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Oral History Project

Transcript

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Williams: This is an interview for the American Association of Immunologists for their Centennial Oral History Project with Dr. Max D. Cooper, who's the Georgia Research Alliance Eminent Scholar and professor of pathology and laboratory medicine at the Emory University Vaccine Center in the School of Medicine in Atlanta, Georgia, and a former president of the AAI. We are the 99th annual [ed. 96th annual] meeting of the AAI at the Sheraton Boston Hotel in Boston, Mass[achusetts]. Today is Sunday, May 6, 2012, and I am Brien Williams.

Dr. Cooper, let me ask you to start out by talking a little bit about your family and your own early background.

Cooper: I grew up in Mississippi. My parents were educators. My mother was a teacher. My father was a mathematician and the superintendent of a twelve-year school in a little town called Bentonia, which was about 500 on weekdays and 2,000 on Saturdays during cotton-ginning time, because we had three cotton gins in Bentonia. So I grew up in a rural background with plenty of room to roam, time to ponder the stars, and free time on my hands to explore all of my surrounding environment.

Williams: You went to local public schools?

Cooper: I, of course, went to the school. I lived on the school campus, and so I was always at school. [laughs]

Williams: So was that through high school?

Cooper: Yes.

Williams: So then what determined where you would go to school after high school?

Cooper: Well, I started on a half football scholarship to a junior college, and I was the slowest man on the team, including the coaches. I was third or fourth best quarterback, and it became pretty obvious that I was not going to make fame and fortune as an athlete. I did better in baseball, but I moved on after that to University of Mississippi.

Williams: At what point did you begin to think about studying in a career in biology and so forth?

Cooper: I had indicated that I wished to become a doctor when I was very young. I didn't know very many occupations, maybe ten or so, and the local physician was the most well-educated person and highly respected person, and he was probably one of the most needed people in town, and I thought maybe that would be a good thing for me to do. Then I learned that it was going to take a lot of study and a lot of years to become a physician and a lot of effort to be a good one, so my interest flagged a bit. My father had wanted to be a physician and grew up in a large farm

family and felt that it was beyond his family's means, so he did not take that career. So he encouraged me.

Williams: So from the start, you were majoring in what at Mississippi?

Cooper: I was a premed student. My brother, who was older than me, was killed in a car accident while he was home on leave in the Marines, and he had indicated me as his beneficiary of his insurance policy, so my excuse was that it would be too expensive to go to medical school, and it got taken away. My father told me I had to do what both of us would have done, so I started in premed and got into medical school after two and a half years in the summer and finished in a fairly short time after that. I wasn't the greatest student, so it was better that I didn't take much longer.

Williams: Do you have other siblings?

Cooper: No.

Williams: So you got your M.D. at the University of Mississippi and then where?

Cooper: I transferred to Tulane [University]. At the time, University of Mississippi was a two-year medical school. They were just converting to become a four-year school. So we were given the option of going elsewhere or staying, and I moved on to Tulane, where I graduated from medical school.

Williams: What kind of experience was that?

Cooper: Medical school for me was a delight. I really enjoyed it. There was so much to learn. It was obvious that it would be useful if I could learn some of the things that we were being taught, and so I began to decide what I would do after that, and I went into pediatrics.

Williams: Then did you practice?

Cooper: Not in private practice, but, yes, I've been a practicing physician all of my career, except for the last six or eight years since I only do research.

Williams: So after Tulane, then where did you go?

Cooper: I went first to Saginaw, Michigan, for an internship and then came back for the residency program at Tulane, a department that was headed by Dr. Ralph Platou, who was a strong mentor of mine. He believed in me at a time when I was beginning to lose faith in myself, and expressed the idea that I should go into academic medicine. He helped me to go to London, a hospital for sick children, for a year. By this time, Rosalie, my wife, and I had gotten married, so we moved to London shortly after our marriage. After a year there, we moved back to the

U.S., and I went into a pediatric allergy and immunology program at the University of California in San Francisco [UCSF].

Williams: Were you thinking that could be a long-term assignment or not?

Cooper: I wasn't sure whether I wanted to go into practice of medicine, but I had lots of other interests and I was looking for something that would give me time to do other things, and that seemed to be a possibility, or if I went into academic medicine I could develop that theme. I'd become interested in immunology, particularly because of taking care of children with familial predilection for infections. Immunodeficiency diseases were just beginning to be described at that time.

Williams: So how long were you at UCSF?

Cooper: For a year, and then back to Tulane on the faculty with my mentor, Dr. Platou. Then it became clear that if I was ever going to contribute anything original, I needed to start all over again. So I applied to several famous immunologists and ended up going to Minneapolis to work with Robert Good at the University of Minnesota.

