retired a couple years ago, she was treating patients with AIDS, maybe 2,000, 3,000 patients. And this, you have to realize in merit, there are various ways to using a medical career. I love research, but I think she has an immediacy with people.

My daughter, who also went to Western Reserve and then Boston for her training, she spent three months in the southwest of Sudan being one physician with a Sudanese physician for 150,000 people, had to do an appendectomy and deal with an amputation there, but got malaria. But then with Healthcare for the Homeless in Boston for many years, but as not only we but my son-in-law's parents, who live right there in Frederick County [Maryland], became older, she brought her three children, husband, to Frederick, in a house right near where her in-laws are. So she's here, she's a physician, a hospitalist at Frederick County.

My son Richard is a hospitalist in neonatal pediatrics in Massachusetts, and my other son is an economist at the University of Rome Tor Vergata. And on the blog is—I have to keep doing research because my son every week pushes me more than anyone else, my son Robert. "What have you done?" He's very nice and supportive.

But, as you know, at eighty-five I'm still co-chief of a branch, still doing a lot of all the work we ever did, and at least it really gives pleasure to sort of accomplish something, learn something in a way that I don't have the alternative at home. Of course I couldn't watch daytime television. Other people who've retired, they have the church and their garden and this, many, many, many things, and I don't have these. I do photographs, but for the most part, have very little else.

Williams: How have you struck a balance between being the head of a family and being the head of a branch? [laughs]

Waldmann: I live twelve minutes away. I go home at a reasonable time. I may work in the presence of everyone. By now, of course, my children—I mean, you're really old when your children are middle-aged or old—they're in their fifties, you see. During the time our children were really young, my wife did not work. Our children's education and health was always our top priority, so although I and my wife went to public schools, with the exception of Richard, our oldest, who went to [Albert] Einstein High School, they went to Green Acres School and Georgetown Day and then Harvard, Brown, wherever. And I thought they were very good, very good schools, and we drove them there. But when we're off, we're off. We had great feeling for the national parks and most recently have gone to Iceland. So we always get together about two weeks at Christmastime. But I think they really feel we were there.

Again, I cannot emphasize more than any sort of nice things like this happening really reflects the other people that have worked with me, as I say, "technician," in quotes, Carolyn Goldman and Jean Decker, but then the fellows that have come through. There are twenty-five people in American Society of Clinical Investigation, twenty in the Old Turks [Ed. nickname for members of the American Association of Physicians], seven members in the National Academy of Sciences. So what that means is very bright people came in and do not take an overwhelming amount of time. In other words, you can give people big-league

directions, and they will solve how to get things done. Not always, not all the people know. So if you have Stan [Stanley J.] Korsmeyer or Warner Greene, those people there are able to do—and this is not true only of me, right, of David Baltimore or whatever, you know, they've had people that have made the great discoveries.

So you can make a balance, but in part, there's a stereotypically traditional family. My wife, by now she doesn't drive, so I do most of the things that used to be done by her, but she does the cooking and the cleaning gets done. So it was done. I didn't think either side had a big sacrifice. You have to think about it. I do not go traveling all over the place for meetings all the time as some people do.

Williams: Tell me what experimental photography is for you. I saw that term and I thought, what's experimental about it?

Waldmann: You know, in the era when I did it, the sixties through the eighties, there were many aspects. Some aspects were nature photography, close-up nature, butterflies, insects, maintaining light, impact by simplicity, the nature of the design. But then when it was experimental, the era now, like science, has developed so you could do in a few moments what took a weekend. But I would, let's say, want to take a picture that had certain interesting designs and convert them to a poster, so I would make a Kodalith so that they'd be totally black or totally clear, and then you could do that with converting each of the black areas to a color like red or green or blue. So you could make what was either an abstract design or you could make things you didn't want go away. If there were a window that was coming in that was too bright, you could make it black and so forth. But now, first of all, it became you have to pare away things in order to keep going in the two parts you said, home and the lab. [laughs] So that had to go. But also it became too much like the laboratory, right, I mean, the photography, and with digital it became too easy to do that.

But I did go this Monday to the Natural History Museum [Ed. Smithsonian National Museum of Natural History] where what is called "The Best of the Best," and every year they have a competition for nature photographs from around the world shown in huge—but this year, they took all the winners of all the years and have shown them. It's really worth going to. I brought my grandchildren, including one who from Rome is going to Binghamton University in New York. It really is fascinating pictures. But, again, if you share interests with your children or grandchildren, you know, if nature and natural history and whatever, then what is pleasure is also one's responsibility towards one's children.

I've told you IL-15 has dramatic impact on the cells of the immune system, NK cells, CD8 cells, markedly increase and activated. But it is, in part, like having your foot on the gas pedal of the car without having a steering wheel. So that part of the future is to give specificity along with IL-15, and we do that with

antibodies to the tumor. So an antibody to the B cell tumor, an antibody to breast cancer, along with IL-15, dramatically increases, thirtyfold increase in NK number, two- to six hundredfold in $CD56^{bright}$ NK number, and these cells are the cells that are normally involved with a phenomenon called antibody-dependent cellular cytotoxicity. So we would give IL-15 and anti-Herceptin, anti-CD20, Rituximab, and IL-15. We think we can make the effectiveness of the antibodies much better and much longer lasting.

Number two, we feel that the dramatic increase in the number of so-called memory phenotype, CD8 cells with IL-15, that they are really not specific. They're helpless. They haven't had adequate CD4 help. But with anti-CD40, we have shown with prosthetic cancer models we can, with anti-CD40 alone or with anti-IL-15 alone, have no increase in tumor-specific CD8 cells, but we can have a tenfold increase if we give anti-CD40 with IL-15, and such anti-CD40 the group at Rockefeller [University] will be using.

Great interest, vast enthusiasm for checkpoint inhibitors, anti-CTLA4, anti-PD-1, PD-L1, taking away the hand brake and foot brake on the immune system. But we have shown if you give all three with IL-15, you dramatically increase the effectiveness of the trio. So that will be a third area. So that each of these is very much in the works, very much getting final approval for such studies, because I feel combination therapy will be the only way that IL-15 will move to the future. Another area, we've discussed IL-15. I don't have time to discuss blocking IL-15, but the centerpiece malignancy for us has been HTLV-1 adult T cell leukemia. In studying this, we have found that due to the virus HTLV-1, it forces the cell to make IL-2 and the IL-2 receptor, IL-15 its receptor and IL-9. All of these go through Jak1 and Jak3 as signals. And a future that's enormous is we find that virtually all the T cell malignancies have disorders of the Jak/STAT system. So a major future is to use inhibitors, Ruxolitinib, Tofacitinib, new ones to Jak1 and Jak3 in the treatment of the malignancies of the T cell. We've talked about the value of the T cell, we've talked about loss in AIDS, but leukemia is an orphan disease and much poorer prognosis than other lymphomas, and I feel that we have defined abnormalities of the Jak/STAT system and that this as a partial target monoclonal antibodies to the T cell and agents that block the death system, plus these Jak inhibitors, I think will revolutionize the future of T cell malignancy therapy.

Williams: Thank you.

Waldmann: Thank you. Good.

Williams: You've had an incredible career so far, and—

Waldmann: As I say, there's future. I'm only eighty-five. Come on.

Williams: That's right. [laughter] Very good. Thank you, Dr. Waldmann.

[End of interview]