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Transcript

William E. Paul, M.D.
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Interview conducted by
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Williams: This is an oral history interview for the American Association of Immunologists for their Centennial Oral History Project, with Dr. William E., “Bill,” Paul, currently a National Institutes of Health distinguished investigator and Chief of the National Institute of Allergy and Infectious Diseases. We are at the American Association of Immunologists headquarters in Bethesda, Maryland. Today is Wednesday, April 18, 2012, and I’m Brien Williams.

Dr. Paul, let’s start with you giving me a little bit of your family background.

Paul: Okay. So I come from a family. My dad came to the U.S. as a boy, actually, from Russia, and came at about the age of eleven, didn’t get a lot of education, had a small business. My mother’s family was in the U.S. somewhat longer. Her mother came to the U.S. In my grandmother’s family, it turns out there are quite a lot of scientists, interestingly enough. I’m hardly unique amongst those.

I was born in Brooklyn in New York City, educated there through college and medical school, and then after that and marriage, I was off to Boston for an internship and residency. I came to the National Institutes of Health initially in 1962 to do the equivalent of military service. I worked in the Endocrinology Branch of the National Cancer Institute and had the great good fortune to be associated with a group which had developed the first cure for metastatic cancer with drugs. This was for a disease called choriocarcinoma, which is a malignancy of the trophoblast. Roy Hertz, who had been the head of that unit, had shown that methotrexate treatment could cure, literally cure 70 to 80 percent of the affected women. So I spent two years on that service, a year as a clinician, and nightrimes the first year and full-time the second year doing actually immunologically-based work in endocrinology. The best accomplishment from that era was our development of the first radioimmunoassay for thyroid-stimulating hormone, which I did with a senior advisor, Bill Odell, and a colleague, Jack Wilber.

So that brings me through 1964. At that time I had pretty much decided that I wanted to do immunology, and I had, during my internship somewhat earlier, worked nights again, and we had a bit of an elective with a rheumatologist who was interested in amyloidosis, a man named Alan Cohen. Alan wanted me to come back, which is where I had done my work, as a member of his rheumatology group, but I felt before I could imagine that, I’d have to get better training in immunology.

I applied to several groups. There were two in particular that I really wanted to go to. One was headed by Henry Kunkel, who, of course, most immunologists will realize as one of the great figures of our science. But Henry demurred and didn’t find he had room for me in his lab.

But the other person who I was terribly anxious to work with was Baruj Benacerraf, and indeed Baruj was able to take me. So I worked a mile south of the Rockefeller University at New York University with Benacerraf. That turned

out to be one of the really best decisions and events for me in terms of training. I got to work in a small research group at the time Benacerraf, who was subsequently a president of the AAI, a chief of the Laboratory of Immunology, department chair at Harvard, the head of the Dana Farber Cancer Institute, and, of course, a Nobel laureate. At the time, Baruj doing his Nobel Prize work had a terribly small lab, and it was just four or five of us working together every day, and that was my introduction to what I would call the mainstream of immunological science.

I worked with Baruj at NYU for four years. At the end of that time, he was having some difficulties with the institution, and I was as well, so we both felt we had to leave. He was recruited to NIH and was generous enough to ask me to accompany him, so in 1968 he and I and another colleague, Ira Green, came from New York University to the Laboratory of Immunology at NIAID. Baruj didn't stay very long, however. He heard the siren song of Harvard, and by 1970 he was away. While the NIH was interested in getting a distinguished individual to succeed him, they failed and turned to me, at the age of thirty-four, to take over Baruj's job.

So that brings us up to date, so to speak. I undertook the job I have today at the age of thirty-four in 1970, and it's now forty-two years later and I still have the same job. So you could say I rose to my level of incompetence very early in life, and I've been at it ever since. [laughs]

Williams: Good review. Let's go back for a moment. I'm curious. What year did your father come to the States?

Paul: My dad was—let's see. He was born in 1899. He and his mother and his younger siblings came, I think, in 1911. His dad and older brothers had come a year or two earlier, which was not at all uncommon in that era. So they came in 1911 and into the New York area. He did have some schooling, I don't really know how much, but he set himself up in a small business, which is what he did for the rest of his life.

Williams: What kind of a small business?

Paul: He had an automobile repair business.

Williams: In Brooklyn?

Paul: In Brooklyn. That's correct.

Williams: Tell me a little bit about your mother's scientific family background.

Paul: So my mother, my grandmother, came from a large family. Her maiden name was Geschwind. There were a lot of brothers and sisters. There were in my

mother's generation three boys, her cousins, who all became quite well-known scientists. One was Norman Geschwind, who was the professor of neurology at Harvard Medical School, known for being sort of the father of behavioral neurology in the United States and a very extremely well-thought-of individual.

His older brother, Irving Geschwind, worked on protein hormones. He had worked in the laboratory of the leader in that field, a man named C.H. Lee, and then went off on his own and was a leading figure at the UC-Davis.

Another cousin, Stanley Geschwind, was a physicist. I think he headed for some period of time, at least, the Theoretical Division at Bell Labs. Stanley, his two sons, both of whom are very well-known neurobiologists, who are one at UCLA, I think, and one at UCSF.

Another cousin was also in the physical sciences. Strangely enough, there have turned out to be quite an interesting number of individuals who did science basically in my mother's generation and, to a degree, in mine.

Williams: So how did you come to realize that you wanted to pursue a career in science?

Paul: Well, so it's not unusual in Jewish families, the oldest son is expected to go to medical school, or at least in our family. [laughs] I can't say I felt exceedingly enthusiastic about it. I wasn't unenthusiastic, but it wasn't as if I had awoken one day and felt I must be a physician. It was sort of anticipated I were to do that. And I was a good student. That's a common tale. I'm sure all the people you will interview will have been good students. I was a good student.

I go into medical school, but I really was much more interested in the scientific aspects of medicine. That became clear very quickly, and so I always thought I would try to do that. Then in that era, physicians were still subject to a draft. We're going back now into the late fifties, when I was in medical school. In 1960, when I graduated, you would be subject to a draft, and the way the draft worked is youngest to oldest. So the youngest people in any year were the first to be drafted.

It turned out just by accident that when I was an assistant resident in medicine at a hospital then called Massachusetts Memorial, we had only four assistant residents on our service. Of those, two were drafted. I would have surely been drafted because I was the youngest, but I had had the good fortune to get into this NIH program, which I had arranged in advance. So in that era, you could fulfill your military obligation if you were fortunate enough to get a position at NIH, and that was an entrée to science, not just for me, but for a whole generation.

NIH was filled with bright young physicians, mainly, but not exclusively. But since everyone wanted this appointment, because it was a way to not go into—well, in that era there was a Berlin crisis, so it wasn't Vietnam, it wasn't Korea,

but people would still prefer not to be in the service if they could avoid it. So the talent in that era at NIH was stunning, and indeed it populated most of the medical schools in the next generation. The leadership had all in common that they had all had an NIH experience for two, three, four years. Some stayed much longer, but at least you can go around and look at that era and you'll discover in everyone's background was this common experience of two, three, or four years in Bethesda [Maryland] at that time. So that was a great experience, both got me into science.

I had already, though, decided I wanted to do that and was already looking for where I would go to do immunology, even before I arrived in Bethesda, but that confirmed me in the idea that I wanted to do science, and immunology was very attractive. As I said, I found ways to do immunology, even though I was in an endocrinology lab. I worked on radioimmunoassays. I worked on immunological properties of protein hormones. But I realized I was still doing what you would call applied immunology and not work that was aimed at the core of understanding the character of the immune system. I had pretty much decided to do that, so the opportunity to go a lab was something I really wanted. I applied to lots of labs, but in the end my two first choices were Kunkel and Benacerraf. They say Henry wasn't able to take me, although years later he absolutely denied that was true. [laughs] I pointed out to him that he had demurred, but he said, "No, no, it can't be so." So I took it as a mark of acceptance.

But Baruj was a wonderful mentor and really a second father. I should point out he died in August or July of this past year [2011] at the age, I think, at ninety. We're coming up in June we'll have a memorial symposium for him. He was a great man. Of course, Kunkel was also equally, both giants of our field.

Williams: Was NIH unique in being the place where you would go to avoid the regular military service, or was Harvard or other places also available...?

Paul: So I'll put it differently. To *fulfill* your military obligation. NIH was not fully unique. It had the biggest program and probably the best, but there were good programs at Walter Reed [Army Medical Center]. A lot of very fine scientists spent time at Walter Reed in their Institute of Research. The Navy had very good research laboratories. So there were other ways you could fulfill your military obligation, do science, but the NIH was clearly the biggest and it had the greatest concentration of absolutely topnotch staff, permanent staff, really extraordinary, and this enormous aggregation of young people who were really the cream of young American medical science.

