The American Association of Immunologists Oral History Project

Transcript

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Williams: This is an interview for t

Williams: So youcontinued your clinical activity.

Cooper: Yes.

Williams: But you were committed at this point to research, clearly.

Cooper: Yes.

Williams: So what part of this hotbed of activity, what piece of the pie did you concentrate on?

Cooper:

two compartments of the immune system. One depended on the thymus and featured by lymphocytes, most of them small lymphocytes. They were responsible for cell-mediated immunity because thymectomy and irradiation prevented development of skin graft rejection, graft-versus-host capability, delayed type hypersensitivity, whereas bursectomy and irradiation led to lack of plasma cells, germinal centers, and they were completely agammaglobulinemic made no antibodies. So that was the thymus-dependent and bursa-dependent populations of cells for cellular or humoral immunity respectively.

The ones without the thymus in that system of cells also didn't make antibodies normally, even though they had lots of germinal centers and plasma cells. So it suggested that they work together in some way. So those thymus-dependent, bursa-dependent, eventually those populations of cells were dubbed T and B cells. That was my early claim to fame.

Williams: You were the "T-B" man. [laughs]

Cooper: I was fortunate enough to be in the right place and work with the right people.

Williams: You conducted all this work while you were at Minnesota?

Cooper: That's correct.

Williams: So then what prompted your move back to Alabama?

Cooper: I needed to know if I could do other than run well on someone else's treadmill. And I wanted to develop a career. I considered for a while going and taking another apprenticeship to learn some molecular biology, which was just becoming possible about that time. This was in the sixties. I explored the possibility of working with people who were adopting a molecular approach to trying to understand cell differentiation in specialized cells like T cells, B cells, I cells, and so forth.

But my family and I, we had three kids by this time

marrow transplants with hematopoietic stem cells, and Good showed in a Wiskott-Aldrich patient I mentioned earlier, the first successful bone marrow transplant to restore a disease, to treat a disease satisfactorily.

Williams: So did you stay pretty much on this line of research while you were—

Cooper: Well, it also asked several questions that needed to be answered. Where was is our bursa equivalent? We don't have a bursa of Fabricius. If the T cells can't make immunoglobulins, what do they use to see antigens? Also, how do the T and B cells cooperate? So all these questions were simple, but it took years for people to answer them. One of the ones that we spent a lot of our time on was trying to find out what's the bursa equivalent in mammals, because we needed to know that in order to study the earliest features of the development of our B lineage of cells. I thought originally that it might be the tonsils. I thought it would be a follicular lymphoid organ, probably near the junction of the ectoderm and endoderm, and that seemed to be. I removed the tonsils of lots of baby rabbits. It made it hard for them to eat, but it didn't bother their development of their immunity and antibody production one whit.

Then we focused on intestinal lymphoid tissues like the appendix and the lymph tissues called Peyer's patches. In the experiments, Dan Peery, a surgeon in Good's group with whom I worked, we showed that we could take the appendix out as soon as the rabbits were born, but the Peyer's patches were more difficult. There were eight of them. The last one was at the ileocecal junction, and it required dissection of the intestine and anastomosing it to put it back together, and that was pretty complex surgery, particularly at the time of birth.

So we took the appendix out at birth, and then Dan took the Peyer's patches rabbits, about ninety-something of them, and then we irradiated them and waited for them to recover. We ended up with six surgically galtectomized gut-associated lymphoepitheal tissue removal rabbits versus irradiated controls, and indeed they had defects in antibody production and not of cellular immunity. They could reject gramx5o<</MCID niO10(y)20(pr)1i4(e)6(d)]ex5o<</MCID0(r)3(a)-d(bb

put it back into the uterus, and two weeks later we took those out, and B cells developed perfectly well. The idea was that if they were coming from these gut associated lymphoepithelial tissues, if you remove the source, you wouldn't have B cells, and that clearly wasn't the case.

The same week, John Owen and Martin Raff, with whom I was working at University College, John had devised a way to take fetal liver and little pieces of it and float it on a Millipore filter on media so that it got nourishment from below and atmospheric oxygen and the right amount of CO_2 from the top. So we found out exactly when B cells appeared in fetal liver, cultured the fetal liver much earlier, and then after a few days of culture, after a week, let's say, we looked again and B cells developed there. So it became obvious that they could be generated. Later on, John devised a way to grow little femurs, little long bones, and after they had grown [illegible]

occurred later. So we had then a much better, crude, but nonetheless, an outline of the early history of antibody-producing cells, and we knew where they were being produced, some of the features, and much, much more has been learned since then, of course.