Williams: So you were briefly back at Tulane and then moved north.

Cooper: Yes.

Williams: What was the Minnesota program like?

Cooper: It was an exciting group who worked with Bob Good. He was a charismatic figure, a leader in the field of immunology. He and his colleagues had just discovered the role of the thymus in the development of the immune system along with others, particularly Jacques Miller in England at that time, who also discovered the importance of the thymus in development of the immune system.

Good's group were diverse and a group of very active, intelligent, energetic young people who were working with trying to understand transplantation limitations and transplanting organs, tissues, and autoimmune diseases and development of the immune system, immunodeficiency diseases, which was one of the reasons I went there. Good was also interested in evolution of the immune system, phylogeny of the immune system. So there were lots of things going on in terms of animal experimentation, inherited diseases as experiments of nature, and so it was a perfect place for me to land and try to learn enough to begin to be able to do something original on my own.

Williams: Still within pediatrics or not?

Cooper: Yes, we saw patients as well, both children and adults.

Williams: So you continued 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: I ended up working—well, I did experiments with lots of different models, guinea pigs, rabbits, chickens, a range, in addition to the clinical work that we were doing. But the work that I did that was most telling was in the chicken. So in the chicken they have a thymus as well, the function of which hadn't been well elucidated then. They have a hindgut lymphoid organ called the bursa of Fabricius. Bruce Glick, as a graduate student or a postdoctoral fellow at Ohio State University, had done experiments with chickens. He thought the bursa of Fabricius might be important in sexual development of chickens, and so he removed it and it didn't affect their behavior. But a colleague asked to borrow some of his chickens to use for demonstration of antibody production and came back some weeks later and said that, "Bruce, you spoiled my experiment. A lot of those chickens didn't make antibodies."

So Bruce twigged to the fact that it was probably as a consequence of his bursectomy, and they did experiments together to confirm that. They sent their paper in to *Science*, and they were told that the data looked convincing but the paper was not of general interest. So they published their data in *Poultry Science*. Not many immunologists were reading *Poultry Science* in those days, but a few individuals took note, and my group was one of them and an Australian group. A group in Wisconsin showed that you could treat with a male hormone, testosterone, and that would prevent normal bursal development and gave the antibody deficiency as a consequence as well.

Noel Warner and a colleague of his in Australia noticed this. They treated chicks with testosterone, chick embryos, and they noted that some of them not only had antibody deficiency, but a few didn't reject skin grafts well, and in those, there was some damage to the thymus as well, and so they proposed that these two organs had different functions. But their interpretation of the functions didn't fit very well with mammalian data, and so I was interested.

Actually, I did experiments to try and test that idea by bursectomy, and we could easily reproduce the bursectomy results but not the thymectomy results. At the time, most people thought there was a single lineage of lymphocytes that were dependent on the thymus and that those lymphocytes could become antibody-

producing plasma cells. In fact, Gowans, who had traced the circulation of lymphocytes in the body, had shown by labeling lymphocytes that some of them could mature into antibody-secreting plasma cells. So the thymus was thought to foster the development of lymphocytes in the body, and some of them matured to become antibody-producing cells.

There are two types of immunity had been shown at that time, and particularly by Chase and Landsteiner, who showed that, as many people before them, you could transform humoral immunity by transferring serum or plasma from an immune person or an individual to another, but cellular immunity, like tuberculin skin reactions or poison ivy reactions, could only be transferred if you transferred lymphocytes. So there was this debate about how cellular and humoral immunity differed from each other, and so we did experiments where we went back to the chicken model because of observations of patients with a syndrome called Wiskott-Aldrich Syndrome. These were boys. It was an excellent pattern of inheritance. As they became older, they become not only susceptible to chronic ear infections and eczema and low platelets, which were the three elements that led to the description of this syndrome by Wiskott and then by Aldrich, they became extremely vulnerable to viral infections. A simple fever blister of the lips, Herpes simplex infection, they couldn't contain it. It spread and it was lethal in them.

So going and looking at their histories, their charts, and their tissues that were obtained by postmortem examination, I found that they were very deficient in lymphocytes but they had oodles of plasma cells and high levels of the immunoglobulin products of the plasma cells, the antibodies. That didn't fit very well with the single lineage idea that was a prevalent view at that time.

We went back to the chicken, and by that time we knew that different animals matured their immune systems, or their immune systems had variable degrees of maturity at the time of birth, so a mouse would have a very immature immune system at birth, some strains more than others. Rabbits had more mature immune systems at birth, and you could not take their thymus out any longer and show a drastic effect, for example, whereas you could in mice.