The number of Nobel Prizes that came out of that are astounding. There was one group of one or two years where five or six of the people in a relatively small group all got Nobel Prizes. So this was an astounding place to be, probably will never be created again in the United States because there are now so many great centers of science. There is no particular reason to, quote, "force" people to go somewhere, so there are many wonderful places today. So that's a gain. But that

was something quite unique about that time in the late fifties into the probably early seventies when NIH had essentially a throttle, a control, if you like, on the spigot of contemporary science.

Williams: Were you at that time part of the [U.S.] Public Health Service?

Paul: Yes, I was a commissioned officer in the USPHS. Actually, while in medical school, I had some one summer at NIH doing really more clerical. I mean, it was science, but not very high level, but in order to get that job, I had to get a commission. Then I went into the inactive reserve, and then when I came back again, I reactivated my commission. Everyone in these program fulfilling military service did so as a commissioned officer in the Public Health Service. I was thereafter in the reserve, both active and inactive, for a long time, actually rose to the rank of two-star admiral because I had an administrative job that called for that rank. That's the only reason.

Williams: Was that when you were an Assistant Surgeon General?

Paul: Right. I was the Director of the NIH Office of AIDS Research. That was responsible for controlling all of the resources that NIH expended for AIDS research, about 1.3, 1.4 billion dollars in 1993. Today it would be substantially more. The head of that office, that called for a senior appointment, and I sort of was able to negotiate two stars rather than one, because there were certain advantages for doing that.

Williams: I was intrigued only because Joycelyn Elders was the Surgeon General at that time, and that was a kind of a rough time for the Public Health Service.

Paul: Right. So I'm trying to think back whether [C. Everett] Koop had finished his term. I can't recall. Koop had been the Surgeon General, and I know I would see him from time to time, particularly when I'd go to see [Anthony S.] Tony Fauci, and Koop might be there or something. I just can't recall now. Oh, now I remember. So in that era, there was an Assistant Secretary for Health. I don't think that position exists today. The Assistant Secretary for Health was a man named [Philip R.] Phil Lee. So the Surgeon General reported to the Assistant Secretary for Health, so the responsibility of that job was to really be a bully pulpit for medicine or Public Health. The real power, if I remember correctly, lay in the Assistant Secretary for Health's office, and, of course, in Donna Shalala's office. So I didn't really deal at all much with the Surgeon General. I did deal with Dr. Lee, and from to time with Secretary Shalala.

Williams: One last thing about your family background. The eldest son goes into medicine, so you have siblings?

Paul: I have two sisters.

Williams: Are either of them—

Paul: No. Neither of them took a scientific bent.

Williams: As I hear it, you sort of moved from possibly doing clinical work to the endocrinology and then to immunology. Was that the progression?

Paul: Well, that's correct in the sense that, I mean, I had been trained as—I have an M.D. I'd worked in labs in the summers while I was in medical school. I think I had always had the expectation that I would do science. I probably didn't really have a clear understanding of what that would be. So whether I had intended to do clinical science and then change to lab science, I'm not sure about that. I probably was all along thinking of finding a career in laboratory science, but, of course, that didn't necessarily have to be. There were a whole set of, I have to say, lucky breaks that made it possible. If I hadn't gotten to the NIH, for example, and I'd stayed, I might have been in the Service in a clinical realm. I might have not been able to find a slot in a really first-rate lab. There's all sorts of ways the world could have turned out very differently.

Williams: The way you describe the NIH as this sort of wonderful place to be, was that during your first tour there or during the second or both?

Paul: I came as a clinical associate. That was our title. That era was really special. Then I finished that in 1964, and then I went to Benacerraf's lab in New York University for four years, and we came back in '68. When we returned, of course, my position was very different. In '62 to '64 I was, you know, a young person. I didn't have any standing there, other than being a clinical associate, but I would get to know all of the other people of my same era. Everyone was excited.

When I came back, I was now a principal investigator, and now it was time that I had to really do some stuff that really mattered. We had, I must say, on our floor in Immunology quite a remarkable collection of people, and it was early, so we say, in terms of modern immunology, we were early days. There were just an enormous number of things to do and everything you did could turn to gold. That was not only true of my own group, but many others. So it was very exciting, that's true, as I think back now, both in the early days.

You know, it's even unfair to say that, because I like to say when I started in immunology I thought we were in the midst of a revolution, and my understanding of scientific progress is that it goes in fits and starts. You have eras of great accomplishment, new ideas, new paradigms, and then you have long periods of consolidation where you build on these foundations and then you spring off to another era of revolutionary change. That's my academic understanding.

So I came into immunology seriously in 1964. It seemed to me it was a revolutionary period. I'm still waiting for the consolidation to start. [laughs] Every era seems to bring new changes. The field is continuously fascinating. In fact, I've often thought a good title for either a book or a lecture about immunology would be *Endless Fascination*.

Williams: What was driving this? Was it personalities? Was it technology? What was behind all of this?

Paul: Well, firstly, immunology is a very interesting field, in contrast to, say, biochemistry. Biochemistry is a way of doing science. You use biochemical tools to study particular things. Immunology is a coherent body of knowledge that you bring distinct tools to, and everyone who calls themselves an immunologist, particularly in the era when I was growing up, would share certain core knowledge that we would all have to know.

So it was a community of people who I would say, both at NIH but in the greater world, had a very common world view of this science, and, as you said, things were changing. Both there were new technologies, there were also new ideas. So as you probably know, immunological science is a young science. As a concrete discipline, in contrast to as just accidental findings, most people would date it to the latter part of the nineteenth century, to Louis Pasteur and Robert Koch and most, importantly of all, to Paul Ehrlich, and it was still looking for, so to speak, a central idea, a central theory that guided it.

It struggled with that for a long time, and it was only in 1957 and '59 that the central theory was enunciated; that is, what is called the clonal selection theory of immunity. In 1957, two papers appeared, one that's given all the credit by [Frank] Macfarlane Burnet, but actually an earlier one, which was really first, by David Talmage. Talmage was then a young assistant professor at the University of Chicago, went on to spend his career in Denver at University of Colorado, is still alive. I don't know if David was a president of this organization. He may well have been. If he was, you should interview him. He's a wonderful man.

So Talmage and Burnet enunciated the clonal theory in '57, and then in '59 Burnet published a really magnum opus, which described the clonal selection theory in detail, and beautifully written, and in many respects earned him the great status he has in the field, because the two initial papers were rather sketchy, but this book was wonderful. So it was really only until '57 to '59 that we had a grounding of a theoretical construct to underlay immunology.

So I'm coming into the field in the early sixties, only a few years after people were accepting this shared vision of what immunology was about. There was still people who didn't accept it, but by '64 most people did, and now you could rethink what you were doing in new terms. There were new technologies coming

on, but it wasn't only the technology that was driving it. It was just the ideas, people recognizing what you could do.

It is true that people were understanding the structure of immunoglobulin. That was being developed at this time. [Rodney R.] Porter and [Gerald M.] Edelman were doing their work. The specificity of reactions, there had been a great effort in the twenties and thirties by Landsteiner to understand the specificity of antibody. But in Benacerraf's lab and my research project, we were interested in understanding the specificity of what today we would call T cell responses. Of course, we didn't know there were T cells and B cells in that era.

But it's true also that shortly thereafter, people understood the function of the thymus. All these things were unknown. And while the technology was important, even with some very modest technology, a lot of exciting work could be done. But it is true, as time went on, new and newer technologies kept being available, and immunologists were very fast to take them on. In fact, it can be said that monoclonal antibody use as an analytical tool almost certainly was best developed in immunology. Cell sorting was developed by immunologists, and we were the first to use it very aggressively, not so much the gene knockout technology, although even there immunologists were very early. Sequencing, there were more sequences done on immunoglobulins than everything else combined.

So we adopted the technologies early. I think it's true that technologies were important, and there's no doubt that without them the field would have leveled off. Each few years brought a new technology available to allow you to go forward. I used to say you can do today experiments that we would have called science fiction five or six years ago. That's certainly true.

So, yes, it was partly that, but not that only. It was a very strong sense of excitement of what could be accomplished, and I can certainly tell you on the eleventh floor of the Building 10—our NIH buildings have very poetic names. [laughs] Building 10 is the largest brick building in the world. But on the eleventh floor we'd be up and down the corridor. Every day was a new day. So it was very exciting, I have to say. That's certainly true, now that you remind me and send me back in the years to that era.

But that wasn't the only era that was terrific. So I had very good fortune, if I may go on, in my postdocs. So I came to NIH in 1968 with Benacerraf. I had been his postdoc at New York University when he asked me to join him, which I was very grateful for. The arrangement we made was that I'd work on my own projects half-time and the other half-time as a partner with him, which was fine with me. In that era we had fewer postdocs, so there were one or two postdocs that worked on the projects that I did with Baruj, and then I had one who worked on the projects I did myself, and everything was fine.

