This is an oral history with Dr. Franklin Alan Sher on June 17th, 2021, about his career at the National Institute of Allergy and Infectious Diseases (NIAID). The interview is being conducted via Zoom. The interviewer is Dr. Victoria Harden, Founding Director, Emerita, Office of NIH History and Stetten Museum, National Institutes of Health.

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

Sher: Yes. My name is Franklin Alan Sher. I go by the name Alan, most of the time, and I understand that this interview is being recorded.

Harden: Thank you. You were born on the day that President Franklin Roosevelt died, on April 12th, 1945, in Nutley, New Jersey, as the only child of Dr. Seymour Cyrus Schuman, a physical chemist and Dr. Roslyn Lepow Sher, a microbiologist. Would you tell me about your early life through high school and about any family members or teachers who encouraged you towards a career in research?

Sher: I thought I might open with a few words about my parents, because they were obviously a major influence on me. My father was a physical organic chemist. He had just finished working with the Manhattan Project in Manhattan when I was born. It was of course top secret research and he took the train from New Jersey into New York every day with my mom having no idea what work he was doing.

My mother was also a Ph.D. scientist. She was a microbiologist and obtained her degree in the early 1940s when it was still extremely rare for women to pursue doctoral programs but she did. She continued to work in the laboratory at Hoffman La Roche and later the Montefiore Hospital in the Bronx until I was about 6 years old. Although neither she nor my father pushed me toward a career in science, they at least supplied me with the appropriate genes. There is a wonderful photo of my parents as Ph.D students at Penn State (Pennsylvania State University) in the early 1940's that I sent you.

Harden: I was going to ask you about the photograph. Can you tell me who the three people in the photo are? I presume your mother's the woman, in the middle.

Sher: Yes, my mother is in the middle and my father on the left. Standing next to my Mom on her right is her younger brother, my Uncle Lee, who was the real inspiration for my scientific career. Although everyone called him Lee for short, his real name was Irwin Howard Lepow. The photo was taken at State College when Lee was staying with my parents while taking a summer course, I believe. The photo is wonderful in capturing all three of them in the prime of their youth. I later learned that my father had been an enormous influence on Lee that summer. Lee would go on to get both an M.D. and a Ph.D. and later, as Professor of Pathology at Case Western Reserve Medical School, he did classic work on the biochemistry of the

complement system. He later become a co-founder of the University of Connecticut Medical School and its Chair of both Medicine and Pathology and served terms as President of both the American Association of Immunologists and the entire FASEB [Federation of American Societies for Experimental Biology] organization. He was at one time a candidate for Director of the NIAID, the position now held by Tony Fauci [Dr. Anthony S. Fauci].

I should also mention two other scientist family members who served as important professional role models and, interestingly, both of whom were women. The first was Lee's widow, Marty, [Dr. Martha Lipson Lepow] who also recently passed away. She was a well-known pediatric vaccinologist who ran the first trial of the Sabin polio vaccine. The second person, was my mom's cousin and best girlhood friend, Gertrude Belle Elion [Dr. Gertrude Belle Elion], who shared the Nobel Prize for Medicine in 1988 with George Hitchings [Dr. George H. Hitchings]. While "Aunt Trudy" (as we called her) never influenced my decision to go into research, she was a great source of advice and encouragement in my later career. A point I'd like to emphasize is that, probably unlike most people who choose a career in medical research, I came from a hard-core family of successful scientists.

My parents got divorced when I was about three. My mother remarried three years later, and she and I moved to be with her new husband and my adopted new father, Jack Sher [Dr. Jack Edward Sher], an

MD in private general practice. I spent the rest of my childhood with them in the Boston area. Sadly, both my birth father and Lee died early deaths (in their early 50's and 60's respectively). They were heavy smokers and died of cancer- or heart-disease-related illnesses. My uncle, in particular, as a Chairman of Medicine and a distinguished pathologist was in a great position to know the danger, but he just couldn't stop smoking. I also smoked as a young adult but quit and have been fortunate in surviving a great deal longer than either of these two important male figures in my life.

I went to high school at a place called the Boston Latin School, which is in fact the oldest public secondary school in the United States. It was founded in 1635 as a preparatory school for Harvard, and it has a very proud tradition. At the time I attended, it was an all-male school that became co-ed ten years after I graduated.

As a high school student, I rebelled against my family's interest in biomedicine. I really didn't want to have anything to do with it. Maybe it was a bit of insecurity on my part in that I felt that I didn't want to live in their shadows. I was much more interested in humanities. For college, I went to Oberlin College, a small liberal arts school in northern Ohio. I began there as a classics major and was fascinated with classical history and culture. But I decided to take some biology classes because they seemed important to me as part of my liberal arts education.

Like most kids in college, I needed summer work, and I really didn't have any connections to get one except through my family. And so Aunt Marty got me a laboratory job working at the Boston Children's Hospital with one of her collaborators, a man named Fred Rosen [Dr. Fred S. Rosen], a clinical immunologist who became a very important physician-scientist at Harvard Medical School. Indeed, there is a major lecture hall named in his honor there.

At this time, polio was still not completely controlled and my first work in the lab was with Fred (and Marty as collaborator!) measuring maternal antibodies against polio virus in meconium, which is the first bowel movement of the neonate. That was my first exposure to the lab, but I considered it merely as a summer job, not a stepping stone for my future career. This was just a way to "stay out of trouble" and make some money during the summer! But that being said, Fred Rosen and that summer experience in the end had a major influence on me. Fred was an incredibly fascinating and talented man who spoke three or four languages and had major outside interests in literature, opera, history, antique furniture, etc. He showed me that that being a scientist didn't mean that you had to be a laboratory drone and did away with many of my ill-conceived notions of what a life in research meant.

Harden: You also realized that you had a knack for doing this, maybe?

Sher: No, no. I have to say that I've never had that particular realization. Instead, I eventually grasped the excitement of research and was motivated to work hard at it. I have many colleagues whom I consider much more scientifically gifted than myself and I often think that maybe I could have been a better historian. I don't know, but this was the path that I fell into and decided at one point that I wanted to pursue.

I can remember a formative moment connected with this when as a college student I decided to abandon my plans for a career in the humanities. It occurred when I was working on a term paper about Greek lyric poetry. Then as I do today in science writing, I composed a tentative title to focus myself on the topic. I then went to the library at Oberlin, looked through the stacks—as one used to do in those days—and came across a book written in 1898 with exactly the same title as the one that I had written down as subject of my paper! That's when I said, "This is not for me. I don't want to spend my life rediscovering what other people have already done." That was a formative moment. And then I realized that I had taken the biology classes already and would just need to catch up on some chemistry in order to switch into a biology pre-med major, and off I went.

Also, fueled on by my experience as a summer student in Rosen's lab, I applied to both Ph.D. and M.D.-Ph.D. programs, but failed to get accepted in any of the latter so I decided to go the Ph.D. route Many years later, I was giving a seminar at NYU [New York University] Medical

School, which is one of the places that had rejected me for M.D.-Ph.D.admissions. I was walking down the corridor with Victor Nussenzweig [Dr. Victor Nussenzweig], the person who was hosting me, and I told him about my NYU rejection. And he said, "Yeah, there you go. That shows you what a great admissions committee we have." But in reality, I probably didn't have the grades to get in there or my MCAT [Medical College Admissions Test] equivalent exam scores weren't good enough.

The happy ending was that I wound up in a wonderful Ph.D . program at the University of California, San Diego [UCSD]. At that time, it was a brand new campus of the University of California. It was in La Jolla, which was an absolutely beautiful place to live after being in the dreary Midwest for four years. They had just poured tons of money into building UCSD into a science campus, recruiting people like Linus Pauling [Dr. Linus Pauling] and other big names. The biology department was almost brand new and the faculty were all top notch researchers whom they recruited from mostly Midwestern universities (also escaping to California!) so it was a very exciting place to be. I was one of the early grad students there. I believe I was in about the fourth or fifth Ph.D. graduating class in the university.

Harden: I want you to begin by telling me about your graduate education in general. Your mentor was Dr. Melvin Cohn, and I want to know how you

picked your dissertation topic, which is in very basic immunology, and about your dissertation research. Let's do that piece of it.

Sher: One of the really nice things about UCSD at the time and in the biology program was that you could work off campus. The two satellite institutions available then—and they're still there—are the Scripps Research Institute and the Salk Institute. The Salk Institute was also brand new then. It was housed in a beautiful building designed by the famous architect Louis Kahn built right on a cliff overlooking the Pacific. It's a classic piece of modern American architecture. They had just received a heap of funding from the National Foundation for Infantile Paralysis [later name: March of Dimes], and had hired Jonas Salk to be Director. It was a very, very interesting place at the time. I'll go into that in a minute, but let's answer your question about why I chose Mel Cohn as my Ph.D. supervisor.

Cohn, like Fred Rosen, was another important influence on me but in a different way. He was a basic immunologist. He had no clinical interest at all. He was trained as a hardcore molecular biologist and had worked with Nobel laureate Jacques Monod [Dr. Jacques Monod] at the Pasteur Institute on the Lac operon. When he came back to the U.S., he decided that he wanted to focus on understanding the immune system as a biological entity.