So it seemed likely that to really see the roles of the thymus and the bursa respectively, one would need to go back and remove those organs earlier in embryonic development, which I wasn't able to do. And as an alternative, it seemed likely that if you could destroy the immune cells that had developed before hatching, then you could more clearly determine the roles of the thymus and bursa by removing them.

So I did the experiments where I removed either the thymus or the bursa or both or neither, and then the next day took them and irradiated, gave them a near-lethal dose of irradiation and then let them recover and then looked to see what immune capabilities they had. Those experiments made it absolutely clear that there were

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 south?

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 and we'd sort of run out of fiscal and emotional reserve, and I realized I was going to have to hopefully keep learning the rest of my life, and I needed to do that on the job, so to speak. So I began to look at possibilities, and fortunately had several, and ended up going to University of Alabama at Birmingham, which had a large Pediatrics Department and could allow people to do clinical and research.

Williams: So as you took your position there, your aspiration was to continue the work you were doing in Minnesota?

Cooper: As soon as we developed this model, it was clear that you could divide the immune deficiency diseases into either T cell defects or B cell defects, and it was clear that there had to be some communication between them. It was also clear

that you could divide malignancies, that malignancies of the lymphoid system were either affecting the T lineage of cells or the B lineage of cells.

In fact, one of the key people whom I worked with in Bob Good's group was Ray Peterson, and Ray Peterson had been doing experiments with a scientist, Ben Burmester at the U.S. Regional Poultry Laboratory at Michigan State.

At the time it was known that you could prevent development of all the different types of experimentally induced lymphoid malignancies in mice by removing the thymus very early in life. In fact, in trying to understand how the thymus—its role in development of the lymphocytic malignancies, Jacques Miller noticed that if you took the thymus out at birth, then the mice became scruffy and runted and susceptible to infections and died. That gave him a clue about the role of the thymus in the immune system development.

At any rate, if you induced lymphocytic malignancies in mice with ionizing irradiation or chemical carcinogens or with certain hormones, you could prevent all of them by early thymectomy. So Peterson and Burmester were working with a virus-inducted model of lymphoid malignancies in chickens called avian lymphoid leukosis. If you infected the mother or you infected the newly hatched chicks, six or seven months, six to nine months later they would develop a generalized lymphocytic malignancy. So they removed either the thymus or the bursa, and the thymus had no effect, and the bursa prevented it completely.

Later I worked with Peterson when he showed that you could remove the bursa at any time up until six months and still prevent the malignancy. So that led us to know that there would be—and we could see with this model of two lineages that certain malignancies like myeloma or plasma cell malignancy must be of a B lineage, follicular lymphomas or malignancies of germinal centers, which was part of the B lineage. Some kids who had leukemias also had prominent involvement of the thymus, that seemed likely to be T lineage.

So we began trying to divide lymphoid malignancies in one or the other. So those were some of the immediate things that changed the way we looked at immunodeficiency diseases and lymphoid malignancies. Also we knew from other people's work that the cells that were developing in the thymus came from bone marrow, from irradiation that people had shown hematopoietic stem cells could give rise to multiple, all the blood cell types, and particularly in the thymus. Ford and Micklem had shown that in England, and it seemed likely that that would be the case from the bursa as well, that those stem cells for the B lineage would come from there.

So it let us draw up a crude model that gave us sort of a map that could be used to try, as you defined immunodeficiency diseases as to whether they were thymus-dependent T cells or the B lineage of cells or both, how to begin to repair with transplants of thymus if the thymus was missing. If both were missing, bone

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. One was, where 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 lymphoid tissues called Peyer's patches, and so we did experiments. Dan Perry, 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 these 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 re-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 out of 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 grafts perfectly well. So that fitted our hypothesis.

So for the next ten years, both Dan and I—I moved to Alabama and he stayed there for a while and then went back to Canada, where he was from. We both did experiments that were consistent with that idea, but didn't prove it.

On my first sabbatical in London, I developed a collaboration with people at Oxford who did fetal physiology in lambs, and I worked with people at University College who thought that the gut wasn't the place where B cells were generated, but the hematopoietic tissues were. Early on, hematopoiesis occurs mainly in the liver of fetuses. So in the lamb, we took out—they were twins. We would remove one twin, make sure there were no B cells. This was at about 60 days, 60, 65 days of gestation out of 155. And the other one, we moved the entire intestine,

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 gotten stem cells, they could generate B cells in those bone marrow hematopoietic sites as well.

In the meantime, my colleagues and I had done experiments showing that you could block B cell development if you ligated their B cell surface receptors early in development. If you did that with antibodies against the IgM class, you could block not only cells that made IgM type of antibodies, but also IgG and IgA, other forms of antibodies as well. So that led us to propose a switch hypothesis where cells started out making IgM and later switched to make to IgG and IgA as well.