Then when Baruj left—let me see if I’m getting this right. Oh, yes. So the first group of postdocs came in the door after Baruj left, some of them thought they were going to work for him, but he was gone, were terrific. I had unbelievable postdocs. One, as an example, a leading example, was [Charles A.] Charlie Janeway. Charlie was subsequently a president of the AAI, one of the most influential of immunologists. Unfortunately, he died as a young man, not so young, but younger than I am, from a brain lymphoma. But he revolutionized immunology. So Charlie was a postdoc. [John] Jack Stobo, who subsequently was the Osler professor of medicine at Johns Hopkins, several other. [Joseph M.] Joe Davie, who was Chairman of Microbiology at Wash[ington] U[niversity], and people of that sort, terrific postdocs, outstanding. I said, “Well, this is easy. Nothing to do.”

So that was one era, and then about ten years later, again, quite without any planning on my part, I had a second group of postdocs of equal magnitude, and they included Mark Davis, who cloned the T cell receptor while he was in the lab. Also one of the leading figures in our field today, Laurie Glimcher, who’s been a president of this association, now the dean at the Cornell Medical College. Maureen Howard, with whom I discovered IL-4. Tony DeFranco, who was Chairman of Micro at UCSF, and several others, I mean, quite remarkable. So I’ve had really good luck with postdocs, but they come in bunches, and that gives you an optimistic view of the world, I tend to think.

Williams: Take me back to circa ’68, you and your mentor working together. What was it like day to day?

Paul: So it was very interesting. As I said, we came to NIH from New York University. There were three of us: myself, of course Baruj, and a colleague named Ira Green. Ira and I had been postdocs together for three years. Then he went back to his original institution, but when Baruj came to NIH, he invited Ira, so we worked together, and we were talking all the time.

Baruj’s wife, Annette, was always in the lab. She spent really her lifetime with him. They were never apart. She was in the lab every day, and at four o’clock in the afternoon in his office, now today mine, she made tea, and Ira and I and Baruj and maybe one or two others would be there. But we were talking all the time. It was a really exciting moment. Now, of course, a lot of that talk was speculation about things you couldn’t possibly do, but not all of it. A lot of it turned into work, really, of the first magnitude, critical work to understanding in the end what we call today the function of major histocompatibility complex genes, what we used to refer to as histocompatibility restriction, what T cell specificity meant, even though we were just beginning to understand that there were T cells and B cells.

Dendritic cells didn’t yet exist. Ralph Steinman hadn’t yet discovered them, but we knew there were antigen-presenting cells and we knew how essential they

were. So the answer was, it was really exciting. We probably talked about science too much. I'm sure my wife found we were insufferable, and she's quite right, you know. There was not a lot of balance in those days. [laughs] But I'm sure that was true by lots of young people. Most people you'll speak to who, I'm sure, think back to their youth see it in very glowing terms.

Williams: It sounds like the word "collaborative" would also apply.

Paul: You didn't really know in the end, when the day was over, whose idea it was. In a sense, you'd be talking, and everyone was talking all the time. Someone would bring up an idea, and then someone would elaborate on it, and someone would say, "It's crap," and then they would say, "Well, maybe not." Then toward the end of the period, you'd have an idea. Then you say, "Well, whose idea was this?"

It's like *Rashomon*. You ask each person in the group whose idea it was, and you'll get a different response today if you interview them. Unfortunately, they're not all alive anymore. So you could easily hear, "Oh, that was my idea." But in reality, someone had the idea first, obviously, but there was a great deal of collegiality. Not everyone was the nicest person in the world and there were arguments, and etc., but it was a fundamentally exceedingly exciting time.

Williams: This will be a naïve question. Were you working mainly with petri dishes or with electron microscopes or—

Paul: So our work at the time was fundamentally of two types. We did some work in which we studied the behavior of intact experimental animals, where we might transfer cells into them or alter them in some way and see how they behave. In the early days, we worked with guinea pigs.

In fact, just a good story, why did Benacerraf come to NIH? He was not the government type, you would have to say. Just by way of a bit of a diversion, he was born in Caracas, Venezuela, from parents who had emigrated from Morocco. His father made a fortune early in his life, moved to Paris. Baruj was brought up in a wealthy home in Paris, left France in 1939, just ahead of the Germans, came to New York City, had to finish his education, and the French and American systems don't jibe very well. So he sort of fell between the cracks.

He ended up in the School of General Studies at Columbia [University], met his wife, who is also a French émigré, a woman who's from the Dreyfus family, actually. They hit it off right away. He could only get into medical school at the Medical College of Virginia, not to say that wasn't a great school, but he had a lot of difficulty getting into medical school, but he did get in.

So he would not have been regarded as a typical government type. He had been in France doing science. He was at New York University. He saw himself in an

academic setting, but there was one great thing at NIH. So he had discovered the phenomenon for which he eventually got a Nobel Prize, and that was that the ability to develop immune responses against simple antigens was controlled by individual genes, was unigenically controlled or monogenically controlled. It turned out eventually that the genes that controlled it, which we called immune response genes, eventually were proved to be major histocompatibility complex genes, and that was, in the end, a great finding.

He had this work in guinea pigs. The guinea pigs were not all inbred; they were outbred. It was very hard to do good genetics in them. There was only one place in the world where there were inbred guinea pigs available in any numbers, and that was NIH, and he desperately wanted these guinea pigs. So when the offer came, he was very receptive to it. Under other circumstances, I suspect he would not have accepted it, but he was really anxious to have the guinea pigs. Indeed, at NIH he completed the work for which he would eventually get the Nobel Prize. Harvard takes credit for it, but he didn't do any of the Nobel Prize work at Harvard. It was all done at New York University and NIH. He may have done a few final bits that got him there, but the basic ideas were NYU and then NIH ideas.

I wanted to go back. I loved it. I'd been there from '62 to '64, so when I learned he was thinking of going, I walked into his office and I bargained hard with him. I said, "Baruj, if you take me, I'll go with you." [laughs] But he was very good to me, I have to say, so I loved it.

I remember to this day, in a good sense, he said NIH is a factory for research. He didn't mean it in a negative way, but he did mean it wasn't the sort of place where you might have other interests, which is really not correct, but that's how he saw it. He saw it as one purpose, one purpose only, which is true, of course. The United States government funds the National Institutes of Health for one purpose only, that we do things that are going to advance the health of the nation, whether it's right, but still more mono-dimensional than you might see at a great university. He always, I think, in his mind, that's what he wanted to be, so when the Harvard opportunity came, that was quite clear he was going to take that.

So now, where were we? We were talking about the excitement.

Williams: Methodology.

Paul: So we worked with guinea pigs, but at the same time when I had been a postdoc in Baruj's lab at New York University, I had come across a paper by another very eminent immunologist, Richard Dutton. I don't know if Dick was a president. His wife may have been, Susie Swain. I think Susie was. You may have the list. I don't know.

But Dick was in that era in London, and he had reported that he could take cells from rabbit lymph nodes and expose them to certain stimulants in vitro and then measure their response by their synthesis of DNA using the uptake of tritiated thymidine. I read this paper and I thought this is terrific. I immediately started doing it in our system so I could now study the things we had been limited to study before in animals. I could study them in not petri dishes, but little culture [unclear]. It was transformative. Today, of course, the technology is not used quite the same way, but fundamentally we all still do the same thing. We culture lymphocytes in tissue culture, expose them to what we believe to be their cognate antigens, and then manipulate them in various ways. Then once we know that, what controls that, we try to understand fundamentally what's happening.

Now, of course, what's happened in modern science is we've recognized that in vitro can be misleading, so you always have to refer back to the animal. But in that era, we'd been always referring to the animal, and now we had a chance to get a better picture of what was going on, so we relied exceedingly heavy on the in-vitro stuff, and it was somewhat later, again, technology made it possible for us to fold that back into animals. So I would say we did both. We worked with whole animals and we worked in tissue culture.

Williams: And half your day was spent following Baruj's line of inquiry, and then the other half was—

Paul: I wouldn't say half the day, but, you know, part. You know—

Williams: The question is, were your own projects coordinated with his, or are you following separate lines or not?

Paul: Baruj's dead now, so he can't be offended, and I would never want to offend him. He was really quite remarkable and wonderful to me, but, you know, all of us have our little foibles.

We had been together at New York University, and I had met a man named [Avrion] Av Mitchison, who is one of the great figures in British immunology. Av and Baruj knew each other quite well. We recognized we were going to move from New York City to Bethesda, so Av and Baruj worked it out that I'd go and spend two or three months in Av's laboratory in London just before the move, and so we went as a family.

