Pierce, Susan 2020

Dr. Susan Pierce Oral History

Download the PDF: Pierce_Susan_oral_history (219 kB)

This is an oral history with Dr. Susan K. Pierce about her career on December 14th, 2020. Because of the COVID-19 pandemic, the oral history is being conducted via the internet with Zoom software. The interviewer is Dr. Victoria Harden, the Founding Director, Emerita, of the Office of NIH History and Stetten Museum.

Harden: Dr. Pierce, would you state your full name, that you know that this oral history is being recorded, and that you give your permission for the recording?

Pierce: My name is Susan Keen Pierce, and I understand this oral history is being recorded, and I give my permission to have it recorded.

Harden: Thank you. You were born on April 19th, 1950. You were the middle child and only daughter between two brothers. Your mother was a homemaker and your father, an agricultural chemical company executive. Would you tell me about your early life through high school, especially about anyone who encouraged you towards a career in science?

Pierce: Thinking about people who might have influenced me, I wonder whether, as a young child, or even in high school, you can really be aware or understand what science and research are, and what a career in scientific research would be like. My mother was a Roman Catholic, and as a consequence, I was educated through sixth grade in a parochial school, taught by nuns. We didn't have science in our curriculum, and so I didn't have any science other than math. I didn't have any real exposure to any formal teaching in science. Because my father had a background in entomology—that's how he got into agricultural chemistry—he was always aware of nature and pointed out to me things in it. It was through my father that I gained a real enthusiasm for birdwatching, because it's something he liked to do and something he liked to do with me. But in terms of entering science, I think that I found science appealing in that it was concrete. I thought that I'd try literature and enjoy history, etc., but I really found science to be more appealing. I enjoy the puzzles of science, and I was okay at it. I think that when you find yourself okay at something, you tend to get into that flow, and go where it takes you, because there's no reason really to fight it. You can do whatever you'd like. So I think that there was no single individual who nudged me toward applying to college as a science—as a biology, microbiology—major, but more just a flow with the way my education went.

Harden: You went to Penn State [Pennsylvania State University] for your undergraduate work, and you graduated in 1971 with a B.S. degree in microbiology. What drew you to microbiology, say, as opposed to chemistry or physics? And were there particular professors there that encouraged you to go on to graduate school?

Pierce: Penn State was, at that time, a pretty conventional place, in terms of the curriculum. It was a time when things were beginning to happen in molecular genetics, and in the more molecular aspects of cell biology. Penn State's curriculum was not, I would say, modern or cutting edge. I had no affinity for chemistry at all. I think it's a language I've just never learned. And I don't say this with any particular pride, but I did flunk organic chemistry the first time around. And, this I attributed somewhat to the fact that that was during what I think of as the revolution with the Vietnam War. And there was the shooting, the horrible shooting at Kent State, which is across the Pennsylvania border in Ohio. As a consequence of that, the Penn State campus was just in shambles. The administration said, "You can take any of your courses, pass/no pass." I took chemistry pass/no pass, and didn't pass.

I liked biochemistry. It was a language I could better understand. But, what I really liked was biology. There really wasn't any cell biology, to speak of yet at Penn State. So, the next step was microbiology, and in microbiology, what I became interested in was virology, and virology became the focus of undergraduate independent research on polio viruses and herpes viruses. Those were the decisions I made. Now, in terms of someone encouraging graduate school, I would say "No," other than mentioning it, but I don't remember anyone really taking me aside and saying, "Wouldn't that be a good idea, given your interest?"

I went to work as a technician when I graduated from Penn State in 1971, which was early because I went through the curriculum a bit faster than a four-year curriculum. I was working for a virologist, a young enthusiastic assistant professor, but what I realized was that I was as capable as he was and that if I didn't get an advanced degree, I would work for other people my whole career. From a very early age I didn't like being told what to do. I felt that 'no one was the boss of me.' So I applied to graduate school. And there, I got advice from my undergraduate research advisor about universities that had good virology departments. That's why I applied to and went to Yale.

Harden: You went to Yale for your master's degree, which you've got in 1974, also in microbiology. You did your first research on murine leukemia virus, and if I read the paper correctly, the virus's affinity for B cells. You were working with Dr. Frank F. Richards, who was interested in a number of things that have characterized a part of your later career: developing new techniques, antibody diversity, and molecular parasitology. So would you comment on him as a mentor? And then tell me what you learned during your master's research that had an impact on your later work?

Pierce: I went to Yale with the full intention of doing a Ph.D. at Yale but decided after two years that it wasn't the right place for me and left with a master's degree. I found when at Yale that I had a fair amount of catching up to do. This relates to my comment about the nature of the curriculum at Penn State. I just didn't have the molecular genetics background that I needed. So, during my first year, there was a lot of hard work to be done. It felt as though all I did was work, but I enjoyed what I was doing. The lab work at the time was only rotations. The bottom line is that I began to feel that Yale was a top-down rigid place, in terms of the faculty. They were very competitive, young, starting-out faculty, and they were very aggressive. I just found that it was not a place where I could think creatively. I felt as though I was always under attack and on the verge of retreating. It wasn't a happy place for me.

I recently talked with my very good friend Wendy [Dr. Wendy Macklin], a woman who was in my class at Yale. We spent all of our hours working and studying together, having dinners together, etc. When I left Yale, it was interesting. The faculty were surprised that I left, which I guess from my perspective, it shouldn't have been a surprise. They really wanted me to stay and tried to persuade me to stay, but I said, "No, I'm going." I lost touch with Wendy, whom I thought stayed at Yale. That was pre-internet/email and cell phones, so it was difficult to keep in touch. It turned out that Wendy left Yale several months after I left. She went to Stanford to complete her Ph.D. We caught up with each other recently while she was on a study section at the NIH. It turns out she's a very successful cell biologist of the nervous system, and a Chair at the University of Colorado. We compared notes and concluded that we both had similar feelings about our time at Yale and no regrets about leaving. She also told me that there were two other students who left the program at the same time, which underscores my thinking that it wasn't a well-run program at the time.

The research that I did was with Frank Richards. He was a surgeon, a pulmonary surgeon, and a very creative guy. And his wife, Martine Armstrong [Dr. Martine Y. K. Armstrong], along with Nancy Ruddle [Dr. Nancy H. Ruddle], who were also on the *JNCI* [*Journal of the National Cancer Institute*] paper, worked together with me. It was Nancy with whom I really became friends and who mentored me, my whole career. She's been very supportive of me and a real role model.