So back to the fetal cultures. We did that in those with the antibodies to IgM heavy chains, and it blocked development of B cells. But in looking at what remained, John Owen said, "There's still lymphocytes here." Seemed unlikely to me. Lymphocytes are pretty nondescript-looking cells characterized mainly by mostly nucleus and very little cytoplasm, little round cells when you take them out and culture them.

But Marty Raff said, "Well, maybe if we permeabilize these cells and then look to see, maybe they're making immunoglobulin or antibodies inside." I thought it was a good control, but I didn't think it was going to show us anything. So in the fetal liver cultures where we had treated with antibodies to IgM heavy chains and then wiped out the development of the cells that expressed surface antibody receptors, we found that they still had cells that had the immunoglobulin inside them. So that let us identify precursors of the B cells, and we went on to show that that the case in rabbits and humans as well, and that began to allow us to map out earlier stages.

Colleagues of mine said, "Well, they really are not making total IgM antibodies. They're making heavy chains and not light chains." John Kearney and Peter Burrows did experiments that convincingly showed that. At about that time, immunoglobulin genes had just been discovered by Susumo Tonegawa and then others. So my colleagues worked with others to show that the rearrangements and expression of the heavy-chain genes occurred before the light-chain genes, which

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 confluency 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

agammaglobulinemia, who didn't make antibodies. The first immunodeficiency disease to be described by Ogden Bruton, in a boy who had recurrent infections and whom he showed did not make gammaglobulin, gammaglobulin fraction of plasma proteins had been shown to contain antibodies, and he replaced them. He gave gammaglobulin crude preparations to his patient, and he did it at monthly intervals, and the boy was freed of these recurring infections.

So others had shown that these boys didn't have germinal centers or plasma cells, and so the defect turned out, once we knew where they were being formed, to be at a very early stage, a pre-B cell level or thereabouts. Whereas other people who had a late-onset form of agammaglobulinemia had B cells, but they were arrested in their terminal differentiation and so on. So it was possible to begin, at least at a cellular stage, to define different points where the genetic defects were impairing development of antibody-producing cells.

So we spent a lot of time on that, and we spent a lot of time trying to—we had gone back and looked at the chicken model. I mentioned to you that if you give this leukemia virus early in life, six to eight months later they develop this lymphoid malignancy. You could prevent it by bursectomy, removing the bursa anytime up until around six months.

So we went back and did examine chickens and their tissues every month during that time, and we found that the reason for that is that there are these follicles I mentioned of lymphocytes in the bursa, which we thought was going to be the case in the appendix and Peyer's patches, an equivalent. In a way, it is, actually. But we could see involvement of one or two of the 10,000 follicles in these bursas as early as one month, and those grew, but slowly, but didn't spread elsewhere. So that meant or suggested that there had to be more than just the virus-induced change in the genome there, but other genetic events that were required over that six-month interval to make them predisposed to migrate elsewhere and grow in a malignant fashion.

So we began trying to look at B cell malignancy from the same standpoint. We knew where they were being formed. We could identify the precursor stage. We could identify the B cell stage and so on. We started looking at different types of lymphoid malignancies. For example, children with an acute lymphocytic leukemia, which was fatal at that time—now it's treatable—we could show that those were of B cell origin and they were pre-B cells or pro-B cells. They staged just before expressing heavy chains in their cytoplasm. We spent a lot of time trying to use this sort of map of the development of the immune system to explore immunodeficiency diseases, lymphoid malignancies, and so on. So that's what we were mainly occupied with.

Williams: During the period of time that you were in Alabama?

Cooper: Yes.

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 transcription factor. It regulates expression of genes that are important for hematopoiesis, blood cell formation, and particularly for B lymphopoiesis. He had indicated that it was in cells that looked like lymphocytes in hematopoietic tissue. That raised the idea that lamprey had lymphocytes and, indeed, lampreys had been shown some time ago to be able to respond to immunization by making some sort of blood protein that could clump if you immunized with human O-positive erythrocytes. They could make proteins that could specifically clump or aggregate O-positive human erythrocyte and they could reject skin grafts.

So we, Jan and I, decided to go back, but no one had been able to show how that worked. So Jan and I decided to go back and look for the roots of our adaptive immune system, the one that we share with all jawed vertebrates, every jawed vertebrate, all the way back to cartilaginous fish like sharks, skates, and rays have a thymus and T cells, cell-mediated immunity, have B cells, make antibodies, humoral immunity. They have the genes, the VDJ genes that are recombined to make T cell receptors or B cell receptors. They have the enzymes that initiate that recombination. They have histocompatibility genes, major histocompatibility genes, class I and class II, that T cells need to see peptides presented by these to recognize and respond.