When I was there, I got to see what Av was doing. He was doing what I thought were just unbelievably beautiful experiments, working out the notion that there was cooperation between two different types of lymphocytes. So in Baruj's lab, we had understood that the determination of whether an animal could respond to an antigen and the actual specificity of the response were two differently regulated functions, and we understood this, but we spoke about it really in a sort of theoretical construct. But Av had actually done it in an experiment. He had

realized that that was so, and one cell did this and one cell did that, and the elements of specificity were, if you like, segregated to different cells, and you could physically get a hold of them and do experiments. It was just astounding.

So when I returned from London, I said to Baruj, "I'm going to do that. That's what I'd like to do for my own work," follow up on what Av had done. I thought it was just magnificent.

Baruj said, "That's good. That's fine. This is what we'll do together."

Then, of course, I started working on it and a lot of good results started coming, and Baruj got very interested. We had a technician who had worked with us at NYU, who had come with us to Bethesda, and he was working with Baruj. He said, "Well, you know, Edmund can help you." Then one of the postdocs came on. He said, "Well, David can help you." [laughs] So in the end when we published this paper, we're all of us on it, which was fine.

But I must say Baruj never put his name on a paper that he didn't deserve to be on, never. His contributions were always very clear. In fact, the great frustration for a young person like myself working in this setting was not that he was unfairly putting his name on my papers, that was never the case, but that his intellect was so strong that it was hard to establish your own true independence in a setting of that sort, where you're always talking all the time. Where did his ideas end and mine begin and vice versa? Well, who could tell? So he helped me by going to Harvard, and then that was over with.

I loved the time and I enjoyed working with him, but I was getting a little antsy, because I was beginning to feel that I wasn't completely able to establish my own stuff, although we did. I'm overstating it a bit, and, as I said, I probably wouldn't say this if he was alive to hear it, because he had been wonderful to me. It really isn't a complaint. It's the true reality of how science is done. He was always there, always interested, always excited.

So that's sort of the story. We got it from that from whole animals and tissue culture. So I guess we wandered a bit, as they say.

Williams: Very usefully. Before we leave the real strictly science parts of things, can you describe what you consider your major accomplishments and in somewhat laymen's terms?

Paul: Sure. So they come in several components. So early in my career, when I worked with Baruj, and then after he left, we were fundamentally interested in what we would subsequently recognize to be antigen-derived specificity of T lymphocytes. That is to say, lymphocytes are divided into T cells and B cells. T cells mediate what we often call cellular immunity. T cell receptors, although we didn't know what the receptor was at the time, seemed to fundamentally behave

differently in their specificity than B antibodies. I was very interested in that problem.

My colleague Ira Green was working with Benacerraf on immune response genes. After Baruj left and went to Harvard, Ira and I and our colleague Ethan Shevach, who was working as Ira's postdoc, began to realize that these two subjects were not different. They were really the same. And we undertook experiments that were aimed at understanding how these immune response genes worked. I mean, we knew if you had the gene, you could make a response to an antigen. If you didn't have the gene, you couldn't. But what did that mean?

We did an experiment which established what I call histocompatibility restriction. It was that and follow-ons that Ethan did with another colleague, anticipated work by [Rolf M.] Zinkernagel and [Peter C.] Doherty, which was done two to three years later, for which they got a Nobel Prize, which established that in order for the T cell to be activated, it had to recognize two things: the, quote, "antigen" and the MHC molecule of the antigen presenting cell. That was what was called histocompatibility restriction.

We did that in a system not as tractable as Zinkernagel and Doherty, and they were able to do more, and their work was crisper, I have to say. But my own view is our work, and most particularly Ethan Shevach and Alan Rosenthal's subsequent work, was very anticipatory what they did. So we established, in my view, that how immune response genes worked was that they control the capacity of T cells to recognize their cognate antigens, the antigens to which they responded, and did so by the expression of certain major histocompatibility complex proteins on their surface. So I regarded that as an exceedingly important discovery. I was done jointly with my colleague Ira Green, who I had worked with in New York, and with Ethan Shevach, who was then Ira's postdoc. So that was a big deal, I thought.

Then I got another group of postdocs and we began to work on B cells, and one of my colleagues and I, the work I think extremely important, made certain observations about the character of antigens that could activate B cells. Antigens in that era were thought of as requiring T cell help and possibly some that did not. So what [Donald] Don Mosier and I showed was those antigens that did not require T cell help were of two separate types: one category, which were capable of innately activating cells, which today we would call TLR ligands, and another set that were not, but were highly polymeric. We distinguished them as Type 1 and Type 2 thymus independent antigens.

We also pioneered—we were not the first to show it, but I think we were extremely influential in the idea that what was on the surface of the B cell, through which it recognized antigen, was a true receptor. There was an argument that B cells expressed on their surface a cell-associated form of antibody. One school of thought argued that the only purpose of that was to attract the antigen

and then something else about the antigen would stimulate the B cell, that the immunoglobulin was not a true receptor in the sense that when it was occupied by its antigen, it did not transmit biochemical signals into the cell that would activate the cell, but rather it acted as a glue to bring to the surface of the cell a molecule that was intrinsically stimulatory for entirely different reasons. So that was one view.

Don Mosier and I argued, no, this is a true receptor, and we had many reasons. I can recall we'd go to meetings, and those who thought differently were very eloquent, and they'd win every argument. But we were right in the end. [laughs] Not completely. There were some truth on their side. The notion that the membrane immunoglobulin was a true receptor is, of course, true. I think more than any other group, we were the ones who really pushed that idea.

Then what happened was at that time Don Mosier, who had been my postdoc, became independent. So I said to Don, "Well, you take the B cell project and I'll do something else."

I started going back to my interest in T cells, which I had worked with earlier, and I'd worked with several other people, a colleague named [Ronald] Ron Schwartz, and we developed—one of the big problems with T cell biology in that era is for reason that to this day I can really not truly understand, it was very difficult to culture mouse T cells. It was easy to work with human T cells. Guinea pig T cells, which we'd worked with, were no problem. But we couldn't find good ways, good conditions, for working with mouse T cells.

The reason that was so important is the genetics of the mouse are so well understood, and the chemistry of the mouse protein so well understood, that to work with the guinea pig was like working, you know, with a handcart when someone's got a steam locomotive running by you. It was crazy to stay with the guinea pig. So Ron, particularly, but as my postdoc, he cracked that problem, got it to work. We were then able to move very quickly through repeating all the guinea pig stuff and moving forward, and that was really important stuff.

But the next big deal was my interest, going back to my B cell era, in growing B cells in tissue culture. We had this very curious finding that if the cell density was high, we could stimulate the cells with their antigen, if you like, to divide. But if cell density was low, we couldn't. We said, "Well, there must be something we're diluting out, and let's look for it."

So Maureen Howard, who was a postdoc, and I started looking. What we found was one of the first of the cytokines was a molecule called interleukin-4, which Maureen and I discovered and purified and with another postdoc got the sequence, etc. IL-4 is something I still work on. We discovered it in 1990—when was it? Ninety-one? No, it was before that. I can't even remember now. In

the eighties. Yes, in the mid-eighties. I don't know. I used to say it's twenty-five years ago. I still work on it. So was it a blessing or a curse? [laughs]

So the discovery of interleukin-4 and then understanding all of its biology, understand it turns out to be the principal regulator of all allergic and inflammatory disorders. Without IL-4 you don't make IgE antibodies, the type of antibody that is responsible for allergic diseases. So this is the central player.

Then we also discovered how you differentiate cells in vitro to become from being naive cells to become TH-2 or TH-1 cells. Susie Swain's lab and my lab were the first to do that. So that was the second really big deal.

So those, that I would say, many other discoveries building on these, that is the central role, that you need IL-4 to make IgE, that was a really big discovery. Other cell types that make IL-4, many other things, but I would give those the highest priority.

You had asked about disappointments. So, you know, you always realize you could have done something differently than you did. Was I ever scooped about something? You know, we lost out in the race to clone IL-4, so that was a disappointment. But when I looked at how we were doing it and how the people that had done it successfully had done it, I felt that they had done it better than we had. That was okay.

One of the things, I wouldn't call it a disappointment, quite the opposite, but I've had good luck with people doing things in the lab that I wasn't directly involved in. The best example, we had a wonderful example of what could be done. So I had a postdoc who came to me again quite, I would say from my point of view, very accidentally. This is a man named Mark Davis. So Mark had been a Ph.D. student at Caltech working with Lee Hood, who's a great figure. Lee Hood, of course, had been fundamentally a great protein chemist, a great sequencer. Mark came to his lab just at the time when the molecular biology era was really getting going, and just at the time when Susumo Tonegawa had figured out that you could understand the mechanisms through which the antibody genes were assembled.

