The American Association of Immunologists
Oral History Project

Transcript

Paul M. Allen, Ph.D.
April 28, 2014
Bethesda, MD

Williams: This is an interview with Dr. Paul Allen for the American Association of Immunologists Oral History Project. Dr. Allen is the Robert L. Kroc Professor of Pathology and Immunology in the Department of Pathology and Immunology at the Washington University School of Medicine in St. Louis. He was President of the American Association of Immunologists from 2005 to 2006 and served as an AAI Council member from 2000 to 2005. We are at the AAI Headquarters in Bethesda, Maryland. Today is Monday, April 28, 2014, and I am Brien Williams.

Dr. Allen, thank you very much for being with us today, and I'd like to start by you recounting something of your own family history.

Allen: Well, I was born in a little town by Hannibal, Missouri, called Louisiana, because my father was a chemical engineer and during World War II worked in Texas making chemicals critical for synthetic rubber. Then after the war, he moved up and U.S. Bureau of Mines was working there, making oil from coal, and so a bunch of chemical engineers went there. Then I was born there, and my sister as well.

Then about 1953, the oil companies pressured the U.S. government to close down this competition making oil from coal, so then at that point we had to relocate, and we ended up going to Midland, Michigan, where my father worked for Dow Chemical.

Williams: What about your early life, elementary school and secondary and so forth?

Allen: In retrospect, it was a pretty idyllic, easy childhood, because Midland is—everybody's father was a chemist or a chemical engineer in a town more or less in

knowledge and creativity and liked science, and I'm sure the English teachers probably, on the other side, realized I did not have a talent for creative writing, etc.

Williams: So you got the science bug pretty early in your life.

Allen: Yes, exactly, because I think it was more by osmosis. You didn't realize that, but that was just kind of—we always used to joke, the toughest job in Midland was being a high school chemistry teacher, because everybody said, "My dad says that the book is wrong," etc., stuff like that. So I think it was just part of that process. Either you embraced science kind of from that environment, or you seemed to reject it. So I was one who embraced it.

Williams: What were the steps that took you then to the University of Michigan?

Allen: Well, I guess I wasn't that adventuresome to go too far away. Ann Arbor in the late sixties and early seventies was a pretty active and dynamic place compared to Midland, Michigan. So I went out there and started out to be in oceanography, but it finally dawned on me that there was no real ocean nearby Michigan. But that was in the School of Engineering, so that was still the same kind of bent, and then I switched to microbiology.

I always thought it was a school that kind of gave you enough freedom. I was confident enough that having a large school—because I think some people feel a very large school, you can get lost, but I really embraced that, because I think it was a fun time in Ann Arbor. You could learn and also now just all the anti-war movement in the sixties and everything like that was happening there as well. So, compared to the quiet, relatively easy life of Midland, Ann Arbor was a pleasant change.

Williams: What led you to microbiology?

Allen: Well, hmm. Good question. I'm trying to think that there was a bunch of people that would go into, like, biology or something, and I just took a course, I think, as a sophomore that had a little bit of it in it, and then it got really interesting, and so I just got interested in it. Then they had a—for a long course that doesn't exist anymore, but it was two semesters. It met twelve hours each week for two full semesters in microbiology undergrad majors. There was this huge full immersion, and once you got into that, you just found it was fascinating. So I just kind of grew into that.

Williams: And that was as an undergraduate?

Allen: Yes.

Williams: So then you did the master's and the Ph.D.

Allen: Yes. So trying to decide what to go into, I remember I had, in addition to one section there was in immunology, I actually took an evening course. There's like three hours a week for once a week, a survey course of immunology. And I took that, and I found it interesting but didn't understand very much. I hate to say that was more the basis of why I went into it. This field seemed interesting, but it was not like I understood it all and this was a really rational decision why I went into immunology. It was a fast-moving field. There was, you know, lots of acronyms and jargon, but it just seemed interesting enough. I'm not sure what sparked it. I just decided that's what I wanted to go to grad school in.

Williams: So you made that decision sometime in your junior or senior year.

Allen: Yes, exactly. So I was a bit of a late bloomer, I think, and I'd never done research in a lab before I went into grad school, so I wasn't exactly a hot commodity. So the truth is, I got into one grad school, Michigan, and so it worked out well for me, but it was pretty funny that that was the one that I guess they knew me from undergrad before and stuff like that. So I stayed in the same department for undergrad and grad school.