As a first year grad student, I did a rotation in his lab. He was such an engaging personality and so dynamic intellectually that I decided to

make the unusual move of leaving the main UCSD campus to work with him. It was just about three quarters of a mile down the road. You can walk it, but I didn't do that often. After my first year of courses, I spent most of my time at the Salk Institute working with Mel. I had been interested in immunology from the get-go because of the influence of my family role model Lee, who as I said was an accomplished immunologist, and also from the work that I did at Children's Hospital with Fred Rosen. I had also read a book that I now like to give to young scientists to tell them about how I got turned on by immunology. It was a book by Sir McFarland Burnet called *The Integrity of the Body* [Cambridge: Harvard University Press, 1962] in which he formulates the major questions about how the immune system functions and in particular how it distinguishes foreign antigens from self. And indeed, Mel Cohn's interest was in these broader basic issues about immunological recognition.

My thesis project focused on the genetics of idiotypes, which are markers on immunoglobulins. By studying the inheritance of them, I was able to glean information about how the constant and variable portions of immunoglobulin molecules are synthesized and the genetic basis of their expression. Nowadays, you would call what I was doing immunochemistry or B-cell immunology, because B cells make antibodies. Mel was famous for assigning people problems that were incredibly difficult, and my initial project was no exception mostly because the tools to answer the questions that he wanted me to answer

hadn’t been invented yet! And thus I floundered for a good three or four years trying to get somewhere with the first question he assigned to me .

At the same time, there was something else important going on in my life and those of my contemporaries, the Vietnam War. I did not want to get drafted and be sent to Vietnam. The longer I stayed in graduate school, I could escape being drafted—that is, until the draft lottery was instituted. Depending on what lottery number your birthday was associated with, you might either be called up immediately or would likely never be called. There was one very stressful evening when I watched the lottery drawings on TV and fortunately, I “won” it. I mean, my birthday was beyond the cut off date for being drafted. At first, there was a deferment for graduate students. But as the war raged on and more and more people were being sent to Vietnam to fight, there was pressure even to bring in people who were working on Ph.D.s in graduate programs. I had friends my age who actually escaped and went to Canada during that time to avoid serving in Vietnam.

Harden: I remember this well. You were not married and didn't have a family at that time, so you couldn't claim that deferment.

Sher: Yes. That was factor number one. Factor number two was that I really enjoyed being at the Salk Institute, even though I was struggling with my project. The Salk Institute was an amazing place. It was more than just a scientific research institute. There were people interested in both arts and

science and addressing fundamental questions like the origin of life. The Institute was like a think tank with a broad cultural atmosphere. The Salk had a board of directors that included many of the leaders in modern biological science at the time. Francis Crick [Dr. Francis Crick], Jim Watson [Dr. James D. Watson], Salva Luria [Dr. Salvador E. Luria]—people like that would come for board meetings and we'd get invited to go out to dinner with them. As one of the few graduate students, I got to meet a lot of these important figures. It was a very exciting place and time, despite my two problems of having the war hanging over me and my project not really taking off for the first few years.

Finally, my thesis project began to come together. I had to convince Mel that there was no way I was going to win a Nobel Prize for him and that I needed to write a Ph.D. thesis. And so I finished with the project I described to you previously and had a memorable experience on the day of my doctoral defense. Mel was being visited by a very famous immunologist, Elvin Kabat [Dr. Elvin A. Kabat]. Kabat was one of the founders of immunochemistry. And so on the morning of my defense Mel walked down the hall to my desk and said, "You know what? I've invited Elvin to come along to your Ph.D. defense." I should mention that I had actually had a collaboration and publication with Elvin Kabat, but had never really met him. I just provided some of the data.

Harden: No pressure.

Sher: That situation would be scary normally, but I have to tell you that Kabat was known as a tough customer who was very aggressive in criticizing other scientists. I wasn't aware of this at the that time, but I learned it later. There he was sitting in my Ph.D. defense, and he did ask a couple of questions, but he didn't shoot me down, and I was most grateful for that. I survived!

Harden: In a 1991 article about coming into the field of parasitology from another discipline, you wrote about how your group of students and postdocs at the Salk Institute wanted to do something relevant to medicine with their knowledge of basic immunology. Would you tell me that story?

Sher: Yes, but before I do I need to talk about my involvement in the anti-war movement in San Diego. That was one of the reasons that I didn't do much in the lab the first year of my project. I spent most of that period doing what at that time was referred to as radical politics. There was a grass roots movement on the west coast called the Peace and Freedom Party that I became actively involved with. This was an anti-Vietnam war party that was linked to the civil rights movement and, somewhat unfortunately, also with the Black Panthers. I worked on getting this party on the ballot in the state of California, and somehow, I managed, as a 22, 23 year old kid, to become the state election committee representative for the party for all of San Diego County. The movement was centered in the Bay Area, and we were the people in the sticks of conservative San Diego

(then known as a U.S. Navy town). I would go up to San Francisco to attend their state-wide meetings.

I spent about a year and a half working with the party, and then there was a big split between the civil rights and the Vietnam War peace movement advocates amongst the membership. The civil rights people became very aggressive, particularly those involved with the Panthers, who, as you may recall, advocated violence as a solution and wanted to release every black person incarcerated in prison. That was actually part of their written platform. You can imagine the problem. We were trying to get an anti-war ballot on the ticket in the national elections and knew that it would be impossible to get the white majority (and particularly those in San Diego County) to agree to something like releasing all black prisoners from jail. This split and its aftermath left me disillusioned with radical politics but also with a sustained feeling that I really needed to do something in my life beyond a purely intellectual pursuit of basic science.

Therein lies the background story of the article that you are referring to. We had formed a little group of like-minded young scientists at the Salk Institute to discuss the areas on which to focus our scientific careers—like cancer or virology, or other forms of human health oriented medical research. This was also the time that Surgeon General William H. Stewart was quoted as saying that the war on infectious diseases was over. He talked about the fact that we now had effective antibiotics, and vaccines for polio, smallpox, and many bacterial diseases. Thus, there was

no longer a need for a big effort on preventing and treating infectious disease. It was time instead to focus on cancer and other medical challenges. In fact, if one goes back and looks carefully at his remarks, he really didn't say this, but everyone likes to attribute these words to him nevertheless. Anyway, it turns out that there was one glaring exception to this generalization. And this was that in the case of parasitic infections, we still had no vaccines and only poorly effective therapeutics. What also attracted our interest was that parasitic disease was (and still is) largely a problem of under-resourced countries and was thus very much a humanitarian issue.

Realizing this four of us ("The Salk Institute Four") decided to go into parasitic disease research with the goal of trying to make a difference in this largely neglected field. We all began by reading up on parasitology in our spare time and were drawn to a particular helminth induced disease called schistosomiasis. My colleagues in this venture were Donato Cioli [Dr. Donato Cioli], who established a schistosome research group in the Institute of Cell Biology and Neurobiology of the National Research Council in Rome, Italy; the late Paul Knopf [Dr. Paul Knopf], who set up a lab working on the immunology of schistosomiasis at Brown University; and Italo Caesari [Dr. Italo Caesari], who set up a schistosome biochemistry laboratory at the Venezuelan Institute of Scientific Investigation in Caracas. I have provided you with a wonderful photo of

the 4 of us on Lake Como at a Rockefeller Foundation sponsored meeting in the early 1970's.

I also chose to pursue this field for my postdoctoral work. The Brits and the Aussies were the most accomplished parasitologists in those days. I decided to seek training at probably the most famous, and at that time certainly one of the top two schistosomiasis labs in the world, located in London at the Division of Parasitology of the National Institute for Medical Research at Mill Hill.

Harden: Before we talk about your work in London, would you be kind enough to describe in general terms, for any reader of this oral history who doesn't know, just what schistosomiasis is and why it's harder for medicine to address than some other infectious diseases.

Sher: Schistosomiasis is a parasitic disease. It's transmitted by contact with fresh water. The parasite gets into the water from aquatic snails that serve as its intermediate hosts. The parasite penetrates the skin of humans bathing or working in infected water and develops into adult worms that reside in the vasculature, shed eggs that deposit in tissues causing tissue pathology. There are three major species of the parasite. The one that I worked on, as well as most immunologists, is *Schistosoma mansoni.* There were no vaccines to prevent schistosome infection. Indeed, at that time as I mentioned already, there were no vaccines for any parasitic agent.

Harden: When you went off to London, what were you hoping to do and learn?

Sher: Because I was an immunologist, I was familiar with immunologic approaches and techniques, and there were not many immunologists in the field of parasitology at that time. For a little bit of additional background, when I announced my postdoctoral plan to Mel Cohn, he was quite upset. He had his own vision for me. He wanted me to go to work either with Jacques Monod in Paris or to the lab of Manfred Eigen [Dr. Manfred Eigen], a physical chemist in Germany, who like Monod, was a Nobel laureate. So when I said that I was going to work in the field of parasitology, he warned me, "You're going to commit professional suicide." That's what he told me, because parasitology was a scientific backwater at that time and certainly not an area where state-of-the art biomedical research was being done.