I'd say that at Yale I learned a lot about viruses. Frank, Martine, and Nancy were interested in tumor viruses. This was before the discovery of retrovirus reverse transcriptase, which was discovered while I was a student. It was of interest to know if retroviruses might be playing a role in the transformation of lymphoid cells *in vivo*, under certain conditions, so they sent me off to two places to ask that question. One was the NIH, in Bob Gallo's [Dr. Robert C. Gallo] lab, where I learned to do a reverse transcriptase assay and measure enzyme activity in proliferating lymphoid cells. They also sent me off to the University of Pennsylvania to learn how to isolate individual B cells in Norman Klinman's [Dr. Norman R. Klinman] lab. I thoroughly enjoyed Norm's lab. It was just a breath of fresh air. It had a very different feeling to the place. It was a creative, happy place. So when I decided to leave Yale, I left to go to Penn, to Norman Klinman's lab.

Harden: So you did your Ph.D. work with Dr. Klinman at Penn. I was impressed that you received your Ph.D. in 1976, only two years after your Masters! Would you tell me about Dr. Klinman as a mentor and your Ph.D. work? Was your decision to focus on B cells made here?

Pierce: Norman Klinman was one of the leading experts in B cell biology. He developed a system to isolate individual B cells and characterize the B cell receptors. He was interested in the diversity and the genes that encoded this enormous repertoire. I was new to the lab, and I was more interested in the cell biology of the B cells—how did they interact with their antigens, and what controlled those events?

Norman was committed to science and to training his students and fellows, and I benefited enormously from the attention I received. I learned B cell biology, and I was well trained. The reason the Ph.D. work went so quickly was that I was very focused, and the area that I chose was wide open, so anything I chose to investigate, as far as how B cells recognized and responded to antigens at a single-cell level, was novel. So I was productive—productive enough to write a thesis after two years.

Harden: In 1977, you moved to Evanston, Illinois to begin that September a position as Assistant Professor, Department of Biochemistry, Molecular Biology, and Cell Biology, at Northwestern University. You had received your Ph.D. in June and married Donald A Goodwin in July. Would you talk a bit about this transition and how you your husband balanced careers?

Pierce: The thing that was different about this transition was that I did not do a postdoctoral fellowship. That was unusual at the time, but in 1976, '77, it wasn't impossible. What I wanted to do was to get to work in my own lab. The molecular revolution in science that would allow us to do things like make monoclonal antibodies and clone genes hadn't happened, so there weren't tools that I needed training in. They hadn't arrived on the scene. I felt that if I was in a good molecular biology department, as new methods and strategies came along, I would be in the right company to be able to take advantage of those. That was my strategy. Unfortunately—in some ways fortunately—it meant that I had no colleagues at Northwestern who shared my interest in immunology. It was a very diverse, basic molecular and cell biology department. Sometimes I feel that this was an advantage during the first part of my career because I never chased any ideas that other people were following. I was isolated enough that it forced independent thinking. It was a mixed bag, starting out so early. I was 27 when I became an assistant professor, but it was what it was.

My husband—we divorced around 1999—was at the Wharton School in an M.B.A. program at Penn when we met. Northwestern is in Evanston, which is a suburb of Chicago, and Chicago was a major hub of business activity, so we thought that it wouldn't be hard to have two careers in that environment. So that was our strategy. He eventually found a job once we were there, but the driver was my position at Northwestern, because academic positions were less frequently available than were jobs in business in Chicago.

Harden: You rapidly advanced up the academic ladder, becoming an associate professor in 1983 and a full professor in 1987. Let's talk first about your teaching and mentorship of young scientists. In 1986, you won the Weinberg College of Arts and Sciences Award for Distinguished Teaching. Would you tell me about your philosophy of teaching and mentorship?

Pierce: With teaching, I simply enjoyed doing it. I enjoyed explaining how things worked and seeing young people get interested and be brought into thinking about the problems that I thought were interesting. My feeling was always that you needed to treat the students as equals in a genuine way—that is, we were both interested in understanding, in this case, the immune system, and we were sort of colleagues, senior and junior colleagues in that venture. I still treat students in my lab as younger colleagues and give them the respect and the encouragement and the direction they need to succeed. I've never felt that I would ever give up on a student—let them fail—but sometimes students are just not cut out for what they're trying to do. In that case, I try my best to point them in a direction where they might be more successful and enjoy what they're doing more. That sums it up more or less.

Harden: Have you followed the careers of some of these young people you taught?

Pierce: Yes, I have. My first student was a woman named Nancy Speck [Dr. Nancy A. Speck], who is now Professor of Cell and Developmental Biology in the Perelman School of Medicine at the University of Pennsylvania. When we began, Nancy and I were only four years apart in age. So I was her professor at 27 and she was coming into graduate school at about 22, 23. I've kept in good touch with Nancy over the years. Now that we're both on the same coast, I'm not very far away. I also have an adjunct faculty position at Penn, so I do see her. And also I keep up with other students as well, many of them from the very, very early time. The fellows that I've trained since coming to the NIH I definitely keep up with. I have many pleasant recollections of training students and fellows and I hope it extends both ways.

Harden: Now let's turn to your research. In 1984, you won a faculty research award from the American Cancer Society. Would you tell me about the research for which this award was given, and then walk me through how your research in general progressed during the 1980s?

Pierce: My research has always focused on the same question: For B lymphocytes that have a receptor for foreign antigen and that interact with other cells in the immune system, what at the molecular level regulates that response and their activation? I think what's changed over the years is that in the eighties we didn't have the same tools that we would ultimately have. In the early to mid-eighties, we clearly didn't have the tools I have now to investigate B lymphocytes at that level. When I started out in my area, investigators applied for both basic research grants from the NIH and from organizations like the American Cancer Society to provide a salary and a small amount of research funds. That was the nature of my award from the American Cancer Society.

Harden: Tell me how your research on B-cells progressed in the 1980s. What did you learn, if you can think back to the eighties?