Williams: But you made application to other grad schools?

Allen: Oh, yes. When they invite me to give talks, I remind them that they rejected me from grad school. But it was probably with no research experience. Now I look at the kids coming through the research programs now, it's just they all have so much more opportunity and everybody has significant research experience. So I guess I was at the cusp or I'd had it in classwork, but nothing where it was real research.

Williams: What was the status of the university at that time in the field?

Allen: At the University of Michigan, immunology was a tiny field. We had two immunologists. So there was one that had his lab was pretty full. Then my thesis advisor was a full-time surgeon, his name was John Niederhuber, and he had never had a graduate student. So the other immunologist, named Lathe Claflin, convinced John that he should try and have a graduate student. So I was John's first graduate student, and so then his lab grew and he had multiple ones after that.

Then if you fast-forward, he became the head of the NCI here. He stepped down maybe three years ago. So through a variety of his career and my career, that small world, I always tell my students, "You keep in good standing with your thesis advisor no matter what you think where they're headed or not." So that was the one where it worked out. It was just luck, and Lathe kind of championed my position for John to take a graduate student, so that was really lucky.

have worked out any better, because this is one where I wanted to reduce a whole bacterium down to a protein and then actually the protein down to the fifteen amino acid peptide that are recognized. So what I did is I started out with immunizing mice and figuring out what portion of lysozyme they recognized, and it turned out when this particular mouse strain, there was one dominant epitope, so I'd identified that and characterized that.

So then this is where we use this system to directly show that peptides bound to MHC molecules, so this was huge in the field. So Emil won the Lasker Prize for this, and rightfully so, and I'm 0 Tskn c 0 Tw -2 0 Tsl y rb4u11(ns13(')33)20( )-10(ns13(6S)-4(

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were definitely equal on all of this. But Emil was the one who finally said, "Why don't we just go and do this?" So we had had the system and we'd kind of been going around the edges, and he just said, "Why don't we just come up with this? Let's just do this experiment." And so it was a team effort of Bruce Babbitt, myself, and Emil that did this.

Williams: And Emil gets the Lasker.

Allen: Yes. Oh, absolutely, because he had done the antigen processing, too, before, that he had shown that the antigen presenting cell had to handle that antigen, it had to go through an acidic compartment and needed proteases and all of that. So it was definitely he had been working in that field and continues in that field.

Williams: So you were only at Harvard for one year, is that correct?

Allen: No, I was there from '81 to '85.

Williams: Yes, now I see that. Yes, I'm sorry. Right. Then you moved to Washington University.

Allen: Yes. So Emil then was being recruited to become chair of pathology at Washington University, and so as a funny aside that there are not very many secrets in immunology, in science, so Emil, we always knew where he went on meetings, and then all of a sudden, one time he disappeared and he wouldn't say where he had gone.

So then I had heard Wash. U. was trying to recruit John Niederhuber, m3 0 Tw 184(Yes.)2(,)10(a

there was certain labs you got along with and then you developed a lot of close contacts and colleagues from that interaction, because there were so many people training there. So it's an amazing institution.

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Williams: Niederhuber did not go to Washington University, is that right, or did he?

Allen: No, he ended up becoming chairman of surgery at Stanford, so that was the one.

Williams: But you and Emil continued your own relationship, really.

Allen: Yes, well, my intention was, because I had started this project with the lysozyme, but it was so moving, I didn't have a separate project to spin off. So the question is, so I was going to go there for a like a year or a bit, kind of work, carve out my own part and then move to a different university, was my original intention. So obviously, I was completely wrong on that.

But because Emil I had some frank discussions and were able to carve out how he could have what his lab was known for and what I'd brought, but then also something that I could work with and thpa6(w)(,)-10(w)2(a)4(s)b tould wab-620(w)-2(n of)2(he

going to happen after Emil? But a new chairman came in, and things have continued. So we built up the community, and it's nice that it's self-sustaining.