This didn't annoy me too much at the time, but it did bother me that Mel was upset with me for following this path. Nevertheless, it turned out to be a brilliant career move for me and an absolutely superb decision because I'm convinced that if I had stayed in purely basic immunology, I probably would not have gotten where I am today. It was almost as if I had correctly read the tea leaves. The Surgeon General's alleged thinking about the major infectious diseases now being controlled had many believers but you clearly could not make this statement about parasitic infections—they were the "Great Neglected Diseases" of that era. Consequently, the NIAID and a number of private foundations decided to increase their support of parasitic disease research both because it

remained an important challenge and because of its major impact on the health and economic development of third-world countries. Of course, looking back, the concept that this was the last remaining battlefront in the war on infectious disease was incredibly short-sighted. Within a decade HIV was on the scene as a brutal reminder. Nevertheless, back in the early 1970's there was a growing interest in parasitic infection as a last frontier, and this is the training path that I decided to follow in my postdoc in London.

Harden: What did you learn there?

Sher: I learned to how to work with the parasite. Also, the MRC [Medical Research Council] institute at Mill Hill was a very good immunology research center as well. I kept my fingers in immunology while I learned how to work with the organism, and I produced some studies that are still read, even today.

Harden: Were there particular people there who mentored you?

Sher: My boss and mentor there was Ron Smithers [Dr. S. R. Smithers], who passed away, sadly--about a year ago—and was a wonderful man. He was not a remarkably innovative scientist but nevertheless was a world expert on what little was known about immunity to schistosomiasis in the 1970's and was very supportive of me and my career. He'd never had an American in his lab before, so I presented both a novelty a new challenge

for him! I was very fond of him as a well-meaning mentor and friend and stayed in touch with him all the way to the year of his death.

Harden: Were there were other people with whom you interacted?

Sher: Another immunologist with whom I interacted in particular, during my postdoc was a young investigator by the name of Bridget Ogilvie [now Dame Bridget M. Ogilvie]. She was very interested in the fundamental immunology of the host-parasite relationship, so she and I would talk all the time. Perceptively, she was one of the first scientists to see the immunologic parallels between the response to helminths and the allergic response. She later went on to become the Director of the Wellcome Trust, which she led for many years and was immensely encouraging and supportive of my career in this field.

Although I was only there for two and a half years, I thoroughly enjoyed my UK experience and was able to end this with a several months visit to an endemic country, Kenya, to study schistosomiasis there. Working with a colleague from Cambridge University, Anthony Butterworth [Dr. Anthony Butterworth, FRS], I had my first encounters with diseased patients as well as human immunology, a type of exposure that I believe is so important for young Ph.D.s in the infectious disease field with no previous contact with the problem they are studying.

Nevertheless, I missed being away from the US. I had looked at several junior faculty positions back in California but they had little

connection with parasitology and instead accepted a job offer as a research associate in the lab of a schistosomiasis expert at Harvard Medical School in Boston.

Harden: Before we go to Harvard, let me step sideways. I think it perhaps important to get on the record, if I understand it correctly, that your work at Mill Hill was funded by NIH as a postdoctoral fellowship.

Sher: Yes, indeed, I was grateful to be funded in the U.K. by an NIH postdoctoral fellowship, and that presented an interesting situation. My postdoc stipend was about $5,500 a year, and it turns out that I was making just a little bit less than my boss, Ron Smithers, who was the chairman of the department. Salaries for British academics were still depressed because of economic hard times after World War II. Americans lived well in London in those days. I lived in a very nice flat in Hampstead and would go out to dinner and to the theater all the time. Hard to believe, but as a 26 year old NIH postdoctoral fellowship recipient, I was living high on the hog!

Harden: Also while you were at Mill Hill, you had a summer position at the Wellcome Trust Research Laboratory, Nairobi, Kenya. Were you still under the NIH postdoc, or were you funded by the Wellcome Trust?

Sher: I don't remember for sure, but I believe it was paid by the Wellcome Trust. The lab itself was a Wellcome Trust lab, so that would make sense. My

time in Kenya was a very exciting experience for me, and spurred an interest in developing international projects as a component of my research effort. Years later, I was able to return to Kenya as a scientific advisory board member for the International Laboratory for Research on Animal Diseases (ILRAD).

Harden: All right, back to Harvard. You got the job offer.

Sher: I got to Harvard and I worked there with a senior professor, Franz von Lichtenberg [Dr. Franz von Lichtenberg], a well-known pathologist who was an expert on the host tissue responses underlying schistosomiasis. He had a very small lab, but he still said to me: "Look, you come, and you can share my lab and we'll do some things together. I know you're not really that much interested now in what I do, but we'll work out a synthesis." Franz gave me my first real appreciation of pathogenesis as a subject. He was also a clinical pathologist examining biopsy and autopsy specimens at the Peter Bent Brigham [Peter Bent Brigham Hospital, now a part of Brigham and Women's Hospital in Boston]. But he had this major interest in schistosomiasis as well and really understood the human disease. Franz gave me the freedom and support to produce my first high profile publication in the field (*Nature*, 1976) but I felt stuck and isolated in his little lab.

I actually had a joint appointment in the Harvard Medical School Pathology department, which at the time was a great center of basic

immunology headed by Nobel Laureate Baruj Bennaceraf [Dr. Baruj Bennaceraf], and this was one of the reasons I had decided to go there. I would attend their seminars but the people in the central department (including Bennaceraf) had no real interest in the disease oriented work I was doing or in collaborating with me at that stage. My contemporary there, and still good friend, was Ron Germain [Dr. Ronald Germain]. He's a lab chief here at NIAID and now a world famous immunologist.

Harden: Was it unusual for a Ph.D. immunologist to work in the pathology department?

Sher: No, in fact the major department doing immunology in the medical school was the pathology department. In the Harvard system, as at many other places, you have clinical departments, and you have basic departments. As someone working in pathology at the Peter Bent Brigham, I had an automatic co-appointment in the academic pathology department, but as I said, this didn't seem to be of much help to me.

To tell the truth, I did not like being at Harvard. I was back in Boston and could actually see my high school (Boston Latin) from my lab window. But I really didn't like the hypercompetitive atmosphere. It was a time when a big-name professor would hire two assistant professors and put them to work on the same project. Only the one who succeeded got his (there were few "hers") appointment extended.

Harden: Wow.

Sher: It was that kind of stressful environment, particularly for young researchers in my situation at the bottom of the totem pole.

Harden: When you got a faculty appointment and moved into your own lab at Harvard was that better?

Sher: Yes, it definitely improved. What happened was this. As I previously told you, during that time the problem of parasitic disease was emerging into the limelight and attracting funding. One of the professors at Harvard, John David [Dr. John R. David], had decided that he wanted to move part of his research program into studies on the immune response to parasitic infection. This was in part due to his fascination as an immunologist with the host-parasite interaction but also because of the new funding opportunities for this kind of research. He needed someone to help launch this new effort, and there I was, sitting unhappy in von Lichtenberg's lab and looking for a better environment. So John and I talked to von Lichtenberg, and John offered me a job as an Assistant Professor in his Harvard Division which was then affiliated with Robert Breck Brigham Hospital. This gave me my own first lab. I liked John a lot. He was a very different personality than von Lichtenberg and an immunologist, not a pathologist. I really don't want to say anything demeaning about von Lichtenberg, as he was a fine person and did everything he could for me. He just couldn't provide me with the right atmosphere to grow in.

Working with John David, I had this wonderful opportunity to be present at the start of a brand new program in my field, which later expanded with the addition of three or four other PIs [Principal Investigators] working on different aspects of parasitology. This made it very exciting, and the immune response was our major focus.

John is really a great guy and was genuinely excited about entering this new line of research. His wife, Roberta [Roberta Detulis David], who worked with him, unfortunately passed away several years ago. She ran the lab for him and helped me navigate all sorts of problems that came up with grants, personnel, lab resources etc. As a group we had a lot of fun, too. We'd go on departmental canoe trips up in Maine and traveled together internationally to meetings and locations (e.g. Brazil) where we had field programs. John, now a widower in his 80's stays in regular touch with all of us from that time.

While I was in John's Division, I received a career development award from the Rockefeller Foundation, in a program called "The Great Neglected Diseases of Mankind." It was run by a man named Ken Warren [Dr. Kenneth Warren], who had been a professor at Case Western Reserve University School of Medicine. In this grant program he had assembled top-named scientists in their fields (but mostly immunologists) to work on parasite-related problems. For me, this program was wonderful, because I got to meet and interact with well-known immunologists from around the world. They were diving into and learning about parasitic infections, and I

was one of the few young investigators at that time with dual training in basic immunology and parasitology. It was exciting and a boom time for this research, much like COVID-19 research is today.

Harden: In addition to the Rockefeller Foundation award, you had four different research grants from the Edna McConnell Clark Foundation. I'd like to know more about that foundation. And you also had an R01 grant from NIAID. Tell me about these other grants.

Sher: The Edna McConnell Clark Foundation was a small non-profit that created a program for funding work on schistosomiasis. Eventually, they broadened their scope to include a few other tropical diseases. Because of my background and training in schistosomiasis, it was easy for me to obtain their support. The person who ran it is a wonderful man and a renowned schistosomiasis clinician himself, Joseph Cook [Dr. Joseph A. Cook]. I received several rounds of funding from them during this period. I had also applied for a NIAID career development award but didn't score high enough. Nevertheless, in its generosity, the NIH gave me an R01 grant as a consolation prize! So all of this was going quite well.