Pierce: What the field was focused on during that time was the interaction of B lymphocytes with a cell called a T lymphocyte. And this interaction occurred when both cells, the T-cell and B-cell, recognized through their immune receptors, the same molecular foreign antigen. And the way process played out is that the B lymphocyte would indicate to the T-cell that it had engaged an antigen and needed further growth promoting activities from the T-cell to continue in that response. Briefly, B cells internalize antigen bound to its B-cell receptor into a compartment within the cell where protein antigens are cut up into small pieces, proteolyzed, and then bound to a molecule called a major histocompatibility molecule, which was then ferried to the B cell surface where the T-cell engaged in and provided those additional helper factors to get the B-cell response going. So during that time, we described a lot about that process, which is called antigen processing and presentation by the B-cell.

Harden: In addition to your research and teaching, you had three daughters born between 1979 and 1988. Now, Dr. Ruth Kirschstein [Dr. Ruth L. Kirschstein] at NIH attributed her ability in the 1950s to being able to continue her research as a young mother to the availability of good child care, and she had only one child. Would you comment on what is now called work-life balance in your career and how you and your husband juggled the responsibilities of two careers and three daughters?

Pierce: I think part of the attraction of Northwestern to me was that I felt very supported by the senior faculty. They were excited to have me because I was bringing a new field, immunology, to the department. The reason I went to Northwestern rather than other, the more prestigious universities at which I interviewed was that I didn't have to compete with colleagues and fight to survive at Northwestern. The faculty was going to support me because they wanted to see me succeed. That was one part of the strategy, to be able to have a family, which was something that was very important to me. That was something I was going to do.

I have three daughters, Katherine Goodwin born in 1979, Alice Goodwin born in 1982 and Julia Goodwin born in 1989. Child care was not stable when my children were born. But what I ended up doing when Kate, my oldest, was close to three and her little sister, Alice, was born, was to hire a full time nanny. In my whole child-raising career, I only had two such people. Both of them were African-American women living in Evanston and in Hyde Park. They were both extremely devoted to us and we to them. And it was stable, trustworthy care for the kids. This meant that when I came into work in the morning, I stopped thinking about the kids. They were in good hands; they were going to have a good day. Other than problems that children have, I didn't worry about childcare, I didn't worry that they weren't being very well taken care of. That freed me to focus on my research. My husband traveled quite a bit with his job—a lot of international travel—so he was not always able to be involved with the day-to-day care of the kids. But with the help of those two wonderful women, I was able to more than manage things, I was able to really enjoy my children and my job.

Harden: In the 1990s, you served as Chair of the Department of Biochemistry, Molecular Biology and Cell Biology. And then in April, 1996, you were given the William A. and Gail Cook Endowed Chair in the biological sciences. You also served from '92 to '97 as deputy editor of the *Journal of Immunology*. And before we talk about your research in the 1990s, would you tell me what you learned while serving as department chair and deputy editor of such a prestigious journal?

Pierce: The position I hold now at NIH is essentially a department chair position, and I've held it for 21 years since I came to the NIH. When I was made chair of my department at Northwestern, I realized that at that point in my career, I was too young to be doing it well. I didn't have a calmness about me or a way to help people. I was the person I was working for. I mean, I mattered more than anyone else, selfish as that may sound, but I think that's true.

Coming to a chairmanship in 2000 as a much more mature scientist, I was able to make it a priority to help the PIs in my department, particularly the junior PIs to succeed as best they could. And I think that's why I'm successful. I think I'm unusual at the NIH in making the members of my department my priority, not me. And I think there was no way that I could do that when I was much younger, at 40, still really trying to build my own career. And I just didn't have the same empathy for people who were struggling or people who needed more help. That's what I learned about chairing—or actually didn't learn.

In terms of the *Journal of Immunology*, being an editor just meant more work to me. I think you have to be willing to contribute your time and effort to an organization like the American Association of Immunologists, and you've got to do it as part of being a member of the community, but it's a lot of work. And my contribution to the journal at the time was trying to get it out of its stuffy old way of doing things and try to brighten it up a little so that we could attract the best papers in immunology rather than being the sort of bread and butter journal that members submitted work but not their not best work to.

And I think we succeeded in that. I think there are a couple of things about the journal that lasted until today, for example, a section called Cutting Edge made it clear to the *JI* readership that we would review papers in a short format like the format that you'd write for a *Science* or *Nature* article that didn't make it into those journals. And we just said, "Send them to us, don't bother formatting them and we'll judge them and then format later."

Harden: I want to turn to your research in the 1990s and early 2000s, whose technical aspects become evermore difficult for me to grasp. If I am correct—and please correct me if I'm wrong—you explained the two key interrelated functions of the B cell receptor—(1) signaling in response to antigen for B cell activation and internalization of antigen for processing and (2) presentation to helper T cells. You also discovered, I believe, how the regulation of these functions were managed by receptors called Toll-like receptors. Am I somewhere close?

Pierce: You're very close. The big technical breakthrough for us by that time was high resolution live cell imaging. Imagine, the B cell receptors as a protein sitting out on the cell surface that will grab an antigen and then signal. The B cell receptor will transduce the information that it has encountered an antigen to the cell nucleus and induce changes that lead to cell differentiation, and it will physically internalize antigen, carry it into the cell, cut it up and put it on the MHC display molecules for the T cell to recognize. Advances in imaging let us view all of this for the first time at the resolution of single receptors on cell surfaces.

And we had also expanded our interests to the function of what are termed innate immune system receptors. These are receptors that are not diversified. You have millions of different antibodies in your immune system. You have only handfuls of innate immune system receptors, including the Toll-like receptors that we studied. And what these receptors do is survey the environment for pathogens, genuine pathogens that express molecular patterns that will bind to these receptors in B cells and alert the B cells to their presence. What we wanted to understand was: How was all this information assimilated from the moment the B cell touched an antigen until it responded by proliferating and differentiating to the antigen? As I mentioned, the big breakthrough came technically in imaging technologies—that is, microscopes that allowed us to focus on an individual B cell and see, literally see in real time an individual B cell receptor grabbing onto an antigen and beginning this process of signaling and internalization. And that was just it. We learned so much. We've proposed a model, a mechanism for how the initial signaling is triggered so that the internalization occurs, how the presentation to the T cell occurs, and what the effect of Toll-like receptors is. We've taken good advantage of this new technology to watch at a whole new level of cell functioning.

Harden: You also described the role of lipid rafts in the B-cell antigen receptor signaling. I want you to tell me just what a lipid raft is and how it functions.