So I think it was fun being part of that, where you could really build on it. A lot of us were at Harvard, and so we behave a little differently in St. Louis than we do. If you put us back in Boston, we'll go back to that model and we can exist in it just fine, but in St. Louis, it's a little more collegial, and so that's just kind of the standard that's when you do—a student gives a work-in-progress talk, there's never any discussion about, "Oh, let's not talk about that, because somebody might take our idea," where at Harvard those discussions did enter.

Williams: Other differences between the two institutions?

Allen: They're so different, because I was at Harvard Med School on the Boston side, but it's so enormous, the number of people there. So it's probably not fair comparing the whole enterprise. I was at University of Michigan, which was a public institution, then you went to Harvard, which was just the most wide open, and then you go to Wash. U., which was private, but it's a little more constrained. It has some Midwest judgment to it. So I think the combination of those. So I think Harvard is basically you can do whatever you want, but you have to bring 100 percent of your funds in, kind of stuff, so there are a lot of incredibly bright and motivated people there. Then at Wash. U., there's a little more institutional support. I mean, we still bring in a lot of—you know, but there's still kind of a different business model. Like Harvard would build a building on debt service and say, "We'll just fill it up with bright people." And Wash. U. will save money and build a building when they have the money and then fill it, kind of stuff. So it's just different business models.

Williams: This may be a naïve question on my part, but what is the relationship between pathology and immunology? Where do they kind of cross?

Allen: Good question, because at Wash. U., pathology was considered a basic science, and in a lot of places, it's not. But the department was always known for its basic science. Our previous chairman was a man named Paul Lacy, and so he was a leader in diabetes and islet cell transplants. He hl 7l a-6(t)-6(r)-1(ani()-1(i)Td ( )Tj EMC /P

me about it, because it's named after a hamburger chain, more or less, but it's a nice endowed chair, and I'm really appreciative I've gotten it.

Williams: Let's talk about your science now for a little bit. I think you've probably covered a good deal of it already, but namely about the earlier stages. What have been the accomplishments in more recent years in your career?

Allen: Yes, I think it stems from something we were talking about previously, when Emil and I were—I was trying to carve out my own niche. So we'd known that MHC molecules bind peptides, but at that time we didn't know if they could distinguish between a foreign peptide or a self. Because that's the hallmark of the immune system is it has to distinguish foreign from self. So it's easy to make an immune system that can recognize everything, but then you're going to attack your own body. So how do you develop that fine balance?

So I said, "Why don't I look at self peptides binding to MHCs." So that was where I took off and started this own little line of research. So I first showed that the MHC molecules didn't distinguish. It didn't know if this was a lysozyme from chicken egg or from mouse. It bound them the same. So now I had a fundamental change about how that—and that's where I've taken off of trying to look at how the immune system handles self-antigens and what's their influence in the whole development of the immune system. Because most of us are healthy.

So an antigen-presenting cell in these MHC molecules, they want to have a peptide bound to them. They need to, to be stable. So if you're not infected, their only choice is self-peptides. So you could say, "well, that's just kind of a placeholder till an infection happens." But, no, it really turns out that those self-peptides play an important role in developing your immune system and maintaining it. So that's where I've spent a lot of my career is really working on that fundamental aspect of T cell recognition of a self-peptide MHC.

Williams: And what practical applications derive from that?

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predisposes them to get diabetes. They live in the same household, they have the same infections, that the chance that both twins will have diabetes is only 40 percent. So there's something else going on here that we don't know. So that's kind of why we haven't been able to make more advances of blocking the autoimmune diseases.

I think most of that is due as your immune system is randomly generated, so Twin A and Twin B will have the same genetic makeup, but their immune system is randomly generated by fragments of genes put together. So from those, maybe one has a few more T cells that might be autoreactive, and then they're not going to cause disease, but then when they both get the same infection, those T cells might then cause a disease. So, fortunately, I think we're getting closer and closer, but it's hard to disrupt the whole process because then you would be sick. If you eliminate CD4 T cells, that's what HIV did. So it's hard to target an intervention at this point.

So I'm trying to think of other things. Yes, the autoimmune diseases have been really hard because you treat the symptoms so you can do that, but you don't yet treat the underlining causes.