Williams: Was similar activity going on elsewhere? You have referred to other labs that were doing similar work.

Cooper: There were two groups who, at the same time we were doing these fetal organ cultures, who were tracing the development of cells that began to express antibodies on their surface, or B cell, in bone marrow, one group in Switzerland and one in Australia. They discovered that the cells in those tissues but not others that made the expressed antibodies on their surface came from cells that did not. So there was a coherency of results, and so that helped to establish the principles.

Williams: So I'm a little confused. This was work you did mainly in England?

Cooper: On a sabbatical, yes.

Williams: That was a very productive year.

Cooper: It directed most everything my group, my colleagues and I did for the next decade. It was extraordinary. It gave me relief from doing both clinical work and laboratory work, and by the time I left, I was jumping back and forth so frequently that I'd become so paranoid that even I recognized that. I thought if I could just get away for a year, maybe I'll get my sanity back regardless of whether I find anything useful or not. [laughs]

Williams: You mean after that year because—

Cooper: Before that year, that was the condition I was in. So it worked out much better. Whether I got my sanity back or not, it was scientifically extremely productive. [laughs]

Williams: So you brought a lot of that interest back then to Alabama?

Cooper: Yes.

Williams: You made further discoveries over the next, you say decade, along those lines. I don't know if we have time to go into all of the details, but where some of the highlights of that work?

Cooper: We started trying to apply it to patients, and we could show that X-linked agammaglobulinemia was a very early arrest in differentiation. They got to a previous cell stage, but not beyond. That was sort of a bottleneck point in development of B-lineage cells in these young boys with X-linked

Williams: So then what motivated your move to Emory?

Cooper: It was time to move on by that time, for me and probably for University of Alabama. So for several years I was a Howard Hughes Medical Institute investigator, and I had decided to try and find a gracious exit to do some other things that I was interested in, and so I resigned from the Howard Hughes Institute. By resigning, you have to reapply for your job in Howard Hughes every five years, and so I chose not to reapply.

But in the meantime, I had gotten interested in and started to work with Jan Klein, who is a famous geneticist, immunologist, biologist, who was then head of the Max Planck Institute in Tübingen, Germany. He had discovered in lamprey, a jawless vertebrate, a gene that was orthologous to a gene that is a (I)13(w)2ctt is tebrost i

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advanced postdoctoral fellow, Zeev Pancer, to join my group. So Zeev and I decided if we could catch the cells responsible for these immune responses in the act, maybe then we could discover how they did it. So we made a library of complementary DNA from jus

developed to make monoclonal antibodies, human antibodies, and then use those for therapy. So it would be a discovery tool and not a therapeutic tool.

Williams: Leading to therapy.

Cooper: Yes.

Williams: Which is what we hope.

Cooper: That's going to take a while. [laughs]

Williams: It sounds like you're very patient.

Cooper: Persistent is perhaps a better word.

Williams: Yes, yes, yes. I was going to ask you about the hotbeds of immunological activity in this country, and the South, I guess, qualifies.

Cooper: The South is becoming more and more contributing, I would say, in all kinds of ways than before. I mean, the economics dynamics, the population changes, they've all changed the South, and so it's a totally different place than when I was a kid growing up with all the social constraints and economic constraints. That's a very different place at this point, so, yes, there are hotbeds throughout our country and elsewhere as well.

Williams: Remind me of why you decided to leave Howard Hughes.

Cooper: I thought it was time for me to—well, I had several reasons. I was assured of support to the age of seventy-three, and I thought, "That's probably long enough for me," and I had to make that decision eight years basically before. And who knows if I would wish to do research any more at that time, who knows if I would be capable of doing anything by that time, and moreover, if I were going to invest it, I would invest it in someone younger anyway.

Then it's stressful to reapply for your job, and it's up or down. Sr

Cooper: No. She's a teacher and she is specialized in teaching young children with learning, reading difficulties howto read. She does that now only on a volunteer basis.