So we went back to try and trace the roots of that adaptive immune system, and we couldn't find any of those cardinal genes. We isolated cells that looked like lymphocytes from hematopoietic tissue or hematopoietic tissues, and we did an analysis scanning of transcripts, messenger RNAs that they were making, by making a complementary DNA library and then getting high-throughput sequencing and then annotating our catch. We found no T cell receptor genes, no B cell receptor genes for antibodies, no MHC class I or class II genes, no recombinase activating genes I and II. We thought, "Well, it's true. This is not really real."

But I knew some of those studies and knew that there had to be some explanation for those. So we went back, and by this time a molecular biologist came as an

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 just cells, lymphocytes that were stimulated to start dividing, get bigger and to undergo proliferation, and then started sequencing that and then looking to see what we would find. We still didn't find the cardinal genes of our adaptive immune system, but we saw a lot of leucine-rich repeat protein sequences, which didn't seem so interesting until we noticed that every one had a different sequence. None of them were the same.

We did more from different lampreys and different ages, and they were all different. So finally we realized that this would be the kind of variability that you would need to make a huge repertoire of receptor-bearing lymphocytes that could recognize any specific potential antigen and respond to it and amplify and to have a protective secondary immune response, to have memory.

So we began to look into that, and we combined with other people, in particular Chris Amemiya from Seattle, Washington, who had a genomic lamprey library that he had made using lamprey sperm and had this library in pieces. So we fished through with probes for the receptors that we now call VLRs, for variable lymphocyte receptors, looking to see if there were lots of genes encoding them or not.

It turned out we could only find one in our first go-round, and it was very incomplete. It had the start region and ends of the variable region, but not the middle. But then when we got sequencing of the genome in that region, we found in those flanking sequences coding sequences for these cassettes of leucine-rich repeat sequences, so of a kind that were missing from the mature ones that we had been sequencing before. Then we could show that that assembly of those mature VLR genes only occurred in lymphocytes and not in other types of cells.

We started working with computational biologists, Igor Rogozin and Laks Iyer in Washington at the NCBI, the National Center for Bioinformatics. We gave them hundreds of these variable sequences, and Igor and his colleagues could estimate that they were put together in a very random fashion, just as our T and B cell receptor genes, and that the potential combinations that they could make would be a repertoire of greater than ten-to-the-14^{th} or more, the same kind of diversity as our T cell and B cell repertoire.

So we've done other studies since then, and particularly since we moved to Emory in Atlanta, that show that—well, first of all, we worked with a Japanese investigator, Kasahara, who had a large cDNA library from hagfish. There are only two jawless vertebrates which are a sister group with the jawed vertebrates, and both of them have the same system of receptors. It turned out that they also construct their immune system as we do. They have a thymus equivalent in their gill region they generate. That's one lineage of cells.

So, three of these genes: VLR A, B, and C. B is the one that antibody-producing cells made, and they differentiate into cells that are like our plasma cells, and they come from hematopoietic tissues, it looks like. The VLR A and B, like our T cells of gamma delta or alpha beta, are generated. Those genes are assembled in the gill region and they are seeded elsewhere.

So it's the same basic kind of construction, but a totally different solution on how to make receptors, diverse receptors, and we're still trying to figure out. So each time the answers have come totally different from my predictions, which is what makes doing research so much fun. You can't sit at your desk and figure out nature. It's too complex.

Williams: So this brings up pretty much up to date.

Cooper: That's it.

Williams: So what are you doing right now?

Cooper: We're still trying to understand that and we think that these—in fact, we have good evidence that these lamprey antibodies, which are structurally different kinds of antibodies, have certain advantages. They resist wide swings in acid or base changes in pH. They withstand heat nicely without losing their binding. They're exquisitely specific, maybe even more specific than our antibodies on average. Since we last shared a common ancestor about 500 million years ago, they are not subjected to the same tolerance constraints of the kinds of antibodies that they can make.

So we think we can make use of these lamprey antibodies for diagnostic purposes and we can show that for anthrax, dengue virus, etc. We're trying to make them now against HIV. We think they can be used to recognize tumor antigens that our immune system doesn't see, that allows discrimination of tumor cells in a way that mouse and human monoclonal antibodies can't. So we can make recombinant monoclonal antibodies of this lamprey type, screen them in high-throughput screening systems, and we found that we can indeed make antibodies that have target antigens that have never been seen before in current array of classical Ig-based antibodies. So we're working on that as well.

Williams: You see this primarily as a diagnostic tool?