Pierce: Think of the B cell as a sphere that is encased in a membrane. Membranes are essentially proteins and fats, or lipids, and B cells have different types of lipids in the membrane. These lipids organize themselves. They have different features that make some of them want to form compacted islands and others want to be more dispersed. This behavior of lipids is not so different from what happens when you're making a salad dressing, and you want to emulsify the vinegar with the oil to have a nice homogeneous mixture. But as the salad dressing sits for a while, that emulsion breaks up. The lipids—the oil—makes little globules within the vinegar.

A B-cell receptor—a protein—sits on a membrane, and as it begins to bind an antigen—usually another protein—the B-cell receptor changes slightly in its relationship to the lipids in the cell membrane. And this induces the formation of novel islands or rafts of lipids, floating bits that allow the B-cell receptor to transmit its signal optimally. So a raft is like a island of organized lipids within a sea of disorganized lipids. And they're functionally very important.

The membrane of a cell is not a uniform substance. It's not a uniform material, it has heterogeneity. Imagine a ball with little divots all over. Those divots—those islands—are necessary to organize all the receptors on a cell surface. There are B-cell receptors, but there are a hundred of additional receptors performing other tasks as simple as iron uptake into the cell or the transport of sugars into the cell. So these rafts floating in a sea of less organized lipids are a fundamental feature of a cell membrane and function to keep the B cell's receptors, including the B cell receptor and the Toll like receptor, in a functional organization—that is, being near the right things and away from the wrong things. Once signaling starts, rafts recruit additional molecules and to promote signaling.

Harden: As you learned more about lipid rafts, you found out that viruses like Epstein-Barr could co-opt the lipid raft and block signaling and the antigen transport function of the B-cell receptor. What was the significance of that finding?

Pierce: This is something that we continue to be interested in. The Epstein-Barr virus (EBV) is a virus that causes mononucleosis, and almost everyone on the planet is infected with the virus, to what benefit we don't know. Many B-cell tumors are the result of EBV dysregulation of B cells. The question is, by what mechanisms does this happen? How does the virus alter how a B cell functions? That was our first look at a product that EBV expresses on the membrane resulting in alterations in the function of the B cell receptor. Now we have a much more sophisticated view of what that means—in terms of mechanism—the molecules that are involved and so on. We continue to be interested in this question. As a matter of fact, we have a fellow in the Lab from Ghana, Charles Togbor [Dr. Charles Togbor], who's working on it because EBV-induced B cell tumors called Burkitt's lymphomas are prevalent in African children living in malaria endemic areas. So there's a link between malaria, a parasite, and Burkitt's lymphomas. And because at present we have no effective treatments for African Burkitt's it is currently a focus in my Lab.

Harden: In December, 1999, you accepted the position that you currently hold as Chief of the Laboratory of Immunogenetics in the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases (NIAID). I have several questions regarding your move to Bethesda. The first one, of course, is why did you decide to leave Northwestern?

Pierce: Yes, that's simple. I wanted to use our understanding of B-cell biology to understand the control of infectious diseases. The flip side of that is the initiation of autoimmune diseases. I sat on a review panel for the NIAID Board of Scientific Counselors before I was recruited to join the NIH, and when I interviewed the scientists in the Institute, I was impressed that they were doing cutting edge, outstanding research in infectious diseases and in immunology. These NIAID scientists were really the best in their fields, but they didn't appear to talk to each other. They seldom interacted, so it seemed to me that the NIAID environment was ripe to begin to work at the interface of infectious disease and the immune system and find out how responses were driven in infectious diseases. That puts our work in the context of vaccines.

Harden: Let me stop you before you get into your current collaborations and work on malaria. I'm going to come back to that, but I want to talk for a moment just about your transition from Northwestern to Bethesda. For example, I want you to tell me about the hiring process. What did you want in NIAID to offer you aside from the position and how hard did you have to negotiate to get it as a woman coming into a wholly senior male intramural laboratory environment? I want to know how you were received. So talk to me about the hiring process.\

Pierce: In 1999, the hiring process in the NIAID intramural research program resembled much more closely recruitment at an academic institution. Before that, it wasn't. In the past, the Chief of a Lab or the head of an Institute simply approached a scientist they wanted to recruit. But by the time I arrived, the director of the NIAID intramural research program was a fellow named Tom Kindt [Dr. Thomas J. Kindt]. The rules at that time were that when you decided to open a search—and in this case, I was being recruited to take Tom Kindt's position as Lab Chief, because he no longer was able to manage both the intramural program and his own lab—a search committee was set up. Applications were taken, interviews were held, and the search committee then made recommendations back to Tom Kindt. And Tom then went about the recruitment process—that is, putting an offer together and so on. Because I was senior, I had a long experience with raising money for my Lab through grants, so I knew how much I needed to be successful, what my Laboratory would cost to operate. At the NIH at that time, money was still very available. There just weren't funding restrictions. Restrictions really came in space rather than in money. Most of my interactions during the hiring process were with Tom Kindt. He was peripherally in the B-cell field when I was just coming into the field. So I knew Tom, and it was not a difficult negotiation at all.

You know, the thing about it is that not only was I the only woman when I started, I was the only woman for 20 years, more or less. There really didn't seem to be a genuine effort to pay attention to promoting women in the Institute, I would say. But certainly I personally was given the resources I needed, and to my mind that was fair.

Harden: You mentioned a number of things you had done with NAIID while you were at Northwestern, such as sitting on study sections and serving on the Board of Scientific Counselors for the Institute. Those all let you look at and NIAID from the outside. What most surprised you about federal employment after you joined the Institute?

Pierce: In ways that affected my career or what I wanted to accomplish there were no surprises or only good ones. Resources were more readily available than I had appreciated. At the NIH, there were obviously all the governmental federal rules and regulations that are perhaps necessary but tedious. The intramural program of the Institute is organized by laboratories. Laboratory Chiefs control all the resources for their laboratories and make decisions on how to allocate those resources. These are powerful positions, and perhaps consequently there is little incentive for chiefs of laboratories to join forces for the betterment of the Institution. In a university, for example, if you wanted to develop a training program—let's use, for example, something I wanted to do at NIH, in malaria immunology—the goal would be to pull people into an umbrella organization. This would not be an organization that controlled resources, but a collaborative umbrella organization that would allow the organization to recruit fellows, to train more rigorously in the field, and to create new interactions between people who had different talents and abilities. There are no programs like that in NIAID, and the roadblocks, the hurdles to developing them in my experience are daunting. I've attributed that to the fact, in my experience, that laboratory chiefs are appointed for life. They are reluctant to give up any of their power. Any joining of forces by definition requires you to give a little to get back something more, but that simply doesn't happen at the NIH That was the biggest difference for me between the NIH and universities.