Williams: That's just the point at which the science is today. i whicothePhePhea9 0.002 Tc 22(he)4(s)-21

So you could eliminate the tumor if the T cells were there ahead of time or the tumor was small, but once a tumor got to a certain size, no matter how many T cells you put in, the tumor ignored them. So we thought maybe the tumor was making inhibitory cytokines that a T cell would come in and then it would shut them off. So there were two of these: interleuken-10 and TGF- ransforming growth factor-beta]. So we made mice that didn't have those, respond to those, and that's when we didn't do any more tumor experiments, because these mice got a wonderful model of colitis.

So this is like I was telling you about the collaborative nature of Wash. U. So I didn't know one end of the colon from another, and so I just went up to a young colleague, Thad Stappenbeck, and said, "Thad, we have this interesting model," and he got so excited. Then we did this as a collaboration with my grad student spending much of her time finishing up the project in his lab and so then his grad student who characterized the model. And there were a couple features that were just like human diseases: it was 100 percent penetrant, so all the mice got it, it looked like human disease; and we could cure it with antibiotics. So then it was saying that it was a bacteria and then we could transfer it with T cells, so I was interested. And so then the next grad student figured out what the bacteria is.

So now we've gone back and forth, and it turns out we wrote a grant together, NIH, and it's still wonderful because he's more the inflammatory bowel disease person and I'm the T cell person. So that's one where serendipity comes in, and, we were talking earlier about chance favored the prepared mind, because our mice got sick, you go "Hmm. I wonder what that is." So we could have kept trying to do tumor experiments, but then that took us off in a complete different direction.

Williams: [illegible]

because then there's a process in the next stage of the thymus; it's called negative selection. It's like a filter. You rearrange, you get these T cells, then they grow up. Then all of a sudden, if they're going to respond too strongly, they get killed. Then the ones that pass that test then come out into the periphery, and then that's your immune system.

So the self-tolerance process, that if you made it so stringent, the problem would be that you're not going to have enough immune system to recognize every potential pathogen. And so there's always some T cells that are just kind of on the edge of being self-reactive, and then there are other mechanisms that can keep that in place. So this is the whole process of self-tolerance is purging the T cells in the thymus to not recognize self.

Williams: So it's a good thing.

Allen: Yes.

Williams: Good. Let me ask you about disappointments along the way in your scientific career. Have you had some real down moments?

Allen: Yes. Yes, I think there's obviously ups and downs in science, and some of those are where you go off in the wrong direction. You try a project—and the beauty of the NIH system is that you can write a grant, and you don't have to do exactly what you're going to do. You have to be productive, you have to publish papers, but they don't care if you take a turn.

So some of the disappointments are where you start turning and then you get further and further away from your core competencies, and then you're not doing science to the level that I feel comfortable, or the quality. So I got that a bit, and I did a lot on arthritis, because it started out as a T cell model, but it started getting into neutrophils and stuff. So at the end, it was hard to do experiments and things like that.

So other things mostly, I guess real disappointments are grants—that's where you learn—and papers and that kind of rejection. I'm trying to think of—I've been pretty lucky in continuing on that science. I'm not trying to be Pollyanna-ish, but, I mean, I think some frustrations are when you realize that a project is going along, and then the person graduates or moves on, and then you lose a little momentum. So the question is, do you keep going on or do you go another direction, a little turn?

Then there were a couple times when you could have made more hay. Somebody else made more discoveries in an area because you were really close but just didn't push far enough, stuff like that. So those are some of the disappointments. But there are not that many, and you realize it's going to—I view scientists, each one of us, as a catalyst. We make science go a little faster, but it's going to happen

with or without me. I'm not egotistical enough to say that these peptide-binding MHC, it would have been discovered by others very quickly after that too. So I think that's how I view it.

So I haven't had any really major setbacks. You know, sometimes you get disappointed that some of your most talented students didn't go into academics, more for family reasons, not from the science aspect, but other things going on. So you feel a little—those are kind of setbacks because you put your heart and soul into training them, and you want them to do well, and they're doing fine, but within the academic world we kind of view replacing ourselves with like-minded is an important process.

Williams: Talk a little bit about your merit grant. What was that like?

Allen: Well, that was a really pleasant—that they had started this a while ago, because the NIH grants were only ten years, five years, and then what they did was they decided for—at least in the National Institutes of Allergy and Infectious Disease, you get once in your career. So a certain group of people get a merit award. So it's basically that's what my one grant I'm still in now, almost year twenty-nine or something. That's the one I first got when I was a junior faculty. That's the same grant you got a merit.

