

**The American Association of Immunologists  
Oral History Project**

**Transcript**

Ronald N. Germain, M.D., Ph.D.  
January 21, 2016  
Bethesda, MD

Interview conducted by  
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Transcription: TechniType Transcripts

Transcript copyeditors: John S. Emrich, Ph.D., and Charles L. Richter, M.A.

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**Williams:** This is an interview with Dr. Ronald N. Germain for the American Association of Immunologists Oral History Project. Dr. Germain is the Chief of the Lymphocyte Biology Section and the Laboratory of Systems Biology at the National Institute of Allergy and Infectious Diseases, as well as the Associate Director of Systems Biology and Technology at the NIH [National Institutes of Health] Center for Human Immunology, Autoimmunity, and Inflammation. He was awarded the AAI Meritorious Career Award in 2015. We are in Dr. Germain's office on the National Institutes of Health campus in Bethesda, Maryland. Today is Thursday, January 21<sup>st</sup>, 2016, and I'm Brien Williams.

Thank you, Doctor, for doing this with us.

**Germain:** Thank you.

**Williams:** I'd like to start by asking you to fill in a little bit on your family background and your growing up.

**Germain:** Well, my parents and the family before them were not professionals. My father,

shops are not very good for immunological experiments, at least the type I was interested in doing.

So here my father's garage came into play. He had a customer who was a regular, who worked at a branch of [Memorial] Sloan Kettering [Cancer Center] in Rye, New York. And he said, "My son's trying to do this science project, but he can't get the right mice. Could you help him?" Because this person was the

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was actually at a time—this is 1965, '66—we're within a few years of the actual discovery by Jacques Miller of the putative function of the thymus in immunity. So I figure, why not go to the source? So I wrote Jacques Miller, as a high school student.

My letter followed him around the world, actually to NIH, where he was doing a sabbatical, and he answered me and he said, "This is how you do aseptic th



And she said, “Actually, yes.” [laughs]

So I decided to apply only to M.D.Ph.D. programs, to Rockefeller just as the Ph.D., and the one exception I made was Harvard Medical School. They didn't have a formal M.D.Ph.D. program. But I'll come back to that in a minute.

So I went through this process, and it was interesting along the way. My very first interview was at Cornell. And I've had the beard that I've had since high school, and you have to understand this is in the end of the sixties, the Vietnam protest generation, and there are hippies versus “serious people,” if you will. So I only had a goatee at the time. I was neatly groomed, wearing a ~~three~~ pinstripe suit, white shirt, red tie, Brogue shoes, ~~interview~~ with what I then thought was a somewhat ~~old~~ ~~he~~ ~~was~~ ~~actually~~ ~~only~~ ~~sixty~~ ~~something~~—nephrologist, and he said, “I don't know what to make of you. You look like a hippie and you talk like a scientist.” [laughs] But I was accepted there.

I then had my interview at Rockefeller, for which I showed up a day late, something that I cannot reconstruct to this day, but, surprisingly, the person who was programmed to interview me interviewed me anyway, and that person was Nobel Prize winner Gerry [Gerald M.] Edelman. He had selected me to interview, in part, I think, because of my background, but also I had done a master's as an undergraduate at Brown with one of his former trainees, [John J.] Marchalonis. So there was another connection.

So I went into the very famous office of Gerry Edelman and we had an interview, of which I remember nothing other than the parting remark. He looked at me, he said, “You will get in here, but you won't come here.” And given that I had grown up assuming the only place I would go was Rockefeller, I found that rather strange. But he turned out to be a very smart guy.

So the last part of this story is Harvard. So I was interviewing at NYU and being taken around by Chandler Stetson, the head of the Department of Pathology he said, “Is there anybody else you'd like to meet?” There were two immunologists that had been at NYU, turns out not at that moment. But as an undergraduate, I was reading papers, I'm a little bit out of date about what's happening in real time. I wanted to see Jonathan Uhr and Baruj Benacerraf. Uhr was in Texas, and what he told me was that Benacerraf was at NIH, but he was going to become the head of Pathology at Harvard the following year. Benacerraf was only here for two years.