I should add another very important thing that was going on in my life at this time. This was the beginning of an important professional and later personal relationship with my future wife, Stephanie James [Dr. Stephanie L. James]. Stephanie was one of my first postdocs. She was trained by Daniel Colley [Dr. Daniel G. Colley], one of the U.S. leaders in

schistosome immunology at the time. She brought with her a strong interest in cellular immunity, and she quickly converted me to her cause, transforming our research, which previously had been largely focused on antibody dependent humoral responses against parasites, to studying the role of macrophages and T lymphocytes. In this regard she played a major formative role in building the foundation of our lab's research both at Harvard and later at NIH.

Another important influence in my new lab was the late Tereza Kipnis [Dr. Tereza L. Kipnis], a parasite immunologist on sabbatical from Brazil. There was and still is a lot of parasitic disease in that country. Tereza worked on a major protozoan infection of that country, Chagas disease (caused by *Trypanosoma cruzi*), which she introduced as a research topic to our lab. Perhaps more importantly, Tereza encouraged what was to become for me a career long interest in Brazil and Brazilian science. Over the years my lab has trained 9 Brazilian postdocs, two of whom now hold leadership positions in the Brazilian research community, and I was greatly honored to be elected to the Brazilian Academy of Sciences later in my career.

Everything was going well for me on the surface, but the stress of surviving on soft money in a fiercely competitive institution was getting to me. And although John and Roberta David were extremely supportive, I was spending an enormous amount of time and effort writing grant proposals to help fund the department as well as my own research program

and struggling to find time to produce the work that I needed to climb the steep tenure ladder at Harvard. It was my Uncle Lee, the immunologist, who pointed me toward NIH as a place I might like better. In 1975, he had applied for the directorship of NIAID, a position eventually awarded to Dick Krause [Dr. Richard M. Krause], Tony Fauci's predecessor. Uncle Lee had learned a lot about the intramural NIAID research program over the years from serving on advisory panels, and he was familiar with the work of the Laboratory of Parasitic Diseases (LPD). He knew I was stressed and unhappy at Harvard, and said, "I think you'd really enjoy working at the NIH instead."

Harden: Frank Neva [Dr. Franklin Neva], who was LPD Chief at this time, had come to the NIH from Harvard, but he arrived while you were still in graduate school. So you didn't know him as a colleague at Harvard. Did he come up to Harvard to recruit you?

Sher: I knew he was from Harvard, and I also knew that he had left because he, too, had grown unhappy there. In fact, his wife Alice [Alice Hanson Neva] once took me aside and filled in the details for me. So we had that in common. But interestingly, the one NIAID person whom I did know while I was at Harvard was Ted Nash [Dr. Theodore E. Nash]. He had come to Harvard from NIH on a fellowship and was also interested in schistosomiasis. Ted was probably the person who first told Frank about me, although Frank may have heard from Lee also. I had also met Louis

Miller [Dr. Louis H. Miller] at a meeting and was excited about the strong malaria program he was building in Frank's department. The LPD had an open position and were interviewing all sorts of people for this job trying to decide whether they wanted a biochemist or an immunologist. Eventually they settled on me and I was fortunate to become an NIH investigator!

When I took the NIAID job, people at Harvard came up to me and, said (once again as they had at Salk when I decided to go into parasitology), "You're committing professional suicide. You'll disappear down there. It's just such a pedestrian place, the NIH. Here you can work in the most famous medical school in the U.S. and become a Harvard professor." Parenthetically, while I was at Harvard, the technicians went on strike for better wages and their motto was, "You can't eat prestige." And that's the way I felt, too. To me the prestige had become an intangible. I was looking for a place where I could pursue my work in a stable and collegial environment, so, I was absolutely delighted to join the NIAID Laboratory of Parasitic Diseases and to work under Frank Neva, who was truly one of the last of the gentleman scientists and was instrumental in building my career here. On one occasion during my recruitment, I flew down from Boston and Frank invited me to have dinner at his house to meet his family. This was the kind of warm-hearted open person he was.

Harden: Tell me about LPD, in general, when you first arrived. Who was here? What building did you work in? What sort of resources did you have? All of that.

Sher: When I arrived, my lab was in Building 5. (Actually, I can now walk across the NIH campus and see every building that I worked in—all four of them). They gave me one little module in Building 5, but I had been promised a lot more. This became a source of some tension because I had already started to recruit my group, and here I was, stuck in this one little room right across from the Scientific Director's office[*] At the time, the SD was a man named Ken Sell [Dr. Kenneth W. Sell], who was a kind of a controversial character. He had been hired by the NIAID director Dick Krause. Krause was the distinguished scientist and gentleman and Ken Sell was thought of as his tough guy administrator. I got along okay with them both—that that wasn't an issue—but I really didn't have the resources originally promised me. Stephanie came with me on her own WHO [World Health Organization] funding, and I was able to hire my first technician, Sara Hieny [Sara Hieny], someone that Stephanie had worked with when she was at Vanderbilt and who stayed with our lab for many years. I also hired another parasite immunologist, David Sacks [Dr. David L. Sacks]. David had been at Harvard when I was there. Then he went off to Mill Hill and did a postdoc, with basically the same group of

[*] At NIH, the terms "Scientific Director" and "Director of Intramural Research" are usually used interchangeably.

immunologists with whom I had worked, so he and I had that connection. I had invited David to work with me when he came back from Mill Hill, but he thought that he was going to be at Harvard. He was disappointed that I had moved because he was a Bostonian, and his family was there. He loves New England and still has a place on Martha's Vineyard. Although I felt bad about dragging him down to Bethesda with me, it turned out to be a great opportunity for him too. (You'll be interviewing him, I'm sure, one of these days!) I also hired another postdoc from Mill Hill, Dr. Andrew (Andy) J. Simpson, who was Ron Smither's golden boy at the time. Andy brought molecular biology expertise to the lab and later became a highly successful biopharma founder in Brazil. We were all stuffed into this little module in the corner of Building 5, where our desks nearly merged with the lab bench!

Lou Miller was across the parking lot in another building and had his own semi-independent group. Lou was the LPD's ambitious super star at the time. He was not that involved with the rest of Frank's program. But on the other hand, Lou was the guy who was delivering the major scientific goods, in malaria, and malaria was and still is the most important parasitic disease in terms of mortality. So Lou deserved his resources, and I was just the new kid on the block. But everyone said to me, "If Frank promised you these resources, you're going to get them." And I did. Frank had to kick some people out to do it, which was, I'm sure, very painful for him. But there were a lot of old timers hanging around, and he managed to

ease them out, in as gentle a way as he could, to create both the resources promised to me as well as room to expand.

Harden: I think that's what he was hired to do.

Sher: Research on parasitic disease at the NIH goes way, way back, almost to the institution's beginning. I always liked to stress this when I later addressed the Board of Scientific Counselors [BSC] as lab chief. The LPD is one of the oldest labs at the NIH, and it has a proud history. By the time I arrived, there was a lot of dead wood in the lab, and we younger scientists used to make fun of them for their waning contributions to the department and the field. This left a big impression on me and is actually one of my reasons for considering retirement. I don't want to end up in the same situation!

You asked who was there when I arrived. Of the people who are still around or recently retired, certainly Lou and Ted Nash were there. There were also people like the late Allen Cheever [Dr. Allen W. Cheever], a pathologist and the deputy lab chief. He did a lot of work with us over the years. I really miss the guy. He was a real salty character, and also came originally from Harvard. I think most of the other PI's have passed away or retired. Frank Neva stayed on with us until his retirement and we were sad to lose him a decade ago.

I have to tell you that, within a year of moving down to the NIH I was happy as a clam and really enjoyed being here. I particularly enjoyed

working under Frank, who was low pressure. The scientific environment at NIAID was great, and the LPD offered many opportunities for collaboration in the field. Frank had built the department to broadly cover the field of human parasitic diseases, and there were investigators working on nearly all of them. Instead of only working on schistosomiasis, I picked up two or three other diseases that I was able to build my research program with. I did this first with David Sacks and soon after him, with another amazing postdoc, Phil Scott [Dr. Phillip Scott], who's now the Vice Dean of the University of Pennsylvania Veterinary School and a great colleague. With David and Phil, I built a really strong *Leishmaniasis* immunology research program. With help from Frank and another investigator, Jim Dvorak [Dr. James A. Dvorak], I was also able to resume and expand my work on *Trypanosoma cruzi*, contributing another publication to *Nature*. I was able to do this because there were experts all around me. Having been hired with tenure (there was no formal tenure track in those days) I was also grateful for the security of a civil service position and, of course, being freed from obligatory grant writing.

Harden: Did you have any collaborations with any of the clinical people who had patients with these diseases in the Clinical Center?

Sher: At that stage, no. Collaborations were certainly offered to me because Frank was a clinician primarily, but he never pushed me in that direction. I've found over the years—and actually Lou Miller, I believe, had the

same philosophy, which maybe Lou picked it up from Frank—that a good leader finds out what people are good at and lets them do that thing. You shouldn't try to push them into things that they can't handle.

Harden: Before we get into your research, I want to ask you one more thing. The *NIH Record* article that reported your hiring said that you were to head the Cell Biology and Immunology Section. In 1995, the name of your section changed to the Immunobiology Section. What prompted the change?