Mark learned the molecular biology, and he and one of his colleagues were instrumental in Hood moving from the protein chemistry to molecular biology. In the course of that, they made lots of major discoveries about the organization of immunoglobulin genes, etc. Mark was a star, and he came to visit Bethesda one day. I didn't know why he had come, but we were delighted to have him there. He was terrific. And he announced he wanted to be a postdoc. So he wanted to learn about immunology. He said he knew about chemistry, molecular biology, but Lee Hood wasn't a real "true immunologist," quote, unquote. Lee wouldn't like that, but he was a great scientist. But we were, you know, the hardcore immunologists, and he wanted to learn that.

So he came to the lab, and we worked on a couple of really interesting projects together. Everyone recognized him as a man of surpassing ability. So after, I think, about a year, we all of us—when I say “we,” I mean I was the chief of the lab, but several other P.I.’s in the lab, very good people, and we all agreed this was something special and we should do something. Mark had the idea that it should be possible to identify the T cell receptor. In that era, it was known that T cells have a receptor for antigen, but it wasn’t known what it was. It was regarded as the greatest problem in the field at the time, what the chemical nature of this receptor was. And Mark had an idea of how it could be done.

What we did, we established an instant group. We cleared out a lab for him. One of my postdocs and one of Ron Schwartz’s postdocs was excited, went to work with him. We found him a technician. So he had a little group of four people, and in six-months he had cloned the T cell receptor. It was a great, great accomplishment.

We all looked on from a distance, but we all restrained the idea that our names shouldn’t be on this paper. He had done this all. That was probably the wisest thing I ever did, because it made me a friend for life, because in other settings, in other labs, the lab chief might have insisted that his name go on this paper. It would have been wrong. Absolutely Mark did it. He was a wonderful scientist. He *is* a wonderful scientist. But the great advantage of doing it that way was, we, to this day, have the highest regard for one another. So that was a wonderful experience.

So could I have done it myself? The answer is I would have never, never succeeded. I guess it’s a disappointment that I didn’t do it, but not a realistic one. In other words, you should be disappointed when realistically you could have done the experiment you failed to do, but I don’t think realistically I could have done that experiment, and Mark could. We provided him, so to speak, the setting in which it could be done, the resources to do it. It was a great experience.

There have been a few other examples through the lab where things like that have happened. You know, maybe I’m too good-natured to—I can’t think of great disappointments in that respect. There are always things we could have done better. Maybe I should have—you know, catching new trends, be ahead of the game.

The whole idea of the innate immunity revolution that Charlie Janeway instituted, another postdoc, the idea that Charlie had, which got such prominence, was quite straightforward. He enunciated it in an exquisitely clear way that galvanized the world, but the idea itself that there had to be chemical structures that were held in common by pathogenic organisms that would tell the immune system it should respond, that was probably well accepted.

Indeed, just as an example, the laboratory I had, the Laboratory of Immunology, was created in 1957. The first chief of that laboratory was a man named Jules Freund. Now, you're not an immunologist or a scientist, but everyone knows his name because whenever you try to immunize an animal with an antigen, if you are going to be successful, you have to add something called an adjuvant. The most famous adjuvant was Freund's complete adjuvant. It's adding an oil and water mixture with dead mycobacterial tuberculosis. And why did you do that? Well, we sort of didn't really know, but we knew it sort of juiced up the immune system, if you like. Now, we knew that if you didn't do that, you would get little or no response. So Charlie took that and he clearly enunciated the point, and that had a galvanizing impact.

Then, of course, shortly thereafter, a couple of years later, a discovery in *Drosophila* led to understanding the chemical basis of how this all worked, and now that's been a revolution in science. In fact, last year's Nobel Prize was shared between Ralph Steinman for the discovery of dendritic cells and Jules Hoffman and Bruce Beutler for understanding the chemical basis of one aspect of innate immunity, which was a follow-on to Janeway's work. Janeway would have shared in the prize, probably, had he not, unfortunately, died several years earlier.

I would say that's an idea that one should have had. I wouldn't say obvious, but I can't say in honesty that I look back and say, "Oh, I wish I had done better things." Absolutely there are all sorts of things I wish I had done better, but I don't feel that there's a single thing I didn't do that would have transformed the world.

Williams: When you took over as chief of lab, how large a lab was it?

Paul: Well, so history again. So the lab had been created in 1957 for Jules Freund. Freund was already an extremely well-known scientist. He died, unfortunately, relatively shortly after he arrived, if you like, of multiple myeloma, which one might have found strange considering his adjuvant might have had some role in this process. No one ever knows.

Then the lab was then headed by a man named Maurice Landy, and during that era, the lab really went into a decline. It was really not a good lab. There were a couple of really terrific people in it, but, in general, the lab had gone into a severe decline. When it was announced that Benacerraf was coming from New York University to head it, people got really nervous because Baruj had a reputation of being a really tough guy. He wasn't, but he had that reputation. And that was very fortunate, because it meant a lot of these people who were civil servants were petrified, and they left, which he would have had enormous difficulty trying to move them out of the lab because of—but they all left. So they left us an empty slate, so to speak.

The people who didn't leave were good, and the people who did leave we would have—so then they left. Then Baruj came in, and what we had had time to do was sort of clear the decks. We organized the lab a little bit, and then he left. What he left behind was myself and Ira Green and a couple other people. Basically it was an empty lab, so I was able over the years to recruit.

The lab that exists today, well, now, of course, it's many years later, all of the current staff I have appointed, so there's no one in the lab who was there before I came. I had the good fortune to be able to build this lab, because Baruj had basically done the work, so to speak, of cleaning out the stable, so to speak. He left me a tabula rasa, and that was a very lucky thing because it allowed me to really build something which I think is really quite remarkable and of which I'm immensely proud.

Williams: So today about how many people are there?

Paul: So the laboratory, well, we go up and down, so we have currently seven groups, four tenured principal investigators and three tenure track. The seven groups would probably vary in size. One group's almost twenty people, but most of the groups are smaller, so it's seventy, eighty people. We have, over the years, spun off two other labs.

So in the mid-eighties, my colleague, Ron Schwartz, who had been my postdoc and then was independent, moved from the laboratory of immunology and set up a separate laboratory, which has some very fine people in it. Then just last year, a second one of my colleagues, Ron Germain, moved from the lab to set up another new lab. When these things happen, of course, we lose resources and often we can build them back. Now we're living in an era of constraint, so I'm not as sanguine about how quickly or whether we will ever be able to build back.

So at the peak, we probably had over a hundred people in eight or nine research groups, and each of the groups is completely independent. We often work together, but each P.I. runs their own project. They have to, of course. They're all reviewed, and the programs have to make sense, and they have to make sense for immunology. I don't control what others do, but if someone was going way off the course, I probably would want to bring them back, but I've not had that. I've had a couple people in the lab who I felt over the years could have made better use of their abilities. I haven't been too successful in persuading them to change, unfortunately. I've tried. But most of the time with a few of the successful people, my job is to be sure they have the resources they need to do their work.

Williams: Throughout the entire time, your lab was part of Allergy and Infectious Disease?

Paul: Yes, since '68 when I came. When I came to the NIH initially as a clinical associate, I was in the National Cancer Institute, and then I had spent the summer,

I mentioned at the outset, in 1959 in the Neurology Institute. But since I've been a grownup, so to speak, I've always been in NIAID.

Williams: What effect did assuming a chief's position have on your science?

Paul: Well, it's interesting, you know. I was very young. I think this is correct. When I was appointed the lab chief in 1970 at the age of thirty-four, I believe I was the youngest lab chief on the NIH campus, and it's a big place. I suspect, although I don't know for sure, that I've probably been a lab chief longer than anyone has ever been at NIH. I'm coming up to forty-two years, and it's hard to do the arithmetic. Possibly there are other people that I don't know about.

So that's an interesting question. Did it impede my ability to do my work? And the answer is I think not. In fact, particularly in the early days, the administrative burden was very modest. Today it's substantially greater. In that era, you know, the regulatory aspects were much lighter. It wasn't a burden.

Now, on more than one occasion I was asked to take the next more senior job in the institute, would have been what is called scientific director, and that I thought about and demurred because I felt that I couldn't really continue my work and that it would make it impossible. But being lab chief, particularly in the early days when the lab was very small, I don't think it impeded my work at all.

Later—I don't know if you'll come to it—when I took this job of being head of the Office of AIDS Research, that I did anticipate would have a big impact, and it probably did, but it was an entirely different issue, you know. It was the sort of thing in which I felt how could you say no. We were living through an emergency. Not that I was the only one who could do that job, but if I'd been asked to do that job, I should have a damn good reason for saying no, and I didn't have any damn good reason to say no. It seemed to me that you have an obligation to do it.