What it allows you to do, instead of five years, they give you for ten. So halfway through, you have to do kind of check in and make sure things are going okay, but it's just a really nice time when your things are cooking and your lab is going, and they just feel that this is—it's an acknowledgement, but it's not a reward. It's just allowing you, instead of having to stop time and write grants for that one, why not give you a ten-year—

there's no chance of giving a talk. Well, here, if people read the abstracts and like that, this is how you get your feet wet, and you start at a national meeting. So I think it serves a really important purpose.

Williams: You were an editor of the *Journal* on two occasions. Are there any recollections that you'd like to share about that experience?

Allen: I started out and I was a section editor for the antigen-processing part, and so it was fun because it was my first editorial experience. It was before the *Journal* review process had become electronic, so it was sending things by FedEx and doing all this and calling and faxing, so it was much more cumbersome to do it. And you're more limited on who you could ask for reviewers because you wouldn't send it to Europe because it was really too expensive and stuff like that.

So it really got my feet wet for that, and then it really helped me—I'll come back to being deputy editor. But in between, from '97 to 2000, I was one of the four editors of *Immunity*, and so my *JI* experience really helped me with that, because this is the other thing where you write reviews, but you're never wearing the editor's hat. You don't have much experience. But I did have one where you look at the reviews, and it's amazing how few times there's concordance in the reviews, and you have to decide are these arguments worth, or are they being harsh, or is there an agenda and stuff like that. That really helped me to do this other, the *Immunity* part.

Williams: What does it mean being the deputy editor? It sounds like the Wild West a little bit.

Allen: So what they do is divide up the work, because there's so many manuscripts. So what they do is there's an editor-in-chief, and they mostly do all the really thankless things, where there's fraud or making decisions and keeping the thing going. But all the decisions are made by the—I think there were maybe eight of us, or ten, deputy editors. So basically there's a section editor who solicits reviews, and then what they do is then they take those and they write a summary, and that goes up to the deputy editor, and then they make the decision. So you really are an editor, but not under the official structure.

Williams: Then any recollections about the time, I guess, three years you were on the Awards Committee of the AAI?

Allen: Yes, it's one of those where it's hard, I mean, because you're judging your peers, so it's real easy to say you don't know any and you can pull out these, but now you're trying to decide which peer and with a few awards. So it was really eye-opening, looking at who could write effective letters of recommendation for this and, like, why is this person a good mentor.

Williams: So some of the other issues in your year of presidency, what else were you dealing with besides convincing Congress they should give you more money?

Allen: Well, one of the issues is open access in electronic publishing, because it was just starting to come out, and so the business models were complicated. So AAI fought pretty hard, because there's currently now in its existence that what you have to do is when you have a published paper that's supported by NIH dollars, that you have to send a copy to the National Library of Medicine, and then that's publicly available after each journal has maybe after six months or something.

So, my understanding, all this originated from is some congressman from the Midwest, maybe Oklahoma, had some niece who was trying to do a report, and she looked up something on the internet and found this, and then it said, "You have to buy that article for $25. You don't have access to it." So I guess she tells her uncle, who then starts this whole thing.

So this was a big issue, too, that we took a stand that this was really not necessary, because who owned this? It just was a matter of timing. It's not that this is not publicly available, but to have a journal viable, you can't give your content free. So it was this whole electronic publishing and all these issues about in journalism. So we spent a lot of time on trying to do that, and NIH was trying to work through what should the requirements be. So they still have that requirement. Everybody sends these papers here. I don't know how effective it is.

Williams: And it's still the six month—

Allen: Well, I think some journals are instant, and I think each author can do a little bit. But it seems like it's shaken out that the journals now have adjusted to the electronic world, I think, because it was just the beginning of all these discussions about like *The Journal of Immunology*, because to make your first printed copy costs a whole lot, and then each one is very little after that. So what's the archive if we say we're only being electronic? Back then, you kept going from floppy disks and the storage media and stuff, so it was a very scary thing to say we're not going to print a paper copy. We got some advertising revenue and stuff. So there were lots of really interesting discussion about this, about the fast-moving field and how this affected it, because that's a big source of revenue for the society is the *Journal*. So you didn't want to lose that. And it's also important for society to run a journal, not a for-profit company.