Cooper: And a discovery tool. So once we discover an antigen that's an identifying marker for, let's say, mature plasma cells, and we have such lamprey antibody, and no one has ever made a human plasma cell-specific antibody before, so we are now trying to find the target antigen on our plasma cells. Once we do that, we think we can break tolerance and make an antibody or use various ways that exploit the systems of large libraries of variable regions that people have

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. So all of those things combined to make me think, and I had a desire to spend time doing other things as well. So all of those were good reasons, I thought. I thought my plan was working well, things were going well, but then when the time came, I was working with one of the best groups of young people with whom I've—and I've been lucky all along, and as you can probably tell from what I'm relating, it wasn't all done by me by any stretch. My competitive nature had been stirred up, and I couldn't think of anything I'd rather be doing, so I just continued.

Williams: Where have you gotten funding since the Howard Hughes?

Cooper: Well, I had NIH [National Institutes of Health] grants, investigator-initiated, so called RO1 grants. I had two of them. Since I was fiscally retired, I didn't need to bleed those grants for my salary, and so I could do more with two grants. I had university support of an administrator. NIH has been good to me over the years, and it is the bedrock of scientific support in this country, of course. Then when I moved to Emory, the Georgia Research Alliance helped support my move, as did my department that I moved to, so all those things have allowed us to keep moving.

Williams: You mentioned just a moment ago other interests were competing for your time. Like what?

Cooper: So far, I'm physically fit still. I like to hike; I like to fish; I like to cook. My wife is a great cook, and I've been an apprentice for quite some time now, and except for making serious errors now and then, which she bails me out, I can do reasonably well. I like to read. Rosalie and I have four children and nine grandchildren. Twenty years ago I bought an old house in Brittany, France, northwestern France, so I thought maybe I could spend more than a month there each year if I retired. So those are kinds of things, and family and other interests.

Williams: Have any of that progeny following your career line?

Cooper: I have one clone. [laughs] Michael, our middle son—our daughter Melinda is the oldest of the lot—is a neurologist and developmental neurobiologist, and he is at Vanderbilt University. The two older ones, Melinda and Beau, are both in law, and the youngest one is an architect.

Williams: You mentioned a moment ago that you felt like you were really lucky. So talk just a little bit more about that.

Cooper: You know, I've been extremely lucky, in particular lucky in having good mentors and having good colleagues and people whom I've worked with at all levels. So I've learned a lot from them. I've been supported by them. Probably my biggest luck was marrying Rosalie Lazzara years ago.

I read an obituary a few weeks ago about a French Resistance fighter who, along with his wife, had been deeply involved in the Resistance during the Second World War. It was a really catching story. But he ended up, he was quoted as saying that his wife was perhaps the most important decision he had made. He said, "You know, there are only about three or four important decisions in life. All the rest are luck." And I think he's pretty close to right. [laughs]

Williams: Is your wife of scientific bent?

Cooper: No. She's a teacher and she is specialized in teaching young children with learning, reading difficulties how to 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: Probably haven't very well. In leading a group—and we've been reasonably successful—it ends up that I travel a lot, which I enjoy. I grew up reading a lot as a kid and reading about far places that I was curious to know about and to experience. That's been another fantastic aspect of my career. And that's a two-edged sword. It gets you out of everybody's hair now and then, and that can be helpful at times, but it also makes it more difficult to maintain relationships with your family, with the people whom you are working with. So it's not the easiest balance to do well, and I probably—well, I know I've fallen down a lot in keeping just the right balance.

I traveled probably more because I led this schizophrenogenic existence of doing patient care work and research. Fortunately, what I was doing in both camps related, and sometimes beautifully so, other times not so beautifully. But it means that you are constantly going in two different camps or different spectrum of meetings and things, and that keeps you on the run more, I think, than if you stick to one thing and don't split your brain and try to do more than you can do well.

Williams: Would it be right to say that what you're traveling for with the clinicians is to explain what you're doing on your other schizophrenic half or not?

Cooper: And to learn from them, yes. It's hard to keep on the edge of any field unless you're learning constantly, and you'd like to, just as in your own work do that with the people who can teach you the most, and that's the essential for any occupation, I think, and certainly research. Once you stop learning, you're dead.

Williams: So I'm curious. What would be examples of things that you have learned from the clinicians?

Cooper: Most things, a lot of things that I've learned, I've learned from patient-related activities, because you can tell from this longwinded story I have been telling that I didn't start out with a basic science background, and that's a significant deficit if you're trying to do research. But what I had was a knowledge of human development, human pathophysiology, and, as a pediatrician, development biology, and so that's been sort of my base to build on as I was trying to learn more basic principles.