I should comment that despite the hurtles I eventually did establish the Malaria Research Program (MRP) in NIAID that was a collaborative effort between my lab and two other NIAID malaria labs. The MRP survives today. To quote the website: "The mission of the Division of Intramural Research (DIR) Malaria Research Program (MRP) is to seek fundamental knowledge about the interactions of malaria parasites with the human host and the mosquito vectors that transmit them and to apply this knowledge to prevent disease, enhance health, and improve the quality of life in malaria endemic areas."

Harden: That is very interesting. Now would you describe for me intramural NIAID when you arrived on a very specific basis: Where was your lab physically located? Were you on the Bethesda campus or in Rockville? Who else worked near you physically and provided guidance about navigating the NIAID bureaucracy? Were there other women with whom you could talk either in NIAID or other Institutes?

Pierce: My laboratory was not on the main NIH campus in Bethesda. It was in the Twinbrook NIAID building near the Twinbrook Metro stop in Rockville. The other group that was there was the malaria group that had a Malaria Vaccine Research Center headed by Lou Miller [Dr. Louis Miller]. He had been Chief of the Laboratory of Malaria Research before he took on the vaccine work. One reason I got involved in malaria research was because we were neighbors. I got to know the people, their problems, and interests.

In terms of whom I interacted with—as a Lab Chief, I was the most senior woman in the Institute. My first recruitments were two tenure track scientists, Silvia Bolland [Dr. Silvia Bolland] from the Rockefeller University, with whom I became good friends with over the years, and Tian Jin [Dr. Tian Jin] from Johns Hopkins, who had an enormous impact on my work by bringing new live-cell imaging technologies to the Lab. Tian and I have also become close over the years sharing similar enthusiasm for cell biology and politics. I knew and interacted with many people on the Bethesda campus. I remember one time when I needed help sorting through what I felt was a troublesome interaction with the Kathy Zoon [Dr. Kathryn Zoon], who became the Director of Intramural Research following Tom Kindt. I turned to Ruth Kirschstein. She always had an open door. We worked together on a committee that was tasked with promoting women in science at the NIH. Ruth was a person whom I so admired and who gave me much appreciated useful advice and encouragement.

Harden: When you arrived in Bethesda as a Lab Chief, your lab consisted of three tenured principal investigators and their research groups. Would you tell me who these investigators were and what they were working on?

Pierce: Yes. The first was Eric Long [Dr. Eric O. Long]. He was studying the natural killer cell. Eric is still in the Lab. The other two were John Coligan [Dr. John Coligan] and Mary Ann Robinson [Dr. Mary Ann Robinson]. John Coligan, left the Lab when I became Chief. I can't help but think that he wasn't going to be in a Lab with a woman as the head. That was fine. John returned to become a member of the Lab again several years before he retired. Mary Ann Robinson was a different story. Tom Kindt had promoted Mary Ann to Senior Scientist, but when I arrived, in my judgment she was not going to make it as a tenure track investigator. Within a year or so after my arrival Mary Ann took a job as a scientist in the Research Technologies Branch [RTB] of NIAID. That accounts for the three people in the lab when I arrived.

Harden: The laboratory is now composed of nine sections headed by tenured PIs [Principal Investigators] with their students and fellows and an administrative support team. I'm going to come back to the administrative support team, but tell me first about what your goals were, how you expanded the lab by six more sections, and what research they do now.

Pierce: My goal was to bring in the best possible scientists that I could identify to join the Lab. And it was important that they worked in areas of biology that we could all share or have joint interest in. It was equally as important that they were independent—good, very good scientists, first rate scientists. I inherited two investigators who had been working under the NIAID Director because of some problems I won't go into with the head of their Lab at the time. They were two structural biologists. Peter Sun [Dr. Peter D. Sun] is still with the group and Dave Garbozi [Dr. David Garbozi], who did not receive tenure. Then Eric and Peter and I recruited Silvia Bolland from the Rockefeller and Tian Jin from Johns Hopkins. Both Eric and Silvia and Tian are now senior tenured scientists. Then we were given the opportunity to hire a fellow, Peter Crompton [Dr. Peter D. Crompton], who was a very well-trained physician who had come to the NIH as an infectious diseases fellow and had worked between Lou Miller and me. We took advantage of a program called a “path to independence” that aimed to recruit clinical scientists into the NIAID. Peter competed for one of those positions. Peter is now a tenured senior scientist. Most recently, Peter and I had an open search for a fellow on the tenure track. Just this year we recruited Josh Tan [Dr. Joshua Tan] from Cambridge University. The last bit of the puzzle came together at a point when the Institute wanted to condense labs. There were a few very small labs—two-people labs. They merged one two-person lab with my lab, and the head of that lab retired. The Lab inherited Victor Lobanenkov [Dr. Victor Lobanenkov], who is I believe is, nothing short of a genius, though he's a complicated person who benefits from my support. So that's my Lab.

Harden: I'm especially curious about the new administrative support team that you put together, which included the imaging core, a bioinformatics core, a cell sorting and analysis core, and a pathology core. Would you explain what these components do for your lab and whether they are different from or associated with the NIAID Research Technologies Branch?

Pierce: The biggest investment has been in imaging and the imaging core. We were really interested in acquiring cutting edge imaging technologies, which are of particular interest to the PIs in my Lab, and somewhat in general at the Twinbrook campus. It's not an open facility, even though we are highly collaborative and happy to help people out. But it's really a facility where the facility head, Joseph Brzostowski [Dr. Joseph A. Brzostowski], a very bright guy who has the personality to be a facility head, takes responsibility for all these very sophisticated microscopes. He has one full-time staff member, Javier Manzella-Lapeira [Javier Manzella-Lapeira], and he trains students. So students, or fellows, or even PIs come in with their research problem, and he guides them through the imaging.

The pathology core became the right niche for Chen Feng Qi [Dr. Chen Feng Qi], who came into our lab as a result of the fusion with the small lab. She is a pathologist and contributes to the Lab doing mouse pathology in the mouse models that we use.