Sher: When I was hired, the section was called Cell Biology and Immunology because I was given an existing section. The section originally consisted of myself, Dennis Dwyer [Dr. Dennis M. Dwyer], who was a *Leishmania* cell biologist, and another, older investigator whom Frank coaxed into retirement. Frank created the section name so that the other people could be incorporated. Dennis Dwyer remained in the section with us for some time and retired about eight years ago. When Lou Miller took over as lab chief, Dennis Dwyer was separated off, and I asked that the section name be changed to "Immunobiology," which more accurately reflected what we were doing.

When I began at NIAID, my postdoc David Sacks emerged almost immediately as a highly successful researcher. Frank, who was also interested in *Leishmaniasis* and collaborated with David, was particularly impressed and pushed his promotion. As I mentioned, there was no formal tenure track then. I was hired as a tenured investigator and David

eventually got a similar deal, except that his promotion had to go through a committee. He's younger than me by about four or five years, but he's someone who's been at NIH since I've been here and has done elegant front-line work on the *Leishmania* host-parasite interface.

So David was promoted, and he remained part of my section for a while. And then, in the late 90's Frank stepped down as lab chief, and Lou Miller took over, abolishing all of the previous sections. This effectively was a demotion for me and for the first and only time I considered leaving the NIH and actually looked at another job back in La Jolla at the La Jolla Institute of Immunology. At that point I appealed to Tony Fauci, who by then was NIAID Director, and Tony supported me. I was given more resources to compensate for the loss of my section and Lou Miller made me a kind of informal deputy for the non-malaria portion of LPD.

Harden: That's interesting.

Sher: Eventually Lou decided that he didn't want the responsibility of being Chief for the non-malaria researchers in the LPD. He stepped down to build a new department, the Malaria Vaccine Development Branch—but now I am getting way, way ahead of myself.

Harden: Yes, we've jumped ahead 20 years here. I want to drop back to the 1980s and talk about your research. The drug, praziquantel was found in the '80s to be an effective therapy for schistosomiasis. It replaced the older therapy, antimony potassium tartrate. But because people treated with

either drug regularly became reinfected, my understanding is that your goal, as an immunologist working on this, was developing a vaccine so people would not become infected in the first place. Am I correct here?

Sher: Absolutely correct. And that was the logic from the get-go. A vaccine would have been a great solution for preventing schistosomiasis. But when I arrived at LPD, I began to drift away from that goal. Stephanie and I worked on it for a time with some of our other postdocs, and her studies led to the identification of two vaccine candidates, paramyosin and calpain, the latter having been taken up by another group and currently in clinical trials.

Its important to note here that around this time in the early eighties, Stephanie and I married. Frank Neva and the NIAID leadership did not approve of our working as a husband-wife team.

Harden: There had been other husband-wife teams at NIH, of course. I'm thinking of Earl and Thressa Stadtman, Marshall and Perola Nirenberg.

Sher: Well, at the time, it was frowned upon. Frank didn't want to give Stephanie an independent scientific position. Though an inveterate gentleman, he didn't consider the promotion of women in science a priority for the department. There was only one tenured woman in the LPD who had been hired by his predecessor, and she, I'm sorry to say, had "checked out" by that time. They had shoved her into one little lab module, and her work was of no interest to anyone else in the LPD. Frank

struggled to get rid of her and eventually coaxed her into retirement. There were no other female investigators in the department and Frank didn't want to consider Stephanie as a hire in part because of her marriage to me—one of his other tenured scientists. This was way before diversity and gender equity became recognized issues at NIH.

Harden: So what did your wife do?

Sher: Needless to say we were both deeply upset by this. Stephanie wound up moving to the Microbiology Department at George Washington University Medical School, where she ran her own lab for a number of years with her own funding and was able to continue to scientifically collaborate with our group. However, the research environment there was not particularly stimulating, and she had to commute downtown from our home in Potomac. The demands on her got worse when our first child, Lauren [Lauren Rebekah (Sher) McGuiness] was born in 1985 and for a while she would bring Lauren to work, camping her out in her office. Her technicians, Judy Glaven [Dr. Judith Glaven] and Lisa Desblois [Lisa Desblois], would look after Lauren while Stephanie was doing experiments in the animal room. Stephanie and I are proud to note that from this humble beginning, Judy has risen to be one of the seven senior scientific officers that direct the Howard Hughes Medical Institute.

Harden: You had two daughters, Lauren in 1985 and Alison [Alison Lea Sher] 1987, so you had a lot of childcare to deal with along with your work. I

wanted to ask you about how you dealt with what today is called work-life balance.

Sher: I'm afraid not well at all, and truly I regret than I didn't help more with our childcare situation, particularly when they were babies. Eventually, we found a wonderful daytime Brazilian nanny who helped considerably. Nevertheless, Stephanie did not enjoy the scientific environment at GW at that period, and eventually the demands on her as junior faculty member in a soft money position (writing grants, teaching) as well as primary responsibility for care of our two young daughters led her to accept a position in the NIAID extramural Division of Microbiology and Infectious Diseases, where she could keep more regular hours. There she quickly climbed the ladder and was promoted to Chief of the Parasitology and International Programs Branch by Drs. Lamontagne [Dr. John R. Lamontagne] and Fauci. Her contributions to research in this area were well recognized by the constituent community, and during this period she was elected as President of the American Society of Tropical Medicine and Hygiene. Later in 2001, she moved to the Ellison Medical Foundation, where she served as Foundation Deputy Director and Director of its new Global Infectious Disease Program. There were hopes that Larry Ellison [Lawrence J. Ellison] would establish an organization similar to The Bill and Melinda Gates Foundation [BMGF], but the Ellison Medical Foundation never achieved anywhere near the financial support that Gates

put into his foundation. Stephanie ran her program successfully there for a number of years before being recruited to the Foundation for the National Institutes of Health [FNIH] to help establish the Grand Challenges in Global Health initiative, a major Gates-funded program exploring how cutting edge science could be applied to health problems of the developing world. She became director of that initiative and several spin-offs at FNIH and held the title Senior Vice President for Science until about nine months ago, when she semi-retired. Stephanie remains there now in the position of Senior Scientific Advisor. She's had a very successful career in research administration and has had the opportunity to contribute scientifically to several of the international global health programs she oversees as well as to develop her own projects. A lot of her work (along with her salary) has been funded by the Gates Foundation, the FNIH being a major partner for the funding of NIH projects by Gates and other non-profits.

Harden: That's interesting. I have just learned something!

Sher: Let's wind it way back to your question about my schistosomiasis research. Despite the loss of Stephanie as a collaborator, by the late 1980s, I had mentored some very good postdocs who were producing important work and like her went on to be leaders in the schistosome immunology field. The first was Edward Pearce [Dr. Edward J. Pearce], a Welshman also trained at Mill Hill, who is currently Bloomberg Distinguished

Professor at Johns Hopkins School of Public Health and now a world leader in the field of immunometabolism. Another was Tom Wynn [Dr. Thomas A. Wynn], who focused on pathogenic mechanisms in schistosomiasis and in particular those responsible for tissue fibrosis. While a postdoc in the lab, he produced an exciting study (again in *Nature*) on the use on Interleukin-12 to protect against this harmful response. More about Tom (now a vice president for research at Pfizer) later, but when he became an independent investigator and took his schistosomiasis projects with him, I was already heavily invested in work on other parasitic pathogens and the study of basic immune mechanisms they stimulate and protect against them. What had most excited me in the 1980s was the important work by Phil Scott, whom I mentioned above, on the role of T lymphocyte subsets in the outcome of *Leishmania* infection.

Prior to that time T cells were known to consist of two major types CD4 and CD8. My colleague Bob Coffman [Dr. Robert L. Coffman], who had been a fellow grad student during my time in the Cohn lab, and Tim Mosmann [Dr. Tim R. Mosmann], working at DNAX in Palo Alto, showed that CD4+T cells actually could be further divided into two additional subsets Th1 and Th2 based on their cytokine secretion patterns. They further showed that each had distinct functions in the immune response. Using a *Leishmania* infection model, Phil, Bob, and I showed in a paper published in the *Journal of Experimental Medicine* in 1989 that Th1 cells protect against the infection while Th2 responses actually make

the infection worse. This was one of the first demonstrations that these two CD4 subsets can stimulate different disease outcomes and led our lab into a major pursuit of how the cytokines associated with these two subsets regulate host resistance and pathology in a variety of different infection models.

Harden: Wow.

Sher: Well, the irony of this was that having sworn off basic immunology at the conclusion of my Ph.D work, I was now back in the thick of it, but this time utilizing important human disease models as the context for our work. So I got back into immunology, and of course, the NIH had a wonderful immunology environment to support and stimulate me. Here I am particularly grateful to the late Bill Paul [Dr. William E. Paul], the former chief of the NIAID Laboratory of Immunology, for his encouragement and intellectual support of these efforts.

But then a new research area appeared on the scene to further draw in my interest and involvement: HIV/AIDS [Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome]. At that time, just as today with COVID-19, HIV became a major challenge for infectious disease immunologists. Stimulated by the new funding generated to tackle this important new epidemic, many of us developed AIDS related projects It was suggested to me, probably first by Frank Neva, that I if I was going to get involved in HIV/AIDS, I should study a parasite that causes

opportunistic infection in AIDS patients, and at that time the most important and deadly was *Toxoplasma gondii* ("toxo"). This protozoan became the main focus of our AIDS-related research. I should say, however, that the history of toxoplasmosis as an important opportunistic infection during the AIDS epidemic was very brief. It was causing encephalitis and killing many HIV-infected individuals in the early gay men's cohorts in San Francisco and other populations. But, once physicians recognized toxo infection in CT [Computed Tomography] scans of the brain and in autopsy material, they were able to both treat and prevent the disease with known anti-parasitic agents. If you remember back to those days, AIDS patients took a pile of pills every day. One of them was for toxo and that drug prevented both new infection and more importantly latent *T. gondii* infection from re-activating.