So I kept the lab going. So if we want to get on to that, this goes back to around '92 and '93. Harold Varmus had just come to NIH as the director. In the era just prior to his arrival, there had been a lot of unhappiness in the AIDS advocacy community about the progress against HIV. People were very depressed. There'd been an International Congress in Berlin and just people came back to that, seeing that nothing was going forward.

Now, it hid the fact that a lot was going forward, but it was just at a moment that superficially it seemed things were terrible, and the advocacy community felt one problem was the NIH was not coordinated in how it was using its money for HIV disease. No central decision-making was under way. Money was being wasted. They pushed really hard with the Congress to have decision-making for broad outlines of how HIV resources would be utilized to develop a plan to be under the direction of some one entity, and that entity would be called the Office of AIDS

Research. That office actually existed, but its job was just to collect data. It didn't have any true functionality. It was to be a place where you could information about AIDS. That was really its job.

So the Congress passed a law—I think there's a law that established the Office of AIDS Research. NIH was exceedingly unhappy about this, because the NIH position was that science is best done by following targets of opportunity, and dictating how much resources would go to one disease and centralizing that outside of the normal institute structure would be a bad idea. So the NIH opposed it, but it was passed into law.

Varmus then arrived, and he had the responsibility of making this real. The Director of the Office of AIDS Research at the time was actually Tony Fauci. He just did that as the fact that NIAID was the main place HIV research was done. It was just logical for him to head this office, which was acting as a clearinghouse, but in the new guise, it was felt inappropriate for him to do it since he was heading one of the major institutes.

So they needed an independent OAR director. They tried to recruit. I was on the search committee, and we had response to the search was one terrific candidate, and that was it. The terrific candidate was a man named Bernard Fields, who was the Chairman of Microbiology at Harvard Medical School, a great virologist and uniformly revered, but he had had pancreatic cancer a few years earlier, had had surgery, a Whipple operation, apparently cured. However, it had a big impact, and he said, "Well, I've been given back my life. I'd better do something with it." So he wanted to do this job.

The search committee was delighted, and he said, "Well, I just have one more checkup tomorrow, and if it's okay—" It wasn't okay. He had recurrence of his disease and he couldn't take the job, and then Harold was in a bind, because nobody else on the list did he or we regard as suitable.

So I was nearby. I say my arm looks perfectly straight now. [laughs] You know, Harold asked me to do it. I said, "How could you say no?" So I got off the search committee and was nominated. I did the job.

It was an exceedingly interesting position. I felt at the time, of course, you can recall in the early nineties the advocacy community was very active, and it was a difficult time. They chained themselves to St. Patrick's Cathedral. They accused Fauci of being a murderer, you know, even though he did more than anybody to really stem the tide of the disease, both in his own personal science and in his role in leading the institute, but he was being vilified, you know. It looked like a terrible thing.

So my wife said, "I guess we'll have to unlist our phone." So we said, "Well, let's see what happens."

So the first day I got a call from CBS. I never got a call at home again, so that was great. It turned out it was just at a tipping point. The advocacy community had gone for the view that you were going to make progress against this disease not by yelling at people, but by getting behind what ought to be the way forward, and the way forward was science. They were going to get behind the best science to deal with HIV, not all of them, but the really most insightful ones. Then they became the greatest supports for the Office of AIDS Research. They were terrific, great allies and wonderful people, the ones I worked with, really outstanding.

So it was a great experience. I went into it with a lot of trepidation. We had to develop a coherent plan for HIV research for the country—well, for the NIH component, which was 90 percent of what the country spent. It wasn't that we gave out individual grants or determined individual experiments, but we said these are the big areas and we're going to devote this component of money to these areas, and we're going to ask the institutes to build proposals based on this plan. We would then, based on that, allocate resources to them. That worked very well.

Then early on we convened a meeting with some really topnotch people. I mean, Harold, of course, came, but David Baltimore, [Philip A.] Phil Sharp, really giants in the field. It was in the first couple weeks I was the OAR director, and we'd pretty much decided, in addition to everything, we had to review all the HIV research going on in the country.

We were very lucky. We were able to recruit [Arnold J.] Arnie Levine to chair that. Arnie, at the time, was at Princeton [University], subsequently became the president of Rockefeller University, was really an outstanding individual, discovered p53. So he led it, and we would be on the phone, and that had a transforming effect. It gave legitimacy to the office, of course, and every institute wanted to sign on to agree with Levine. So that was terrific. We had a wonderful experience.

But I was realizing, you know, my research was lagging. I mean, I kept the lab going. I was very lucky. I didn't step down as being lab chief. Perhaps I ought to have, but I didn't. But one of my colleagues, Ron Germain, agreed to be deputy, and he did a lot of work, really critical. Without it, I couldn't have done the job.

I really loved it, and after three years I wanted to leave, but I looked around, and I said, "One big problem is we are not doing enough for HIV vaccine development." I felt very strongly that was the case, so I decided I'd stay one more year, and in that year we did two things: we really ramped up the funding for HIV vaccine grants, and at the same time we were lucky enough to get approval to build an HIV vaccine center.

What had happened was that we'd been invited to the White House on World AIDS Day, which is December first, and this was in, I think, 1996, probably. I can't remember, but I think it was. It was just after the protease inhibitors had come on line, so for the first time a real prospect that you could have an impact on controlling disease. So there were several of us. There was Tony Fauci; Harold Varmus; a woman named Helene Gayle, who was from the CDC [Centers for Disease Control and Prevention]; and myself. We were told we were going to have not a long time with the President, maybe. The order was to be I was last, and they said, "Well, there's a good chance they will never get to you, because once the time is up, it's up."

Tony gave a beautiful discussion of the new drugs which were transforming everything, but they did get to me, and I decided I'd talk about the desperate need for vaccine. The President responded to that very powerfully, plus a lot of other people. I shouldn't take that much credit. The idea was that really we needed a big push, and we got very quickly permission to go forward an appropriation to help build a building.

It turned out that the Office of AIDS Research received certain monies from an agreement between the French and American government dealing with the patents for the HIV and the tests for the blood supply, so we got certain money that came in. In contrast to appropriated funds, which have to be spent in the year they're appropriated, these funds were what they often call no-year money, which meant you could save them, and I had saved them.

So we didn't get enough money from the Congress to build a building, but I had in my pocket seven or eight million dollars which I dumped into that, and that was enough to build this really quite wonderful building on the NIH campus, which is working. It's been really one of the leading players in HIV vaccine development. So that was great. I loved that.

But after the fourth year I said, "It's time." Moreover, it was a very political job, and I knew the day would come when they would probably say, "You know, Dr. Paul, you've done a wonderful job, but now it's time for someone else to do it," and I felt I'd rather decide myself when I would go back to the lab. In any case, I felt if I didn't go back now, I could never go back. The longer I stayed away, the less and less likely it would be that I could ever be a competitive scientist again. The world was moving on.

So I decided in '97 that was enough, and I went back to the lab, and I'm delighted I did it and I'm delighted I stopped doing it. But I loved it at the time. It was a great experience, wonderful.

Williams: Did you have to be approved by Congress, that position?

Paul: No, no, it was not—

Williams: It was not kind of position...

Paul: No. The secretary made the appointment.

Williams: Which institute was Fauci heading?

Paul: He's NIAID. So this was the irony, Dr. Fauci told me. I knew Tony when he was a postdoc, so I still call him. We used to have joint lab meetings in the early days when I was working on IL-4 and he was working on something comparable. His group and mine would meet together. We knew each other very well. One awkwardness was I was a scientist at the institute of which he was the director. On the other hand, I was the head of the organization that was responsible for giving him the money that he needed to fund HIV research. It was a very awkward situation. He was very good about it, you know. We got along fine.

I don't know if you want to go back and talk about my days at the AAI, though.

Williams: Yes, yes, I do, and it's good that Tom has warned us that we're running short on time. But it was just one other question I had sort of following up on all of this, and that is, speculate or talk a little bit about the relationship between politics and science.

Paul: Well, that was a wonderful time in this respect. So there was good leadership. NIH had great leadership. Harold Varmus was a wonderful director, wonderful, I have to tell you. I don't think he ever agreed with everything I wanted to do or did, but he never opposed it, I mean, as long as I guess I wasn't being ridiculous, because, I was, after all, directly under his supervision. At any time he could have said, "No, we shouldn't do that." But he was terrific to work for.