The statistical core was created to meet the Lab’s need to analyze large data sets and to create platforms to organize them. Most of the technologies we use now generate huge data sets and generally the statistics core cannot handle the newest technologies so the PIs form collaborations to analyze these. Most recently, we expanded the imaging core to include cell sorting and flow cytometry by adding an expert in this area. Our goal is to bring in technologies that we need and make them available to increase the productivity of individuals in the Lab.

Harden: If I understand it, your lab discovered something called atypical memory B cells and also determined that they are largely found in chronic infections, such as HIV/AIDS, lupus, and malaria. Would you tell me what atypical memory B cells are and what their role in chronic infections are, especially in contrast to the role of B cells in acute infectious diseases?

Pierce: Your questions sound like questions we get from the reviewers of our manuscripts! We described these cells in the same year that Tony Fauci's [Dr. Anthony S. Fauci] group—in particular, Susan Moir [Dr. Susan L. Moir] described them in high viremic HIV-infected individuals. We have collaborated with Susan in a very productive way since then, in characterizing these cells. In HIV-infected or malaria-exposed individuals, atypical B cells represent up to 30%, even 40%, of all circulating B cells. Now, how do they function? I want to understand how they engage antigen, what regulates the response, and then what they do in response to an antigen. The thing that's hardest to test is how they impact the progression of chronic infections. Right now, our data indicates that they are a separate lineage, a new fate pathway for B cells. Our strong suspicion is that atypical B cells expand in chronic infectious diseases to lessen the pathology of the disease and to avoid autoimmunity.

Harden: As you came to understand more fully the activation and regulation of B cells in chronic, especially auto immune diseases, you collaborated with intramural scientists in the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), even serving as a guru at their annual retreat. Tell me more about this collaboration. I also want to know what the function of a guru is at an Institute's annual retreat.

Pierce: I didn't actually collaborate with the scientists in NIAMS until recently, but the studies that I was doing with the powerful imaging technologies we had available captivated their interest. Generally NIH Institutes have an annual Institute retreat. Some Institutes, when they have such a retreat, will invite an outside expert—informally called a "guru"—in some area to present their work and then reflect, during the retreat, on how their work, in my case, receptor-mediated signaling, is related to the work that is going on in the Institute. Recently, I've had more interactions with NIAMS, having recruited a NIAMS clinical fellow to work directly on B-cell biology in autoimmune diseases. He is outstanding, and I believe we have a good chance to describe the mechanism of activation of autoreactive-B cells that might identify targets for therapy, if we're lucky. I'm also collaborating with one of my colleagues, Silvia Bolland, to understand the link between chronic infectious diseases—malaria in particular—and autoimmunity.

Harden: You also collaborated with scientists in Sardinia, Italy, using a similar approach to understanding B cell regulation in a large cohort of individuals who carry a mutation in the gene encoding the B-cell growth factor, which results in its overexpression and possibly leads to systemic lupus erythematosus (SLE) and multiple sclerosis. Tell me about this collaboration.

Pierce: It does fit a mold, and it comes back, very briefly, to a point I made about the relationship between malaria and B-cell tumors. There is a relationship between chronic malaria and the risk of SLE. It's a complicated pattern.

I was on sabbatical in Rome and went to Sardinia to interact with Francesco Cucca [Dr. Francesco Cucca], who is really an outstanding molecular geneticist. He discovered a mutation in the population in Sardinia that has the highest risk factor for serious autoimmune disease, including rheumatoid arthritis and SLE. They knew that B cells in people with the mutation were dysregulated, that is, they expanded and behaved differently than B cells in individuals who didn't carry the mutation. He identifies the mutation in the gene encoding the B-cell Activation Factor (BAFF) a fundamental survival factor for B cells. The mutation resulted in over expression of BAFF. Now, the reason he wanted to talk to me is that I knew something about B cells, and I knew something about malaria. Cucca believed that the BAFF mutation may have been selected for in individuals living in Sardinia when malaria was endemic on the island—until the 1950s. He believed that increased BAFF levels may have been protective against severe malaria. But when you take malaria out of the equation, Baff over expression may have contributed to hyper activation of B cells and autoimmunity. It's similar to a phenomenon that we've studied in mouse models in SLE. Women of African descent are at eight times the risk of SLE when they move out of a malaria endemic area, but there is no SLE in endemic areas. I believe there is a highly complicated interplay between what's necessary to combat a chronic infection and what causes autoimmunity. What we're doing with Cucca is analyzing B cells from Sardinians to see how they respond to antigen. We have developed a mouse that has the same mutation as the Sardinians, so we can study in vivo what's going on with these cells.

I should comment on one additional collaboration that I find very exciting, with John Schiller [Dr. John T. Schiller], a senior scientist at the NCI [National Cancer Institute], who together with Doug Lowy [Dr. Douglas R. Lowy], the principal deputy director at NCI, is credited with developing the current HPV—human papilloma virus—vaccine that all young people are encouraged to take. John is a vaccinologist. He made a spectacularly effective HPV vaccine, one dose and you're good for life. He's the first vaccinologist that I've interacted with who wants to understand B cell biology. John and I have worked together for the better part of a year now and we are making progress in understanding why his vaccine worked so well which is exciting.

Harden: In 2004, you married Louis Miller, who was Chief of the Malaria Vaccine Development Branch in NIAID. In 2008, the two of you published together about a study done in 2006 and '07 in Mali, assessing the impact of sickle cell trait on delaying the first malaria episode in children. Tell me about this study, about your collaboration with researchers in Mali and why the sickle-cell/malaria subject was of interest.

Pierce: Peter Crompton, who is now a senior investigator in my Lab, joined Lou and me with the goal of understanding the acquisition of immunity in malaria. The underlying phenomena is that children growing up in malaria-endemic Africa, countries like Mali, have enormous exposure to malaria. They have 60-100 infectious bites from mosquitoes every year. Malaria is unlike many acute infections, including measles and smallpox, in life-long immunity after a single infection. Malaria does not allow for or promote the acquisition of immunity. These children stay susceptible for years, until their early teens. They don't ever become resistant to infection by parasite-infected mosquitoes, but their immune systems learn to control the inflammation and the disease aspects of the infection. We wanted to understand how this immunity is acquired.