Williams: How did you achieve a balance between professional responsibilities and interests and family concerns?

Cooper:

genetics and molecular biology revolution, it gets more and more complex. That's one of the reasons you see more and more research efforts that lead to publications involving twenty or thirty or more people, because no one can know everything. No one can amass enough patients to study a rare process or to see how a new therapy is working or not and so forth.

Williams: Besides travel, have there been other major distractions from your pursuing your work?

Cooper: Probably one of the most distractions that I've had was I've had grant application failures and all sorts of stumbling blocks along the way, as most people have, but probably the biggest stumbling or block was at one time I changed my job within the University of Alabama at Birmingham to get more space and a little equipment money. A technician who came with me from Minneapolis was killed in a car accident. I bought a house, and I'd moved around a lot, as you can see, before then, which meant I was stuck in one place. [laughs] I never had that kind of encumbrance before. And a few other things. And our child, Christopher, was born, so a lot of things happened that were more than I could handle well, and I was trying to get grants and get mne-10(10(g)6(et w 4.77 e.b14(gpl)-2(

Williams: How long did this take effect?

Cooper: It took me a year, a year and a half, to gradually get out of it, but for a while my affect was as flat as that tabletop, and in the evenings it's worse, of course, at night. I would have bouts of panic, but I could perform. I could give a lecture. I could even travel and give talks on work that we were doing. But I was afraid I'd get lost in the airport. [laughs]

Williams: Does your situation [illegible]

that everything was governed by the regions of the country and people who lived there in a way that was kind of hard to break into and to modify.

So that has changed, the geographic, and that's changed in a big part on the way that NIH has supported research throughout the country. That had to be done in a way that included the entire country or the politicians wouldn't have the sufficient votes to make it work. So that meant that you could get support, regardless of where you might be, if your ideas and your productivity and your plans were good enough. But all of those dynamics require participation, and they require participation in professional societies like AAI. And AAI has, in part, become more democratic for that reason and vice versa. So I think that's been a very important change.

So the quality of the meetings, which is one of the major occupations of the society, like this one that's going on here now in Boston, and it provides a place where young people can come and present their work and hear people who've already had more to say or whose research can provide information in a guiding way of how you're going to develop your career if you're starting out. I think all those things have changed in a very positive way.

Williams: Talk for a moment about what you see as the status of science in America today.

Cooper: Well, probably I'll just go directly to some of my soapbox issues. [laughs] I think, in general, science in our country is at a very high level, and it's something that all of us should be proud of. It's hard to feel too negative about aspects of American science when you look around the world and see, for example, how well

Academy of Sciences, Institute of Medicine, and so forth, if those societies could support more, and most people and most scientists and most researchers would agree, a majority of them, with the principles that I just described poorly.

Williams: What do you tell or what would you like to tell trainees who are considering a career in immunology today?

Cooper: First of all, not everyone should go into a science career, but there are reasons to go into science training just for educational purposes, even if you're not planning to do research in the long run. If you're planning to make it a career, a research career, and one that will depend on your success in getting grant support to do the work that you wish to follow, you should only do that if you are really interested in the research area that you're trying to learn about. So I guess the first thing is to pick something that you're really interested in, because you're not going to learn very much or very rapidly if you're not burnt up with the interest. There has to be some passion, I think.

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puzzle, of course, but it's a particularly good starting point to try to understand our relationships with all the other living organisms and the biosphere in general.

Williams: Anything we've left unsaid today?

Cooper: I hope so. [laughter]

Williams: One reason I ask that question is because I alerted you to what we were going to be doing today, and you may have given some thought to what you wanted to say, and I just wanted to make sure that you had that opportunity.

Cooper: Yes. But I didn't have a chance to prepare much, I must admit. I've been moving around too much.

Williams: What we're creating here is sort of part of the historical record, and I just want to make sure we haven't left something that is important to you unsaid because I haven't asked you about it.

Cooper: I probably have, but I wouldn't be able to think of it.

Williams: You'll think of it tonight. [laughter]

Cooper: That's right.

Williams: Okay. Thank you.

Cooper: And how badly I misstated it. [laughter]

Williams: Thank you very much, Dr. Cooper

Cooper: Thank you very much.

[End of interview]