Information in any field, whether it's clinical, medical, or pure science, is constantly changing. The technologies are changing. It's almost impossible to keep up with everything, and as that process has been speeded up by molecular

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'd never had that kind of encumbrance before. And a few other things. And our last 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 my research program going.

I went into a clinical depression, and depression is really a difficult thing to deal with. It's actually not surprising that it has a high mortality rate. I'd read a lot of psychiatry and knew how primitive the information was in terms of understanding the physiology of the central nervous system, to have no faith in thinking that I would get any help from psychiatrists, and I felt I might even get some treatment from some pharmacological agent that would plunge me into worse situation. It wasn't the smartest way.

At any rate, to boil it down, I couldn't think of a smart way out of it other than just kind of bull along and hope that I would see light at the end of the tunnel at some point. Gradually it did, and I think that's the history. It's not uncommon for people, particularly in stressful occupations and positions, to have clinical depression. Many of them, although the mortality rate can be high or is high, it's not permanent for many of them. It's a transient thing. Why that is, I don't think anyone knows. It could be related to an undiagnosed infection or some other cause that we don't currently understand. But fortunately for me, with a lot of support from my family, even though I couldn't think of a smart solution, it gradually wore off. So that's probably the biggest thing.

If I'd been more clever and could have found an understanding psychiatrist who had experience at least with the historical outcome of those kinds of things, it would have been helpful, but I don't think my logic was totally wrong in avoiding that. Plus I was afraid that if the university realizes that I'm having central nervous system problems here, I could lose my job. So you're afraid to even acknowledge that you've got problems.

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 say anything special about the relationship between a researcher and a technician, or was it just the fact that this—

Cooper: It was a special relationship because she had become a friend of our family, she'd babysat with our kids, who liked her very much also, and so she wasn't a member of our family but she was close. She was young and she had just met a happy relationship, and they were driving to New Orleans on a weekend. So it was not a happy time.

Williams: Let's talk about what hopefully was a happy time, and that has been your association with the AAI over the years. You joined, I believe, in 1966, so you've had a long period there. What have you seen as the changes in the organization, if any?

Cooper: Well, those changes have been happy, too, mostly, I would say. AAI has grown in membership, influence. Early on, AAI was a different kind of society. Its membership was more restricted, and membership was jealously or zealously guarded to keep people who were not particularly deserving out, and that changed.

One of the most dramatic times of change was a president, someone of an earlier generation of me, Dan [H.] Campbell. He was at Caltech [California Institute of Technology], and he was an interesting man. He was a very disciplined biochemist-based research and immunology. He wrote textbooks. But his idea was that professional societies, and the AAI in particular, shouldn't spend their time working to keep people out; they should be working to bring people in. He said, "You can't have influence on people by shutting the door and keeping them outside. You can only influence them by bringing them in." He was a strong character and had a strong ego and had a nice view of life, had a little bit of a reddish nose as if he was enjoying life outside of research, maybe to its fullest. [laughs]

That changed the society, and gradually we began to be a society that was working to be more inclusive. I think that was a huge step forward. Also, as in many societies, you touched on the slowness in development of the southern part of the U.S, and so education has been strongest in the northeastern part of the country and then the West Coast and to some extent in the Midwest, but large areas of the country were slow to develop, and when they did develop, they found

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. So 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: What about the role of women?

Cooper: That, too, has changed drastically, and our current president is a woman, Leslie [J. Berg]. I just saw her in the hallway.

But that's been slow, and it will take more time, just as in medicine, where now medical school classes are about fifty-fifty or maybe even more females than males. I mean, when I started to school in the fifties, there was one female in my class when I started medical school. There's been a huge change in that way.

But getting back to immunology and American Association of Immunologists, there are now more and more professors who are females, but there are not enough. The proportion of male to female becomes greater and greater the higher the level. So that's a continuing aspect of the puzzle that needs addressing.

Williams: You were president in '88-'89, I believe.

Cooper: I believe that's right.

Williams: Was there any particular issues that you wanted to promote as president?

Cooper: No. The ones I think that I just mentioned, and also I wanted to be sure that the society and the meetings were fun. The year that I was president, actually, the meeting was in New Orleans, which was nice coincidence.

Williams: Would you start that statement again? The year that you were president—

Cooper: The year I was president, the AAI meeting was in New Orleans, fortuitously, and that was a nice coincidence. So we tried to make the meeting not only intellectually challenging and information-wise rich, but also fun. We had Charlemagne Neville and then her group come to play at the AAI party that year, and it was a great party. I don't know if you know that famous family, Neville brothers. Charlemagne is the sister of the Neville brothers and a talented musician and singer in her own right. So the atmosphere of New Orleans and an association of fun in our activity.