So I wrote Benacerraf, like I had written Jacques Miller. I'm bashful about this. And I said since I knew there was no M.D.Ph.D. program, “Would you take medical students in your lab for research?” And he wrote me back saying that if he's convinced of their worth and dedication—those aren't exactly the words, but paraphrasing what he said

So I went through the interview process. That itself was quite interesting. If you don't mind my digressing, there's a very famous psychiatrist who was notorious for torturing interviewees at Harvard. He would do things like nail the window shut and then ask them to open the window, or say, "I'm expecting an important phone call," leave the room, call the phone number, and then see whether the person who was in the room picked up or not. He came back and he said, "I know, if they answered, he'd say, "Why are you answering my phone?" If they didn't answer, he'd come back and say, "Did I get a call?"

And they'd say, "Yes, the phone rang."

He said, "I told you I had an important call. Why didn't you answer it?" And it turns out that the whole point was that he selected students to interview that the school or the institution had concerns would not handle the stress of medical education.

I was programmed to be interviewed by the dean, who then had some late emergency meeting, and so I got summarily moved to an interview with this psychiatrist, having dreaded this forever. [laughs] But I wasn't one of his selectees, but he still had to interview me. So going back to that f4(s)-1(gn)10(oia)13(f)





**Williams:** Did you have pedagogical responsibilities too?



But early on, we were doing molecular dissection of structure function analysis, we then did cell biology, we then did biochemistry and signaling, and then we moved into imaging. So we've really changed the way we approach things. And just as I brought recombinant DNA and molecular work into what had been purely cellular work early on, because I said that's really where it's going to go, I've sort of done that in each of the steps. I sort of try to look and I say where is there an opportunity to really get an enormous amount of additional information that I can use for this integrative purpose.

But this integrative view also is where the systems part comes from. People call it the immune system. What does that really mean? It has a lot of working parts, and you can become an expert on all the details of one little part, or you can say, "I want to look a little bit more broadly and try to understand the principles that exist that allow the different parts to work together to give us either good host defense or that cause disease and to look at it that way." And that's what I've been interested in doing. And part of thinking that way is a realization that I came to many, many years ago, that there's a certain level of quantification that you really need to have. You have to go beyond sort of qualitative observations to understand certain types of behavior. Especially in a system like the immune system, where lymphocytes, in particular, can exponentially expand, small differences are going to turn into big differences at the end of the day, and those are hard to intuit. And if you also begin reading outside of your immediate field, you learn that you start putting negative and positive feedback pathways together in a signaling circuit, you get very nonlinear behavior, and those are not things that we can intuitively figure out how they're going to work when you perturb the system.













lower-level and high-level courses to help train lots of people who are not formal immunologists, who are moving into the field. And they've done a lot of legislative activity. I think those are all positives in the larger sense. So I think that's been very good for the field.

**Williams:** When you were told that you were going to receive the AAI Meritorious Award, which occurred in—

**Germain:** Last year.

**Williams:** Yeah, last year. What was your reaction?

**Germain:** A bit surprised. You know when you're nominated for things, so you know you're in the mix. These are not complete surprises in that regard. But the people that have been selected for that are really terrific folks. And it's a little bit strange because it's called a ~~career~~ award. When you look at who's receiving it, there's virtually no one who's in what you would really call ~~career~~, unless you do an extrapolation and decide that all of us are going to ~~work~~ longer than Michael Heidelberger at 102. But for any of these things, there are lots of meritorious people. There are very few of these; it's one a year. And there are a lot of immunologists, and there are a lot of terrific immunologists and scientists. So I was grateful, surprised that it actually happened and I was eager, also, because I don't, for a variety of reasons, have the opportunity to go to the AAI meeting every year, and so it ~~is~~ a chance to go and interact with people in that venue again, which was really very good. So it was a treat.