Then Harold had a very good relationship between the chairs of the key committees in the House and the Senate, and at was in a time—not to say anything, but I've voted Democratic most of my life. There was a Democratic administration and a Republican Congress, but the leaders of the House and the Senate committee, both Republicans, were terrific people and devoted to advancing science. There were two: John Porter, who was the head of the House Appropriations Subcommittee, and Arlen Specter, who was the head of the Senate. Porter usually gets the lion's share of the credit. The NIH now has a Porter Building. But, actually, Specter was, if anything, more aggressively in favor of doing good for NIH even than Porter. Harold had a very good working relationship with Porter and an adequate one with Specter, and that really helped a lot.

I had to go visit the key congressmen. Usually I would speak to their staff more than the congressmen, but that was essential. The OAR was a creation, a creature,

of Congress. The NIH hated it. I have to say the directors did not like this at all, because I was telling them what they could do with what they thought was their money. They didn't like it a bit. I had some very not very pleasant interactions with some of them who will remain nameless.

Williams: Throughout your tenure?

Paul: During the time I was at the OAR.

Williams: All the time?

Paul: No, not all the time. Most of the time. Look, I knew all these people before. I had been at the NIH for so long that many of the directors I knew personally very well, and we might disagree, but we knew each other. One of them was a little more aggressive, although in the end we got on fine. I had felt that one of the programs they were supporting with HIV money was really inappropriate. I thought you could justify supporting 10 percent of it with HIV money, but not 100 percent, and they were not happy about that. But that was my job and that was his job, so we clashed on that point.

In general, I have to say there's a very difficult problem that the United States faces in the sense of supporting science, and the difficulty lies in that we control very much the amount of resources available for the support of science, but we have very little control over the number of individuals who want that support. So it's very difficult to have a coherent policy. It's not that we shouldn't devote more money to science. Absolutely, of course we should. But there are the laws of unintended consequences. So there was a period that ended now, it must be almost ten years ago, when the NIH budget doubled, and everyone's expectation was, of course, that would be a boon to science, as it was, it was truly a boon, and that it might relieve the pressure on grant support because it would be so much more money.

But, of course, the scientific community responded to the doubling by saying, "Well, it's time to expand." So every medical school around the country started building new buildings and bringing in new people, and in the end, it's much more difficult to get a grant than it was. Now, partly it is because the doubling was followed by flat budgets, which is the worst of all possible worlds. But it's a big difficulty that in contrast to other countries where there's a greater control over the number of scientists who have jobs that let them apply for grants because they're determined by the number of university positions which are themselves funded, the NIH funds the salaries for people.

I'm not saying our system is not as good. In fact, the testimony is probably better, the accomplishments here outstrip everyone else's, but planning is exceedingly difficult, and the Congress is not so suited for that purpose, but we don't have another choice. So I think NIH has been treated remarkably well by the Congress,

and while from time to time there have been unpleasantnesses and people trying to perhaps steer research in one way or another, fundamentally, the Congress has behaved very well. Fundamentally, NIH has still been able to pursue the great tasks that it wants to.

You know, the stem-cell problem has been a difficulty, but I don't feel that the political issues have been such a burden. Our directors have really behaved terrifically, whether they were appointed by Republicans or Democrats. I was a great fan of Elias Zerhouni. Perhaps not everyone was, but I always regarded him very highly. I, of course, think both Francis Collins and Harold Varmus were terrific. So I think we've been very fortunate.

Williams: Let's change and shift over to the American Association of Immunologists, whose hospitality we're enjoying today. Talk about your connection with the organization and its significance.

Paul: So, of course, I can remember, of course, when I started in Baruj's lab, I would always go the annual meeting. In that era, it was always held in Atlantic City, every year. The AAI met at FASEB [Federation of American Societies for Experimental Biology]. We always met as part of FASEB, the organization we're in, and FASEB always met in Atlantic City. It was only when gambling came and Atlantic City changed, but they always met in Atlantic City and it was always a terrific meeting. We all pointed to that.

When I was a postdoc in Baruj's lab, I applied for membership. I was very fortunate. You have to be sponsored by two people. So my sponsors were Benacerraf and then a man named Michael Heidelberger. Michael Heidelberger, who worked in the next lab, was a remarkable man. He was the father of immunochemistry. He had been a young man at the Rockefeller University, then a faculty member at Columbia for many years where he invented this field. He was forced to retire at the age of sixty-five from Columbia. He then commuted for ten years from the Upper West Side to New Brunswick, where he worked in the Waxman Institute at Rutgers.

He got tired of that, so at seventy-five he was invited to the NYU Pathology Department, and his lab, a small lab, was right next to where I was working, so I saw him every day for four years and we got to know each other, so he was my co-sponsor. He had been the mentor of Benacerraf's postdoc mentor. So we had this lineage. So I felt terrific. Heidelberger lived to 104 and continued to work. He published research papers in every decade of the twentieth century, the first one in 1909, the last one in 1991. Wonderful man. So the two of them sponsored me. I thought that was great.

Then I'd been on various committees. I served as a section editor for *The Journal of Immunology*. I was head of the Program Committee, and when I was the head of the Program Committee, I proposed that we change the whole way the program

was done, that we set up blocks, that we have symposia in the morning, and in the afternoon we have the poster sessions and more small sessions. That's a program we still use today, and that was very well received. As I say, it's gone on till this day. Then I was asked to run for the Council, and I was elected, which was great. Then the way it works is you serve on the Council and eventually become president, which I did.

So one of the things in that era, you know, the AAI was a much smaller organization than it is today, but it still had the main functions it still had. It had the function of publishing the journal, holding the annual meeting, carrying out the functions that are necessary for the professional activities of scientists, and representing immunology to the world, and particularly to the Congress.

Now, lobbying was much less of an issue in that era, and I was a government employee. I really couldn't do that, but that wasn't disabling. We didn't have a real lobbyist. In fact, if I remember correct, when I was on the Council, Henry Metzger was the secretary-treasurer. He subsequently was president, but he was the secretary-treasurer. In that era he was the principal, if you like, professional person.

So the AAI wasn't run as a big organization. It was Henry and a woman who is the secretary, a very nice woman named Blanche Reines, and that was it. That was the AAI. It evolved, of course, and then while I was in the Council, Joe Saunders became the executive director, and, I guess the staff, we might have had a little staff.

But there were big issues that had to be resolved, and amongst them was the journal. So *The Journal of Immunology* [*The JI*] is owned by the American Association of Immunologists. Firstly, there was problems with the publisher, and that had to be resolved. We, in the end—I think it is true today—we self-publish. We engage a printer, etc. In those days, though, it was published by a publisher and they control things in ways that really turn out not to be great.

But the more important issue is this, that the question was should *The Journal of Immunology* support the activities of the American Association of Immunologists? That is, should there be money extracted from the journal that would be used to support the AAI activities? Many societies do that, and that seems on the surface a good idea. But my view, and I think others felt the same, *The Journal of Immunology*, while it was published by the American Association of Immunologists, was fundamentally an international journal. It was the largest immunology journal in the world. It is still today. In that era, when there weren't as many, quote, "elite" journals, there was only one, the *Journal of Experimental Medicine*, a larger proportion of really important stuff went first to *The JI*. Today there are other journals that may siphon off some of the very top papers. I don't want to make too much of that.

My feeling was the journal should be responsible for itself. That is to say, it should make enough money to build a reserve. Once the reserve was where you wanted it, any additional resources that came in should be used to reduce the subscription cost, reduce the page charges, etc. It should not be used as a cash cow for the Society, because it was really serving the whole world, and it was really wrong for us to be basically going to people outside the United States and use their resources fundamentally to run our Society. So the idea was the journal should stand on its own legs.

The annual meeting, well, that was more of a complex issue. We were forced to meet with FASEB in that era, and the reason was that there was a big equipment show, and because FASEB was very big, and you have a big equipment show, that brought in money. If you didn't want to meet with FASEB, if you wanted to meet on your own, not only didn't you get the income, you had to actually pay FASEB for the right to meet by yourself, and that was a big era issue we had to resolve. So maybe by today's standards those are small things, but resolving those issues was quite important in that era.

The other big thing, which, unfortunately, was not well handled, was clinical immunology. So at the time, the AAI had a Clinical Immunology Committee, and I have to say it was not very active. It was the era when immunology as a medical specialty was beginning to get going, and there were proponents of developing a separate clinical immunology society, and I felt that would be very unfortunate because it would be better for it to be imbedded in the AAI. We went through that for a long time. In the end, they formed a separate clinical immunology society, which to this day I think was an unfortunate thing, and it's just led to a reduplication of effort.

So those are some of the issues that we grappled with. I mean, fundamentally, immunology was in good shape, the field was growing, it was exciting, important things were being done, the annual meeting was very exciting, and the journal was doing great. I mean, there were no real tragedies. We did have issues with the Congress at the time. There were problems with research funding. Compared to today, we would say, it wasn't so bad, but at the time it looked as if there would be a bad time, and so there had to be efforts done. I couldn't lobby, myself, but we had to have individuals who could, and we certainly pushed that. But those issues were, as I recall at the time, was a simpler time that it is today. The organization was much less complex. I enjoyed very much the opportunity and I hope I did a good job. It's always hard to know.