That being said, it was still important to study *T. gondii* as a stimulus of other forms of disease, and toxo infection of mice as an immunologic model of host-pathogen encounter, which it remains today for many labs in addition to my own. Its host-parasite relationship is quite fascinating, and some of the most sophisticated work in parasitology is done with *Toxoplasma*, which is a close relative of the plasmodia that cause malaria. There are a lot of the things you can't do with malaria that you can do with toxo. The work on this bug took off rapidly in the lab and has been our main parasitology interest now for over 15 years. I had by then acquired an outstanding Staff Scientist, Dragana Jankovic [Dr.

Dragana Lj. Jankovic], who's an exceptionally talented immunologist, and who has been an enormous asset to our program. She too became enamored with the toxo model, and currently leads our research in this area.

Let's do some campus geography. I started out in 1980 in Building 5, in that one little module I mentioned, and later (around 1987, I believe) moved to Building 4. Then, around 2000, I decided that I wanted to work on tuberculosis [TB] which precipitated another work location change.

Harden: Can you hold up for a while? I want to drop back to 1992. I do have TB down to get back to, so I won't forget. But in 1992, the *NIH Record* published a major article on your group. Big photograph, everything. You were working on the understanding of cytokines as the trigger of nitric oxide produced by macrophages. Would you tell me about this work?

Sher: Yes. I don't remember the article exactly, but thanks for flagging it, because a large part of our work in this period became focused on cytokines. They're chemicals produced by leukocytes that mediate all sorts processes both within and without the immune system.

Harden: Interleukin 12 [IL 12] in particular.

Sher: I became heavily involved in that particular cytokine. I even co-organized a meeting on it here the NIH. I had a wonderful collaborator Giorgio Trinchieri [Dr. Giorgio Trinchieri] who now runs the cancer inflammation

program at NCI [National Cancer Institute], who had discovered IL-12 while working at the Wistar Institute. We showed that resistance to *Toxoplasma*, and later other intracellular pathogens, was dependent on IL-12. If you didn't have IL-12, you couldn't develop immunity to those infectious agents. We further showed along with other groups that this happens, because IL-12 triggers another cytokine (interferon-γ) that directly mediates macrophage control of these pathogens through the production of nitric oxide. We were pioneers in understanding the role of IL-12 in infection.

Perhaps a more important contribution was our work on IL-10. In 2008, I delivered an NIH-wide Mider lecture [G. Burroughs Mider Lecture] on this. IL-10 is a cytokine that's produced to protect the body from inflammation. This concept is very relevant today with COVID-19, in which much of the disease is caused by the host's response to the virus, not apparently by the virus itself. We produce regulatory cytokines to reign in the immune system so it doesn't overreact and cause inflammation. In fact, the title of my lecture was "Interleukin 10, protection from friendly fire on the battlefield of host defense," because basically, the immune system is responding to protect you, while at the same time, this response can cause severe tissue damage and death. One of my postdocs, Ricardo Gazzinelli [Dr. Ricardo Gazzinelli], who's now a professor at both the University of Massachusetts and in Brazil—he's quite an important investigator in Brazil—discovered while studying

toxoplasmosis in mice that if they don't have IL-10, the mice all die. But they don't die of toxo. They die of the inflammation that's caused by the host responding to the toxo. That, to me, is a very important lesson from our experiments. I hope we're remembered for this contribution.

This and many other immunologic discoveries came out of studies on parasitic infection models. Nevertheless, none of our findings has so far lead to new treatments or vaccines for parasitic disease, and so in the end, maybe at heart I am a basic immunologist. When I became an immunoparasitologist, I thought I'd said goodbye to this field, but I really didn't at all. I was still a basic immunologist at heart. That being said, in the early 2000's I was left with a feeling that I was not really contributing anything to address human disease, and a lot of parasitic infections were becoming less important epidemiologically than when I started in the field in the 1970s. Although we still don't have any vaccines, except for the partially effective RTS,S recombinant protein-based vaccine for malaria, the drugs and control strategies have substantially improved.

Harden: In 2001, you published a book chapter about coming to a consensus viewpoint on the immunology of schistosomiasis, and that scientists needed to identify an "as yet undiscovered Achilles' heel" of the parasite. Your hope was in genetic studies. Is it fair to say that you shifted gears after this article, and you left schistosomiasis research to move into toxoplasmosis and TB and some of the other parasitic diseases?

Sher: I've long felt that rather than mimicking the host response to chronic pathogens like schistosomes we need to find a target on the bug that is important for its survival/growth and direct our vaccines against that antigen. This is what we have done with SARS-cov-2, and it works! We have to find out what that Achilles' heel is for schistosomes as well as other pathogens that lack effective vaccines.

So, why did I go into TB? Remember I told you that toxo eventually soon ceased to be a problem in AIDS patients?

Harden: Yes.

Sher: Well, this inspired me to find other ways in which we could contribute to HIV research. So one day I walked over to the Clinical Center and talked to a friend and colleague of mine, Joe Kovacs [Dr. Joseph A. Kovacs], who's in Critical Care and who is our expert on opportunistic infection in the Clinical Center. I asked him, "Should I continue to study toxo? As you've told me, its really not a problem as an opportunistic pathogen in AIDS anymore." He said, "There's another opportunistic bug that you might study. It's still a major problem and that's *Mycobacterium avium*." It is an atypical mycobacterium and relative of *M. tuberculosis.* but in contrast to *M. tuberculosis, M. avium* usually only causes disease in immunocompromised individuals, where it can become deadly. It's one of the clinically important pathogens that Dr. Holland [Dr. Steven M. Holland] studies and is an intracellular pathogen like toxo. Joe also said,

"It’s causing a lot of problems in our AIDS patients in part because we don’t have any highly effective drugs," so I said, "Okay. I study intracellular pathogens, so why don't I see if we can contribute on that front.”

So we started to study *M. avium* infection. It was very difficult to work on because it grows slowly and doesn’t trigger easily definable protective responses in mice, but I “got my hands wet” studying mycobacterial infection for the first time, and we published some interesting if not earth shattering work and it was definitely an excellent learning experience. Then, I realized that if I was working on *Mycobacterium avium*, I might as well work on TB because I had the skills now and TB is a disease that remains of major global importance. It's not going out of style. This year [2021] will be a disaster year for TB, because of the loosening of control efforts due to the COVID-19 pandemic. Even before COVID-19, TB was the number one infectious disease killer caused by a single pathogen (1.4 million deaths per year). So I spoke to my Scientific Director at that time, Kathy Zoon [Dr. Kathryn C. Zoon], and said, "I think I want to work on TB, but I need the facilities to do it because it's a containment pathogen." Building 50 was being constructed at the time, and NIAID was going to get the top floor, which has a sweeping view of the campus. She said, "We're going to build some BSL-3 [Biosafety Level 3] labs up there. Why don't we move you to 50 so you can do this research?" So I left Building 4 (the home of LPD) and was

criticized for doing this since, as will I discuss later, I had had just been made Acting Lab Chief and while Building 4 was crowded and run down, I was moving to a brand new “penthouse” lab. “Well,” I said, to those jealous individuals "You'll see. We're going to have to pay a price for this because working in containment is difficult and TB research very challenging.” That's how we got started working on tuberculosis, and our group became split between work on parasites and on TB.

So was this a highly successful switch? Well, I'm guessing we’re probably better known for the other work, but we've made some very important contributions, I think, over the years. Again, these were more basic immunologic than clinical or translational discoveries, particularly on the function of cytokines, and I've trained several people who've done very well in the field. One of them, Dan Barber [Dr. Daniel L. Barber] is now a tenured LPD investigator, and his lab is located right next to mine. His wife, Katrin Mayer-Barber [Dr. Katrin D. Mayer-Barber] is a tenure-track investigator in Dr. Holland’s old department and her lab is located above us in the same building. Here I should mention that after about 14 years in Building 50, we moved to Building 33 because it had far better dedicated BSL3 facilities and more space to expand the TB program and add these new investigators.

Because human TB is so widespread globally, we also had the opportunity to participate in collaborative clinical research projects in India, South Africa, and Mali, I also became involved in clinical research

really for the first time in any kind of depth. This came about in part because of a very talented Brazilian clinical fellow, Bruno Andrade [Dr. Bruno B. Andrade], who has become very successful in the global TB area. He heads several international programs and still helps us with our patient-related work from his lab in the Northeast of Brazil. We've learned a lot from these studies, which have been much more extensive than our few previous clinical research projects with parasitic diseases. The TB field has enormous depth and covers so many different disciplines. It's been fascinating to be involved with it, and there is no question about its continued vast importance to human health, especially now when TB research and control funding is being sucked into the war on COVID-19. Nevertheless, the work is challenging and the need for a good vaccine or host-directed therapy is of even greater importance now.

Harden: Are they still using the BCG [Bacille Calmette-Guérin] vaccine?