Williams: Any other vivid memories of AAI experiences or meetings or anything come to mind?

Cooper: I missed very few and I liked them all. The first meeting that I went to was probably the most vivid. I was so awed by how many people there and that all of them were smarter than I was and had something to contribute, and what a competitive endeavor it was, and why in the world I would be there starting over at the age thirty in such a competitive, high level of research activity that I would have such a little chance of succeeding in, it was a daunting experience for me.

Gradually I realized that my first assessment was correct, but you also realize that a lot of people are feeling the same way you're feeling and that what they learn, they learned in a cumulative way. If you keep at it, you can gradually accrue a fair amount of information if you're focused and steady and persistent and receptive to learning. But that first meeting was pretty daunting for me, I must say.

Williams: You talk about sensing the competiveness of things, but then so much of what you describe in terms of your own career seems to me that you've been very collaborative. So what's the balance there?

Cooper: Science is always competitive, and I think that's not really a bad thing. It has to be controlled, of course. But lymphocytes will get boring after a while, no matter how you look at them. [laughs] Part of the stimulus is the competition with the people who are associated with that research. So although in the final analysis you're basically competing with yourself, but the competition with real people whom you're learning from, competing with, is a very positive thing, I think. If you harness it in a positive way, it's a strong, strong stimulus.

Williams: Have you had experiences where you were unfairly competed with or credit was taken that shouldn't have been?

Cooper: Not really. I think I've gotten probably more credit than I deserve. There have been times when I thought that, but with time you begin to realize a little more balanced view of the competition. Also you end up becoming friends with your most vigorous competitors, and I've been extremely lucky in that 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 we are supported relative to most other societies.

Having said that, though, I think that there's several concerning features of the way American science is directed and supported. One of those ways is that I think that more emphasis on translational research than on basic research, that the equilibrium has become distorted, in my view. Many, if not most of the major advances that have had real impact in biomedical issues than for patient care have come from research that had nothing to do with medical disease or patients' problems, but have come from just pure basic science, molecular biology, for example, which has had such a revolutionary effect on biological research. It had nothing to do with it to begin with.

There were relationships and inherited disorders that fed into the acquisition of knowledge over the years. Many technical advances that are very important in healthcare now came about through research that was totally curiosity-driven or basic science. Nowadays, it's becoming so that any National Institutes of Health grant application has to be proposed on the basis of what the translational benefit is going to be. As a physician, I'm not against translating research. In fact, that's been my whole career. But I think that that constraint in the long run doesn't pay off. Even in the short run, I think it doesn't pay off.

The bedrock of American science has been individual investigator-initiated applications and defended on the basis of the quality of the proposal, the plan, and evidence of productivity once there's a track record. That's where you raise people with innovative ideas. That's where the training comes for people to do work together in larger proposals and projects.

I think that's the part of National Institutes of Health research program that goes in that direction has dwindled, and it's led to anywhere you go in this country you hear cries of woe, how difficult it is to get research funds. You see people opting out. You could argue that maybe there are too many of us. I'm not of that opinion. Should you develop more people who are learning science or more people who are learning economics or investment skills? I would argue that while both are important, science in highly technologically advanced world and becoming more so, you need more and more people in science.

So I think the overall picture is good. I think there's a disequilibrium that needs correcting, but I don't know how to correct it. I think it almost will have to be top-down, although maybe societies like AAI and other scientific bodies, National

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've 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.

If you decided on that, then you've got to figure out how to best go about your training. Part of that is to go to graduate training. That's the first step. You should pick the best place you can go, and then try to pick a mentor who's successful and whom you like or at least whom you can relate with, because if you can't, you're not going to get very much from that mentor. Then you almost have to be fanatical and work hard.

So I don't have any magical formula. Those are some of the things that I would think important in selecting. My philosophy has been that where I don't wish to work with someone who's not going to teach me as much or more than I can teach them, and if you start out that you're going to learn as much and you figure out how to hold up your end of the bargain, that's probably about as good as you can adjust for.

Williams: Last question. What do you see as the future on the road ahead for immunology?

Cooper: There's so much left to learn and so many ideas that will have to be revised once we really understand them better. There's so much of the whole of it. I mean, we can slice and dice in order to learn efficiently about the details, but eventually once you learn about a certain cell type or population individually and the plasticity of those cells and how they relate to other cells, you have to integrate in what's now referred to simply as systems biology.

But immunology has everything. It has medical implications; it has therapeutic implications; it has diagnostic implications. It has more accessibility to understanding the inner workings of a complex organism. In this struggle for survival on our planet, if you really wish to understand that, I can't think of a better purchase than the host defense immunology. It's just one part of the

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]