**Williams:** And what is the merit of your career? What is it sort of focused on or is it just very general?

**Germain:** No, I think it's usually, if you want to use mathematics, an integrative or an integral of what you've done over an arc of a career, whether it's in your reviews or whether it's in your primary scientific work, or whether it's in your training, even though it's not the mentoring award, but in the people you train. They sort of look at the whole package and say, "Has this really made a big contribution to the field where our primary focus is on the science?" So you have to have done substantive things over a very long period of time. The imaging would have been nice, but I suspect that they wouldn't look back and say I'd done anything for the previous twenty years well, maybe that wouldn't quite qualify here, but I think I have and I think all the other people who receive this are in like modes. Some are more of the focus type that I ~~love~~, where they've sort of been somewhat focal in a good way, and others maybe a little broader in what they've done, but there have been these continuous contributions.

**Williams:** I'm curious what do you tell your trainees about a future career in immunology. Are you encouraging it or cautioning them at all?



pretty good bill of health and the expectation that things looked pretty good, it took a while and many years to ~~now~~ for sure it was good, but once everything looked good at that point at the end of therapy, I had to say, "Okay, everything's pretty much shut down." Nobody new's going to come to ~~the~~ didn't bring anybody new in the lab, we hadn't written any papers, wasn't going to any meetings. And I said, "Okay, I had a pretty good career going. This has flattened everything out, if not gone down. I have to go and do something explicit to say I am around and I'm going to keep doing good stuff. I'm not ~~disappearing~~."

So I thought about it for a while. Alain Townsend had just published a very important piece of work that showed that peptide was a really important part of the structure of MHC Class I molecules. And I said, "Well, given what I know, Class I and Class II are pretty similar molecules." And there was this old observation from the Strominger lab about peculiar behavior of Class II molecules, where if you didn't boil them in SDS, they didn't come apart into the two chains. And I said, "That might be an assay for the stabilization by peptide."

There was a great technician in the lab who had been trained by one of my former fellows, Andrea Sant, to do metabolic pulse labeling immunoprecipitation experiments. So I said, "I want you to do these experiments where you have cells and you put a lot of protein in. I know it can be turned into peptide, they can present. And do this boiled/unboiled experiment, and I'll know in a week, when you develop those films, whether we're back."

She developed the films a week later, and we showed that they went from unstable to stable, and that increased in proportion when you put more antigen in they could load them with peptide. There's a lot of other work to be done, but basically I knew when we had the films that there was an important story there, and that was the step back in the lab.

Is that particular observation the most important one? No. But the lesson I tell people is, "You are responsible for your career. When you go out to start your own lab, don't just fill it up with, quote, 'hands' that you hope are going to do all the work for you, that are going to create the wonderful career you hope to have. You're the restrained person, it's your career, and you have to make it work. So that's your responsibility. That's what you have to do."

So just as I told you previously that I went into Benacerraf's lab to challenge myself to see whether I could make it, here there was another challenge where I had to be sure. Nobody was going to rescue my career for me. I had to do that. And that's a lesson that I learned and have known for a long time, and it's one that I keep trying to convey to my fellows, that it is really you. Yes, the best



I'd collected from around the world, just shots at meetings or people on the street, so they are colors and they have backgrounds and everything else, and make them look like that.

And I actually learned how to do that, and I have sort of published my own book of portraits, which look like they're posed, but they're someone in Old Jerusalem or they're someone on the street in Paris, or there is somebody at a meeting inside here at NIH with fluorescent lights and everything else, or the owner of the best rib place in St. Louis, but they all have been reworked to have these nice black backgrounds, all turned into black and whites with all the right kinds of balances. And that's turned out to be so I like looking at that book. I like going back and seeing what I've done with that, because I had to do extra work, not just capture the image. But there are others.

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