When you're looking to understand the acquisition of immunity, for most diseases it's hard to do because so few people become infected at any given time. If you are running a clinical trial to see if a candidate vaccine is effective for a disease, you usually need to vaccinate a very large group because only a small fraction of people will become infected or exposed. When trials were being run to see if candidate vaccines against COVID-19 worked, this was made easier, unfortunately, because with the surges in cases of the virus, more people became infected. This meant that the cohort that you had to vaccinate could be relatively small.

With malaria—and I don't know of any other case where you can do a study like this—you need only a small cohort for a study because malaria is transmitted in very well-defined timeframes. In Mali, the rains begin in March-April after a six month dry period, and as the rains begin, mosquitoes begin to breed, and malaria begins to be transmitted. It will be transmitted until the next January, when the rain stops, things dry up, and the mosquitoes go away. Then the children go for six months with no new exposure.

What this means is that you can take a relatively small cohort of children for a study and expect valid data to be produced. Our initial study was 120 children. We measured every possible immune parameter we could from samples of peripheral blood. We asked who gets infected and when. What you know is that every child will be exposed to 60 or so infectious bites. Our job was to ask what were the characteristics of the child that either made him or her susceptible to infection or resistant, and then, how did the infection, if it occurred, impact those variables. And that's essentially what we've been doing in Mali for over 15 years now. We've been interrogating every factor we could interrogate to ask what controls the ability to generate a strong B cell response that's protective. And we've learned a lot.

After this long introduction, to answer your question directly: Sickle cell trait is highly protective in malaria in that children with sickle cell trait experience less febrile malaria and malaria rarely progresses to severe disease and death.

Harden: In 2009, another paper came out of this study in which you published a major finding, that there was an expanded atypical memory B cell sub-population among Malian people. This was the first description of such an immunological alteration of memory B cells in individuals exposed to falciparum malaria. I thought that this was a much more basic science paper than a clinical paper.

Pierce: I think my contribution to studying malaria is to define the basic science of the infection with a hope that this will translate to a vaccine or a therapy. So if we know what malaria is doing to the B cells or promoting in the B cells of these children, and if we could learn what those B cells do—they represent, as I mentioned, 30% of their B cells—then we might have a chance to design a vaccine or a therapeutic, what they call adjunctive therapies. We already have highly effective drugs for the parasite itself, but we need ways to help the children's immune systems overcome whatever it is that's making it so hard to become immune.

Harden: I have one side question here. Were the researchers in Mali with whom you collaborated a part of NIAID's International Centers for Excellence in Research program?

Pierce: Yes. And before that program, Lou Miller had established the Malaria Research and Training Center in collaboration with an outstanding scientist, Ogobara Doumbo [Dr. Ogobara Doumbo] in Mali. And I think that was really the organization that opened up science in Mali.

Harden: And if I understand it, I presume you all went to Mali for the earlier 2006, 2007 study, but that the politics of what's been going on recently has made it necessary for you to put all the research on hold.

Pierce: Yes, that's absolutely correct. It's very sad. When I began working in Mali, I had never worked in Africa. When I began working with Lou, we always said that despite the large number of ethnic groups in Mali, they all got along. It was a peaceful country, but that's not the case any longer.

My current interest in malaria, other than the understanding of how these atypical B cells work, is in developing a therapy for the most severe form of malaria in young children, which is cerebral malaria. Out of a bit of serendipity, we discovered a therapeutic that had been tried in children before to treat cancers. It's an antagonist of the amino acid glutamine. When a mouse—our animal model for the disease—is in the throes of this disease, their blood-brain barrier is broken down. The brain leaks and swells, and the animal will die within the next 24 hours. When we administer this drug in the morning, by the afternoon, the animals are up and running around as though nothing happened. We hope we'll see the same thing in children. Based on the mouse studies, we are now two years into assembling a team and a support for a clinical trial that is planned to begin in Malawi in March 2022. Malawi was chosen as is a site where they have the infrastructure to study cerebral malaria. And the leader in cerebral malaria in Africa is there, who's welcomed us to carry out the study there. We're very hopeful this that this drug may do in children, what it does in mice.

Harden: If I have it correctly, this is the Johns Hopkins, JHU-083 drug that modified the D-O-N, which is the chemical cancer therapy that worked. That is what you all are using, I believe. But, following up on that, you said you have finally gotten funding for a human clinical trial of this drug in Malawi. Is that a done deal or are you still working to get it all set up?

Pierce: The pieces for the trial are pretty much in place. The main thing that we needed for a clinical trial is the drug. And we've obtained that from NCI, from their 1980s trials of this drug, DON. My Director, Steve Holland [Dr. Steven M. Holland], has been highly supportive and given us the funds to do what they call "fill and finish"—that is, to put the drug in vials for delivery at bedside. We collaborate with an investigator at Children's Hospital, Doug Postels [Dr. Douglas G. Postels]. Doug has spent most of his career working in Malawi. He applied for an extramural NIH grant, which he can do. We in the intramural program can't ask for grant funding. We learned this spring that the grant will be funded in fiscal year 2021, which we're in now. That will give us the money to do the trial. And then we are putting the clinical trial itself together to go to the FDA's CDER [Food and Drug Administration's Center for Drug Evaluation and Research] to get it approved as an IND [Investigative New Drug]. They consider it to be that even though it's been used in about 500 children already for cancer. But this COVID-19 pandemic has been tough for us because the FDA is not responding as quickly as they otherwise might have. But I would bet—if I were a betting person—that we're going to get this drug into trial.

Harden: A year ago in December 2019, you announced that you intended to step down from serving as lab chief and focus on your personal research in the Lymphocyte Activation Section. Why did you make this decision, and what are your plans for your future research at NIAID?

Pierce: I made the decision because I think to have people named to a position of leadership that controls so much of the resources and do that for life, which is what the job is, is not a good thing. I've been pretty outspoken about this, that it just is not healthy. I've been a Chief for 21 years. Michael Gottesman [Dr. Michael M. Gottesman], who's the head of the NIH Intramural Program, announced a new policy year ago—two years ago now in the spring—that specified that if you had been a Chief for more than three terms, that's a total of 12 years, that upon the next Board of Scientific Counselors review, you should plan to step down to create opportunities for another, younger scientist to lead. I thought this was a great idea. I had served in this position for a long time. So I submitted my resignation, but after almost two years, I was still acting as Chief. I was in a sort of never-never land, but recently I resumed my responsibilities as Chief with the pledge by my Director to search for my replacement once resources are available.