Subsequently, I was asked to be the president of one of the international congresses. The International Congresses of Immunology began in 1971 with a congress here in Washington [D.C.]. That was the first, and thereafter, every three years there was another congress. I guess for the congress in the mid-nineties, I don't remember when it was, it was going to be in the U.S. again in San Francisco, and by then I was off the Council. I was asked by the Council to be the

president of that congress, and I agreed. Joe Saunders, who had been the executive director, was there, and he was going to do a lot of the—what's the word I'm looking for? You know, the work necessary to get the congress going, lining up supporters and things of that sort. I would work on the leadership, and Philippa Marrack was going to be the person in charge of the program, and that went great.

Then I was asked to take on the job at the Office of AIDS Research, and I really felt I couldn't do both. You know, it's a three-year or four-year job. About a year and a half into it, I said, "I really have to step down," and Philippa took over as president of the congress, and I can't recall who took over as program director.

But the difficulty for me—it's a little callous to say this—unfortunately, Joe Saunders, who had been a great figure, who had been the executive director, died suddenly of a myocardial infarction during this period, and I recall going to his funeral. Of course, apart from losing Joe, who had been a great guy, this left us high and dry in terms of trying to run a congress. But we did make it.

So I've always had a high regard for the AAI. One problem which is emerging now in recent years, it's a very parochial one. Those of us at NIH are more and more now, I guess, out of the mainstream in terms of service for this organization and others like it. There was a time when NIH people were important parts of it. Henry Metzger was president. I don't know if only the two of us. I think it's partly for two reasons. Firstly, the NIH doesn't like us to have a fiduciary responsibility, because if we do this as official business, then, in principle, we are committing the government to things which the government has no interest in being committed to. It's not its job. We could do it privately and that might work. That's possible.

Then there's the other feeling is that we're not at risk in the research grant arena in the same way that people in the universities are. We have our own risks, but they're quite different. I think more and more as the granting situation has become so difficult, the community, I think, feels more comfortable with leadership that shares their issues. So for that reason, NIH people are being more and more—I won't say excluded, that's too strong a word, but no longer playing as important a role in this organization as we used to, which I feel is unfortunate. I wish it weren't the case, because I, myself, value very highly the roles I played in the organization, and I think there are a lot of wonderful people at NIH who could do that. But I can understand, of course, that these issues—now, I don't know if anyone has explicitly said these things. In other words, I don't believe there's any conspiracy to keep us out. That isn't the case. It's more of an issue, you know, people look at issues and who really relates to the things that they care about, and more and more we may seem not as in the same mode as they are.

We haven't had a major NIH figure on the Council. I can't think of anyone. I can't recall if Henry was president before me or after me. I don't remember that.

But whoever was last, is the last one from NIH who's been on. Several of my postdocs have been president. I've had two postdocs, two former of mine have been president, Charlie Janeway and Lori Glimcher, and two of my predecessors as Chief of the Laboratory of Immunology have also been president, Jules Freund and Baruj Benacerraf. So we have a president lineage, but that does seem now to not be the case.

Williams: But the way you describe it, it's more NIH is pulling away than you're being pushed away, right?

Paul: Well, I think it's a combination. So NIH in the earliest days was very nervous. In the earliest days NIH didn't care. No problem. Then once people started raising questions about what is an appropriate activity for NIH scientists, outside activities or official business, more and more NIH looked and say, well, it's not appropriate for an NIH scientist as official business to have a fiduciary responsibility, because, in principle, since it's official business, the government is being committed to that fiduciary responsibility.

So, of course, you could say, "Well, I will do it as an outside activity." Now, there's some question about that, whether that's a good idea, because this is, after all, very much akin to your work, but you could do it as an outside activity. I don't know what their position on that was at the time, honestly speaking. That happened.

But now NIH, I think, has developed the rules such that that is not the issue to the same degree it was, but I think now there are new issues that come in. In any case, I cannot think of any of my colleagues who has played any major role in the AAI in ten, fifteen years. Since we are a very substantial proportion of the immunology community, there are a certain number of really terrific people who could be used in more useful ways. But I don't think that's a big deal.

Williams: But evaluate the importance of the organization to the profession.

Paul: So, the annual meeting is very important, absolutely. The journal still plays a critical role. Its role in representing us to the world is important. Particularly it is able to speak for us in the political arena, and that's very important. I think those are its main things that I see, and I regard those as exceedingly important activities. It also conducts educational activities. It runs very fine courses.

It does what you think a first-rate professional—I mean, not a professional organization in the way that, let's say, the clinical organizations are, which worry about standards of care and things of that sort, and that was one of the reasons that it made it about the clinical immunology component, because when the clinical immunologists were saying, "We want an organization," they wanted this organization to do things that the AAI wasn't so anxious to do, that is to say, set standards for how you might treat things, to educate not only professional

immunologists, but also individuals who were, let's say, master's-level people, and to take on a whole new set of functions that, let's say, a gastroenterology society would think appropriate to do, but a biochemistry society would not think it appropriate to do.

So we saw ourselves much more as a basic science entity. Nonetheless, I've always regarded it as unfortunate that the scientific activities of clinical immunologists should be—it's not that we have lost them. We still have them. But they're sort of divided into two camps, and I think it would have been better if we had their full allegiance.

Williams: What do you say to people that are considering the field of immunology as their life's career? Do you recommend it?

Paul: Well, that's a very interesting question. So I've thought about that a great deal. So when I was a kid, you know, growing up, immunology, very attractive field. It is true Burnet and Talmage had already spoken, so we had already had our "aha" moment where some fields haven't had that yet, like neurosciences are still waiting for, aha, what's the basis of consciousness. Much more difficult problem, of course, but, nonetheless, you could still be *the* great person. So in immunology there were so many things to do. The field was open.

So now the question is, now immunology is mature, so is it a field that you should recommend for people? That's a very interesting question. I've thought about that a great deal. My thinking goes as follows. So science is changing now in a very dramatic way. We're moving, with the introduction of new technologies of gathering information, we can amass vast amounts of information genome-wide about the behavior of the cells we work with. We are moving very rapidly to a science, if you like, modern physiology, so what's called systems biology.

We are not there yet in the sense that we can use this information in a truly productive way to be predictive of how systems will behave when you perturb them. This is, after all, what we wish to do. Now, my own feeling is immunology is the best field for this, because we have, firstly, vast amounts of information. Our cells are really easy to get a hold of. We can evaluate the system far better than virtually any other field. So my feeling is immunology should lead the way into a new era of, if you like, whole organism systems biology. So I think on that basis, I think it is a very attractive field.

Now, as I say, there many competing fields that are exceedingly attractive today, neurosciences, developmental biology, regenerative medicine, you can name them, go on and on, whereas ten or fifteen years ago, I was beginning to worry that immunology was getting sufficiently mature that the most creative people might find that not adequate scope. Today I don't feel that way. I think that the challenge of a systems-wide approach to truly understand how a living, breathing entity really works and what it will do when you alter it in some way, there is at

least a possibility that this will be best worked out in immunology. So the answer is I'm much more optimistic today than I might have been if you'd asked me that question ten or fifteen years ago, almost as optimistic as I was when I came into the field.

Williams: You have no regrets, your coming into the field?

Paul: No. It's been wonderful to me and I've had a good run with it. I haven't even mentioned the *Annual Review of Immunology*, and fundamental immunology, where I think I've made a contribution. I'm the founding editor of the *Annual Review of Immunology*, just completed my thirty-year term with Volume 30. The *Annual Review of Immunology*, you know, journals are rated by so-called journal citation reports, and so the *Annual Review of Immunology* has never been lower than fifth of all journals ever since its first publication. I think in seven or eight times of the thirty years, it's been first. We've had a terrific impact on the field, I believe.

Then I'm the editor of the major advanced textbook, working on the seventh edition as we speak, almost done, every four years. So I try to make a contribution to the field besides my own scientific work and my role in training people and things of that sort.

No, I don't have regrets. On the other hand, do I think there aren't other fields that were equally interesting? I always thought of immunology, that the information problem, the specificity problem is a remarkable thing, and that always, to me, was the exciting part. So the neurosciences have that as well, but it's so much more complicated. But we used to say years ago, I used to say, in our slavish devotion to immunology as our science, well, what is a heart? The heart is a device to pump lymphocytes. So maybe that shows a certain parochialism. [laughs]

Williams: Where you come out on top.

Paul: Well, maybe, I don't know. [laughs]

[End of interview]