Sher: Yes, but it only protects against certain forms of pediatric infection. We're actually studying BCG at the moment. In a recent publication we've shown in a mouse model system that BCG when given intravenously can non-specifically protect against lethal SARS-Cov-2

Harden: That's very interesting.

Sher: It's an experimental model, but the fact that we're protecting against COVID-19 with something that's totally different is interesting. It's been

proposed that BCG might have this effect, and while one cannot use intravenously administered BCG clinically, our findings could lead to the discovery of disease preventing mechanism(s) that could be stimulated by other means. Learning how to work with a new pathogen (SARS-Cov-2) has been a challenge but we were in a good position to do this research because we have the BSL-3 facilities and experience with containment procedures that is required.

Harden: What is your opinion about the mRNA vaccines? Do they hold any promise against TB or tropical diseases?

Sher: They've been suggested for TB. They're of course quite “in” now because of the COVID-19 vaccine successes. I'm not sure that mRNA is the answer for TB, but it's a technology that worked very well with COVID-19, because as soon as we discovered that a coronavirus was the cause of the disease, we knew that producing a neutralizing antibody response against the spike protein was likely to protect against SARS-cov-2 infection and the new mRNA technology was ideal for this purpose. In the case of TB we still don’t know what antigen to immunize against or exactly what type of humoral or cellular response we need to induce and certainly have not identified an appropriate “Achilles Heel”

Harden: That's very interesting, because TB is such an old infection. It has been studied for so long, yet it's still a mystery.

Sher: TB is a much more complicated problem. It's had millenia to adapt to humans and *Mycobacterium tuberculosis* is a bacterium not a small genome virus. Understanding what immune responses can be used to control *M. tuberculosis* is the topic that I'm most interested in, and I do most of that work with murine experimental models. My colleague, Dr. Barber, whom I just mentioned, has set up a non-human primate infection model to more closely mirror the situation in humans.

Harden: You have mentioned a number of different animal models that you have used. Would you comment in general on the importance of these animal models?

Sher: Since I was a grad student I have worked primarily with mouse models, and in certain respects their immune systems clearly differ from that of humans That being said, I challenge anyone to find an animal model that has generated more information about human health. We use them for generating hypothesis that eventually need to be validated directly in humans or sometimes first in an intermediate model like non-human primates. So many basic discoveries have been made that way. Here's a recent example: checkpoint inhibitors in cancer. They came from basic discoveries originally made in mice. We use the mouse model to reveal immunologic mechanisms because we can easily manipulate these hosts genetically and perform experiments we can't do with patients or other higher animal models.

Harden: In 2000, in addition to your responsibilities of being a Section Chief, you became Acting Chief of LPD. Then, in 2004, you became full Chief of LPD. You've told me some about Louis Miller, his role in stepping away, but I want to hear about the shift from your point of view. Why were you offered the position, why did you accept, and what new goals did you set for the lab when you became chief?

Sher: All good questions. In stepping down I'm guessing that Louis Miller suggested that the lab be split with Tom Wellems [Dr. Thomas Wellems] as the Chief of the Laboratory of Malaria and Vector Research [LMVR] and myself as Chief of LPD. When the position was offered to me, I debated whether or not to take it. I wasn't the senior person in the Lab at that time, but I had one of the biggest research programs. I wasn't really sure I wanted to do it, but was encouraged by one of my respected mentors, the late Bill Paul. He said, "You don't let opportunities like that go by. They may never appear again!" And so, I took on the role, at first, as Acting, and later full Chief when the NIAID administration confirmed the appointment later on. I have to credit Kathy Zoon, my Scientific Director for most of that time, as being just a superb boss and leader. I still interact with her, because of her role in the NIH Oxford-Cambridge Program, which I will mention later on.

I think the most exciting thing about being a Lab Chief is hiring new investigators, and Kathy gave me several slots to do so. The first recruitment that I did was for a mucosal immunologist. This turned into

what I have called the "dream search," because all three of the major candidates for this position have become leaders in the field. The three people were: David Artis [Dr. David Artis], who's at Cornell Medical School and runs a huge mucosal immunology group; Akiko Iwasaki [Dr. Akiko Iwasaki], who's at Yale and has become one of the superstars of immunology, and finally, Yasmine Belkaid [Dr. Yasmine Belkaid], a former postdoc of David Sacks. We hired Yasmine from the University of Pittsburgh. She is now one of our strongest immunology investigators in NIAID if not the whole NIH. She blossomed here as a tenure track candidate and was promoted to tenured investigator in about two years. She is now an elected member of the National Academies of both Science and Medicine and has recently been made Chief of her own NIAID lab, the Laboratory of Host Immunity and Microbiome. Yasmine remains a wonderful colleague and friend.

During my time as lab chief, we were able to hire three other investigators. One of them was my former postdoc Tom Wynn, already mentioned above, who now has left NIAID to become head of inflammation research at Pfizer. The second is Mike Grigg [Dr. Michael E. Grigg], who remains a PI in LPD and is a world leader in the biochemistry and genetics of *Toxoplasma*. The final hire was my current TB colleague, Dan Barber, whom I have also mentioned and who started as an Earl Stadtman [Dr. Earl R. Stadtman] investigator. In addition, during my term as lab chief the LPD, I expanded and incorporated into the

lab two other tenured investigators already in the NIAID, Steve Leppla [Dr. Stephen H. Leppla], who works on anthrax pathogenesis, and for a short time Jason Brenchley [Dr. Jason Brenchley], an HIV viral immunologist. Thus, the scope of the LPD expanded way beyond parasites into basic immunology as well as bacterial and viral pathogens during my "chiefdom" and many have criticized me for this bastardization of our mission.

I had a sense—perhaps incorrectly—that that our focus on parasitology did not have a high enough visibility in the infectious disease and immunology communities and that the Lab would be in a weaker position because of this. Also the malaria researchers had split off from LPD. They focused on the most important parasite affecting human mortality, and so I felt we needed to build other strengths. I encouraged the TB program, agreed to take on Dr. Leppla's anthrax group, and heavily supported the elegant basic immunology that Yasmine Belkaid and Tom Wynn were engaged in. So the lab expanded, and some of the purists have accused me of selling out on parasitology. Well, the lab we built is strong, and although I am not the chief any more, we had a BSC [Board of Scientific Counselors] review in 2021, and LPD got a perfect evaluation. I mean, everybody got an "outstanding" rating. We lost both Belkaid and Wynn along the way, but they have moved into important leadership positions of their own.

Harden: Excellent.

Sher: So LPD maintained its strength despite the broadening that we did. I enjoyed being Lab Chief, but I have a philosophy that you should only do these type of demanding jobs for a certain amount of time. I think once you start to do them for too long, you lose your focus, you get bored, and you become fossilized in your attitudes, so it's time to pass it on to somebody else. I stepped down two or three years ago and my position was given to my deputy, Tom Nutman [Dr. Thomas Nutman], who has done an amazing job of running the lab and replacing the positions we lost because of departures. He's a parasitologist by training and keeps the parasitology side of the Lab going strong, but he's also a superb clinical investigator and heads the world class clinical parasitology program that LPD has maintained for many years now. I have been serving as Tom's deputy since then, helping him when needed, but he's very much in control and doing a great job.

Harden: If I may step sideways, one more time, you talked about hiring a mucosal immunologist, and you have also published on inflammatory bowel disease (IBD), which is mucosal. I interviewed Warren Strober [Dr. Warren Strober] a good while ago, and I'd like to know if there any overlap between what he did and what you did?

Sher: Yes, and Warren and I actually interacted for a while. I developed an interest in IBD because of our work on IL-10 and our concept that it protects us against "the friendly fire of the immune response." Indeed, if

you have an IL-10 knockout mouse, it develops IBD spontaneously, because the cytokine is not there to control inflammation. We developed a model that formally demonstrated (I believe for the first time) that specific gut bacteria can serve as the trigger of this inflammatory response. This model is still in use today by a number of groups in both the IBD and microbiome fields. Our contribution was a small forerunner to the beautiful work by Yasmine Belkaid on the role of the microbiota in immune homeostasis and disease.

All of this stems from my immunology interests, but always there's something with infection involved in the work we do. I've never really worked on cancer or anything of that ilk. Our research always has had a host-microbe focus, and IBD is in a sense a microbial disease. I mean, what happens in IBD is that we begin to react against the bacteria in our gut, suddenly recognizing them as foreign.

Yasmine is now our microbiome immunology expert at the NIH. She is also an important role model for women scientists here and it is rewarding to me that she began her career as an independent investigator in LPD, a lab which historically—as I mentioned previously—had neglected the cause of women in science. As I discussed earlier, my mother was a Ph.D microbiologist, my Aunt Marty was a famous vaccinologist and pediatric infectious disease expert, and my cousin Trudy was a Nobel laureate biochemist. Thus many of my own role models were women scientists! I was honored a number of years ago to receive an

award from the Maryland chapter of AWIS, the Association for Women in Science, for encouraging the careers of women in biomedical research. It's good to feel that I have made a contribution, if only modest, to this important cause.

Harden: I think Dr. Belkaid is one of the two new lab chiefs in NIAID, correct?

Sher: That's correct and she's off to a great start recruiting her own new investigators and programs.