Williams: I think you dealt with the reauthorization of NIH during your year.

Allen: Oh, yes, that's right, because that was the one where they were always worried, because every so—I forget how the periodicity, because then that was the one could they change all the rules, because they can change anything, because the big one they were always worried about is NCI. Because of Nixon's War on Cancer,

Williams: But they are finding places to go.

Allen: Well, I think the Ph.Ds., right, will, but then I think we're also losing even at the graduate-school level, that they're going to go into computer science or they're going to go into something else instead of going into biomedical research. And I think some of that has to start way back in junior high, like we were talking about. I'm the Sputnik generation, so I don't remember my parents saying, "You have to go into math and science because of the Sputnik launch," but I think there was an emphasis on that.

It seems like we don't want to have a Cold War crisis to do that, but somehow we have to spark to get the young kids really interested in this research, because, you know,

think then we can manipulate, we can change things, so we can really test these. I think the whole field of cancer immunotherapy now, with all these checkpoint blockades, I mean, this is an exciting time.

If you look at immunological things, there was like TNF [tumor necrosis factor] blockers for autoimmune diseases, and now you have antibodies against like CTLA-4 [cytotoxic T lymphocyte-associated protein-4] or PD-1 [programmed cell death-1] or PD-1 ligand. Those are huge. So instead of like pinpointing when we were talking about individual T cells or peptide MHC ligands, this is more global. And I think most immunologists thought if you had initially blocked tumor necrosis factor, everybody would get sick. Well, they really don't. Occasionally somebody does, but it's an amazing how once you start proving there. So I think it's an exciting time for immunology.

Williams: And you encourage young people to go into the field?

Allen: Yes. I think it's still just—I look at this. You can eliminate an immune system if you keep your research animal like the mice clean. So it's wonderful. You can do so many things, and it hits all sorts of aspects of it. It's not just one little molecular detail. You can look at cellular reactions. The microbiota is now clearly involved when we're talking about inflammatory bowel disease, and so it impacts in so many different other physiological systems and stuff like that.

If it was really simple, we would have figured it all out of how this all works. So I think you can say the complexity is there, but that's what the immune system is there. More or less, it works pretty well. I mean, we get sick. We can't cure the common cold yet. We still haven't been able to make good vaccines. We can make some good vaccines, but other ones we aren't. But now people have been making all sorts of—you know, influenza, because there's some areas that are completely conserved of the influenza molecules, and then if you attack that with an antibody, that can provide protection, and now they've figured out a way to have the immune system just focus on that little part.

So it's a really exciting time with structural biology and molecular modeling and stuff that you can start coming up with vaccines Because I think that's where—you know, you really look at what benefits has immunology done so far, and vaccines has probably been the biggest contribution to human health.

Williams: I've been asking everyone this question. What does a scientist do for fun? What outside interests do you have?

Allen: Oh, I have lots of—I love sports. I like golfing. I just love to travel. So one of the benefits you get being in this business, you get to travel around. So with groups we've done and gone on photo safaris in Africa and gone to the scientific hajj going to Galapagos. So I think doing that, gardening, woodworking. I realize that science is so demanding, I need a break. And so the excuse I say is

making sawdust in the basement is much cheaper than a psychiatrist because I need something tangible to see, like I made something or I grew a plant and stuff like that. So I find that really helpful to me in getting away.

Williams: You mentioned that your family is in California? Is that—I heard you say—

Allen: Yes, I have a sister. Yes, they all lived out there and stuff.

Williams: Anything else you want to add to this today?

Allen: I think I'd like to still talk about a little bit the AAI staff. I think it's just an amazing group of people, that they really are dedicated in their—and I think it's obviously a good place to work, because the continuity. I look here, I haven't been in the building in like eight years, and most of the names look familiar. So I think Michele runs a great organization. Because putting on the national meeting is just so much work, and they put that on, but they keep the thing going, and they run an efficient organization. They do it. They're advocates for us. *The Journal* is incredibly done well. So I think that's what I'd really like, to give kudos to them, too, because I thinkklo