Harden: That's interesting.

Pierce: Yes, my feeling is that I've done this long enough. It's not a terrible burden, but I think we need to turn things over. It was August, 2019, that I submitted my resignation. I could say, "Okay, that's it. I'm not the chief anymore. Go find yourself a chief. Have a search, do whatever you need to do." But if I do that, I'm going to let down the people who are dependent on me, the other eight PIs in my Lab for whom I work and support. I try to make life better for them. And if there's no one else to step in right now as Chief, then I can't let those people down. It's an odd predicament, but not unusual, I think, within this NIH structure. My solution was to continue to take the responsibilities of Chief until it is possible to recruit my replacement.

Harden: No, I don't think it's unusual either. I imagine that a lot of other Lab Chiefs were also grandfathered in when that decision was announced. Your career has spanned more than 20 years in academia and more than 20 years in the government at NIAID. That means that you are uniquely positioned to comment on the advantages and disadvantages of doing research in each environment. Would you compare them for me?

Pierce: The advantages of working in the government are the extraordinary resources that you can command with very little effort. Also, at NIH there is the exceptional quality of the individuals with whom you can interact. I mentioned my recent collaboration with John Schiller, who is just a remarkable scientist. As a scientist at NIH you focus on your research, but rarely build bridges to other Labs or Institutes. You are your own island. It's your own operation. In a university, on the other hand, there's a sense of moving your field, moving your academic area ahead, planning, seeing where you're going as a group that I miss.

Harden: You've been involved in discussions at NIH about the challenges and opportunities for women in immunology. In March 2020, along with an NIAID section chief, an NCI section chief, and a team leader at a French university, you published an article in *Nature Immunology* about women in immunology. Now, my first question, of course, is why did you feel the need to publish this article?

Pierce: I'll say, I think there is a lot of need to make it clear at the NIH what the current status of women is. I don't think that that's well appreciated. Now, would I have taken this route to do that—that is, a publication in *Nature Immunology*? No, it wasn't my way of doing things. But the three younger colleagues who approached me to join in the effort somehow felt that I would add something. I agreed to support their efforts because it's their future world. My time is coming closer to the end than the beginning. And so I asked what their needs were, what did they need to accomplish? I was happy to support them and was happy to work with them on the review. To be honest, I did not impose my view, which was a little different than their view, because I think they need to say what they're thinking and draw attention to what they want. So I was the old lady, blessing the younguns' attempt to increase the success of women at the NIH.

Harden: My second question is that I think you are the only NIH Laboratory Chief and indeed the only person at that level, serving as an author of this article. Why do you think there have been no other women at NIAID promoted to a lab chief position in the 20 years since you achieved this position? You were outstanding, no question. But it's hard to believe there isn't another female who could have been promoted to lab chief in the last 20 years. Would you talk about this?

Pierce: Yes. I should say that as of this spring, there were two women named to head laboratories in NIAID. In the first 20 years, you're right. But in the 21st year, yeah, it's good.

Harden: Can you tell me who they are?

Pierce: Yes. Pamela Guerrerio [Dr. Pamela A. Guerrerio] is now the Chief of the Laboratory of Allergic Disease. Pamela was chosen right after tenure to take the position of Chief, so she is a bit untested.

The other person is a distinguished scientist, Yasmine Belkaid [Dr. Yasmine Belkaid]. She studies all areas of the microbiota, all the bacteria in your system and how they function. She's an exceptional scientist. Her Lab is newly created [Laboratory of Host Immunity and Microbiome], and I don't know what resources she's been given. She took the position during the COVID-19 pandemic, and I just haven't had a chance to talk to her. I know her well, but we haven't discussed what she's going to be doing.

Harden: I'm going to press you here on the reason that it has taken so long for this to happen. Is it possibly because lab chiefs are appointed for life and people don't want to give up their position and free up a lab? At NIH, labs are often created for a particular person's interest. And often when they retire, the lab is shut down and another person given a lab named after his or her research interest. I don't know if that's true in NIAID. But I also wonder about what might be called systemic sexism, which is simply not recognized at NIH. Dr. Francis Collins, the NIH Director, has declared that he won't participate any longer in professional sessions unless at least one woman is on a panel. I don't mean to single out Dr. Collins here, but does this actually happen? Are such declarations box checking by administrators who then never make sure that the goal is achieved? This is a huge question, but I want to hear your thoughts about it.

Pierce: Within the federal government, and maybe everywhere, there's a phenomena of covering your rear. If you simply look at the number of women who hold leadership positions at the NIH, I would say that it is far lower than in most academic institutions. I think we have a problem. The NIH responded to this problem with a number of bureaucratic fixes: gender equity initiatives, all sorts of things that you refer to as box checking. But within the government, seldom does anyone go back and verify that the actions they took lead to what they hoped to achieve. To solve a problem, you quantify the problem and you put in place a way to measure it. You want to be able to ask, "Did I change that metric?" And if five years down the road, nothing has changed, you have to try something different or try harder. But we don't see that at the NIH. We really don't. I don't think it's unique to the NIH, but it's easy to ignore the problem that women are not succeeding at the same rate as men. And when somebody, for example, Nancy Hopkins [Dr. Nancy Hopkins] at MIT [Massachusetts Institute of Technology], finally says, "Look. Women at MIT are not being given the resources that men are given." And she went around with her measuring stick and quantified the space that men had versus the space women had, she found a huge inequity. And she held MIT's feet to the fire to fix it. So in any situation of pledging to repair the inequity in resources and status for women in science, you must put things in place to make it happen and then quantify that it has happened.

Harden: I'm sure you've had job offers and enticements to leave NIAID for academic posts, and you have turned them down. This question circles back to your earlier comments, but would you tell me why, with all the constraints of ethics rules and bureaucratic red tape, you have decided to stay at it NIAID? What makes it such an attractive place for your research?

Pierce: I think I did comment on this earlier when I was comparing academic institutions to the NIH. If you don't care about building something across the institute but instead only focus on getting your own work done, having the resources to do it, and having outstanding colleagues to interact with, I don't think there's a better place.

Harden: Those are all the questions I have. Is there any other topic you want to get on the record before we stop?

Pierce: I had a short list and we've covered everything that I have. So I would say I think it's been a good, thorough interview.

Harden: Well, I thank you very much for a wonderful oral history.