Harden: In 2008, you received an NIH Director's Mentoring Award, and you have mentioned throughout our discussion people whom you have mentored. You yourself had excellent mentors, so would you talk a little bit about your philosophy of mentoring and how this plays into people's careers?

Sher: My philosophy is pretty simple. I'm a cheerleader. I give my trainee's a lot of freedom in the laboratory to find their own direction except in one area. And that's in writing. I really think that writing is an essential survival skill in science, and, sadly, I have to tell you that 90% of the young people who join the lab don't know how to write well in English (or even in their own language if foreign.) Most importantly they don't know how to put their ideas on paper. And I'm a tyrant about teaching them this.

I was talking to my wife Stephanie the other day—she was originally a postdoc in my lab, you recall—and she said she hated writing with me because I would stand over her and we'd struggle with every

single word. But others have told me that learning how to write was the most important thing they learned in working with me. Because if you can't write, you're dead as an independent scientist.

Harden: I could also hold forth on this issue.

Sher: Okay good. So you know where I'm coming from.

Harden: I know exactly where you're coming from.

Sher: And I make sure that when they leave my lab they know how to write. We have this thing—it's kind of a joke--that they call the "hot seat" because it's not comfortable. They come into my office and I put their manuscript up on my big screen. I give them the keyboard. And I say, "What do you really mean? What are you're trying to say here?" We go through the manuscript, and it takes forever. My colleagues say, "Why are you spending so much time doing this? It must be awful." But I believe it's a major survival skill for going out into the scientific world, because they are going to have to write, write, write, write, write papers, grant proposals, letters all the time. There's no escape.

So that's one aspect of mentoring, and the rest of it I consider as mainly cheerleading. In terms of specific projects, if they have their own ideas, and they are both reasonable and original, I let them pursue them. I'd say that the people from my group who've gone on and become successful researchers were the ones who came up with their own ideas for

projects while they were with us. And that is because they were intellectually engaged, motivated, and enjoyed the process.

If they're doing well, I'm all over them with praise while encouraging as best I can those who are struggling. But if I discover that a trainee lacks motivation and interest, I don't waste my time with them. There's really not that much that can be done in that situation. That being said, I believe I've been fortunate to have more successes than failures and many that didn't work out doing research in the lab have been successful in other science related careers.

Although I have not done much classroom or undergraduate teaching, I served as Director of the Biology of Parasitism course at the Marine Biological Lab in Woods Hole for four years in the mid-80s. This is a combined lab/lecture course that is still in existence and was originally instigated by the funding agencies that were driving interest in the field at that time. It's a wonderful course with loyal and successful alumni all over the world. It was great for our young family, too, as we got to spend those summers on Cape Cod!

I also want to mention another mentoring related activity I've been involved in more recently, the NIH Oxford-Cambridge Scholars Program (referred to as OxCam). It has been going on for about twenty years. In fact, there's a banner on campus now commemorating its twentieth anniversary. It was founded by Mike Lenardo [Dr. Michael J. Lenardo]. It is an NIH based graduate program in which American students get their

doctoral degrees at either Oxford or Cambridge. But they also work at the NIH, so they're co-mentored by Oxford or Cambridge faculty and by NIH investigators. I'm the current Director of the NIH component of the program, and it takes about quarter of my time. I have a really talented staff that works with me along with an executive committee whose members share our passion for this program and our very bright students. The program has an amazing success record with many of our alumni in leadership positions in academia, medicine and industry.

Harden: Are most of your students in this program English?

Sher: No they are American.

Harden: So they're Americans who go to England to study and then come back to do their research?

Sher: Not quite. The UK doctoral degrees do not require any course work. The students do half of their research there and the other half at NIH and are co-mentored. They get the advantage of both types of research institution and actually are allowed to design and form their own collaborative research project between their 2 mentors.

Harden: Are they graduate students or postdocs?

Sher: They're graduate students. There is also an MD-Ph.D component where they receive their MD from an American partnering med school and their Ph.D from our main program.

Harden: Where do they apply as undergraduates for their graduate program?

Sher: They apply to our program, and if they're accepted, they automatically get into Oxford or Cambridge.

Harden: That's very interesting. I didn't know about this program.

Sher: It's been going for about twenty years. I've been the Director for about three years. It's really a pleasure to work with these very bright young scientists. We only accept about 10% of our applicants, and we're competing with all the major universities—Stanford, Harvard, etc. I think its fair to say that OxCam is the elite prestige graduate program at the NIH. I took on the Director role as an older scientist, in part because I had more time to devote to it. The work involved is probably too time consuming for people who are in earlier stages of their careers. It's a trans-NIH program. It's not just for NIAID. There are people working everywhere, all over the campus. That's been another rewarding aspect, because I've been able to broaden my horizons at the NIH interacting with mentors and their students in many different institutes in addition to NIAID.

Harden: In addition to mentoring, you've served your professional societies and you've labored as an editor on the editorial boards of key journals. Would you comment on how you find the time to keep up with all this and what the benefits are?

Sher: Well, the main editorial job I've had over the years has been with the *Journal of Experimental Medicine*, which is an old and venerable journal run by the Rockefeller University Press. My uncle Lee, whom I told you about earlier, published his most important work in it, and I have published many of my own papers there. Serving as one of the senior editors for this journal took a lot of my time, and I lasted for about nine years. I'm still on the editorial boards of several other journals. I was also greatly involved for many years with something called the Keystone Symposia [Keystone Symposia on Cellular and Molecular Biology] and served on their board of directors for three terms, which was also a very interesting and rewarding experience in terms of broadening my professional horizons. I've also organized (or co-organized) a lot of meetings over the years, and I'm the lead organizer for a Keystone Tuberculosis meeting in August 2022 that will likely be my last.

In assessing my own strengths I'd say that being interactive is near the top. What I enjoy most about research is its collaborative nature and putting people together to create novel discoveries. Indeed, I like to think of science as the means that I, as a shy kid, found to socialize and build connections with people. It worked for me as my language, or to use a

different, more colorful analogy, a musical instrument to play in the human orchestra. I'm so glad I found it.

Harden: Reflecting then back to your desire in graduate school to use your expertise in immunology to do something relevant for humanity, how would you characterize your career to your younger self?

Sher: Directly, I clearly have fallen short of my idealistic, humanitarian goals. There are many disease interventions out there that I can't claim to be part of. Yet indirectly, I would say that I succeeded because I've trained a number of people who are making an impact. Indeed, as we discussed earlier, I see the mentoring and career building I have done as my main contribution and as something that I hope will be my legacy when I've left science. As a young academic, I could have stayed with history or classics as my field. In fact, I still love history and devour books on it. But I seriously doubt that as a historian I could have had the same impact I've had as a biomedical researcher.

Harden: You have no doubt had numerous offers to leave the government and take a more remunerative position in academia or industry. But you have stayed at NIH. Would you comment on what keeps you here, despite all the rules and restrictions of a federal career? What has NIAID offered you that kept you here?

Sher: NIAID has been terrific. Most of my time here, our institute director has been Tony Fauci. And I flatter myself by calling myself "one of Tony's boys" (see photo of Tony giving me an award in the mid 80's). I think he's an amazing leader and have enormous respect for him. Although he's really much more clinically oriented than I am, he's still been good to me, forwarded my career and been there for me when I needed him.

While benefitting from the strong support of Tony as well as my Lab Chiefs (Frank Neva, Louis Miller) and Scientific Directors (Ken Sell, Tom Kindt, John Gallin, Kathy Zoon, Steve Holland), most important to me has been the NIH intramural program itself as a great institution and community. I've always found this an exciting environment where we have enormous freedom to be creative and where collaboration is strongly fostered. It's interesting because people outside the NIH like to portray us a factory of boring government drones. That's the way Mel Cohn and others initially described NIH to me. Our major competitor at the time was the late Mike Potter [Dr. Michael Potter] at NCI, and working with him was one option I had considered if I remained in basic immunology, but this negative portrayal of NIH by Mel and other Salk scientists did not make it an attractive option.

While it is true that we have to deal with a lot of paperwork and administrative red tape, you quickly learn to put up with it, and it is certainly less burdensome than constantly writing grants. I say this knowing that preparing grant proposals does help you focus. And I have

had a few small grants—those that I'm allowed to have while I've been here. But I doubt that I could survive now in the world of NIH extramural funding. As I mentioned earlier I only considered leaving NIH once (to return to La Jolla) but it was hard to give up all the advantages we have here.

Harden: What are your plans going forward?

Sher: I'm going to try to ease into retirement. I have agreed to give up my research lab this summer and am considering becoming something called a re-employed annuitant. I will be able to work half-time with my current title and hopefully an office desk. I would be delighted if the lab resources I give up are used to support hiring of a new investigator for LPD. I have involved myself in a lot of mentoring activities and hope to expand this function in my new situation and be of help to NIAID in other areas where needed. In addition I still have a lot of papers to write with fellows who are finishing up, and perhaps I may even do a sabbatical—something I've never had time for previously.

Harden: These are all the questions I have. Is there anything else you want to get on the record before we stop?

Sher: No, except to re-emphasize that the greatest satisfaction I have as a senior NIH researcher is in my contribution to the careers of the wonderful people I have had the pleasure to work with in my lab. Its taken me a

while to firmly grasp this, and it is nice to be winding down my career on such a gratifying note.

Harden: Thank you so much for this excellent oral history.