The American Association of Immunologists
Oral History Project

Transcript

Laurie H. Glimcher, M.D.
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Williams: This is an interview with Dr. Laurie Glimcher for The American Association of Immunologists Centennial Oral History Project. Dr. Glimcher is Stephen and Suzanne Weiss Dean and Professor of Medicine at the Weill Cornell Medical College and provost for medical affairs, Cornell University. She's also an attending physician at New York Presbyterian Hospital, Weill Cornell Medical Center. Dr. Glimcher was president of the American Association of Immunologists from 2003 to 2004 and served as an AAI Council member from '98 to 2003. She was awarded the AAI Meritorious Career Award in 2006 and the AAI Excellence in Mentoring Award in 2008. We are in Dr. Glimcher's office at Weill Cornell Medical College. Today is Wednesday, February 6 [2013], and I'm Brien Williams.

Dr. Glimcher, let's start with a little bit of your family background. How far back do you want to go?

Glimcher: Well, I don't have to go back that far. I am one of three daughters of a physician scientist, Mel Glimcher, and my dad was chair of orthopedic surgery at the Mass General [Hospital (MGH)] and then at Children's Hospital at Harvard Medical College, Harvard Medical School. So I grew up at Harvard, really. I went to Harvard undergrad and Harvard Medical School and then I did my residency training at the Massachusetts General Hospital in medicine, went down to the NIH [National Institutes of Health], where I became an immunologist, and then came back and did a rheumatology subspecialty again at the Mass General Hospital and from that slowly rose through the ranks at Harvard Medical School. So I guess it's sort of boring. I've spent my entire career until last year, January 2012, at Harvard.

Williams: Your father went on then to do work at MIT [Massachusetts Institute of Technology], is that correct?

Glimcher: He graduated from Harvard Medical School and started training as an orthopedic surgeon, but he is very much a scientist. He's a biophysicist and a biochemist, and he did training at MIT for several years on mechanisms of calcification of skeletal tissue, at which point he then went back to the Mass General and completed his training and, at a young age, became chair of the Department of Orthopedic Surgery. So he certainly was both a physician and a scientist, but he really was responsible for building the orthopedic research labs at MGH and then later at Children's Hospital. He was one of the rare orthopedic surgeons who did research. It was really a barren field back in the fifties, and he kind of helped create the field.

Williams: So he was a pathfinder.

Glimcher: So he's a pathfinder, right.

Williams: What about your mother?

Glimcher: My mom was a homemaker. She was the rock of the family, took care of my dad and the three of us. She was always very ambitious for us, although she herself had—and at that time it was the usual thing—had chosen to stay home and be a homemaker. She was very eager that all three of her daughters have careers.

Both of my sisters are lawyers. In fact, both of my sisters are tax lawyers. I was the one who always really enjoyed going into work with my dad, so I would go into the hospital with him on the weekends and go to his laboratories, and also sometimes go on rounds with him. Neither of my sisters could stand the sights and smell of a hospital.

Williams: Where are you in the family order?

Glimcher: I'm the middle, the middle sister.

Williams: I see. Did you feel like your father was steering you, or were you just delighted to be with him on your own?

Glimcher: I would say the latter. I think my parents would have been delighted to have me do anything that I loved doing. It happened to be medicine and science, but I think they're equally pleased with the choices my sisters made.

Williams: Now, you chose to do the M.D. rather than the Ph.D. What was your thinking behind that?

Glimcher: You know, back then most immunologists were M.D.'s. If you look at that generation, it wasn't considered necessary to get both an M.D. and a Ph.D. It honestly never really occurred to me, even though I knew I liked science from working in my dad's lab when I was a college student at Harvard. It just wasn't that frequently done. We had a few students in our first-year class at Harvard Medical School that already had Ph.D.'s. I don't even recall any who got both M.D.'s and Ph.D.'s, and so I never really thought about it. Students always ask me, "Do you think I need to get both an M.D. and a Ph.D.?" Until about ten years ago, my answer was, "No, you really don't need both degrees. If you don't intend to do clinical training and you really never want to see a patient, there's really no point in getting an M.D., just get a Ph.D., and if you want to spend most of your time in the lab, you can do a postdoc, which is what I did, and it'll be fine."

But I have to say my advice is different nowadays. I think the technology, the field has moved so fast. The technology is so complex and the science has just exploded, and the competition is fiercer, and we're in a fiscally constrained time. So I think the M.D./Ph.D. students do really have an edge. They have an edge in terms of getting awards, getting grants, getting positions. Now my counsel is, "Yes, get them both, but we've got to figure out a way to truncate the length of this experience for you." We can't have our M.D./Ph.D. students, who are in

many ways the crème de la crème, not open their own laboratories until they're in their mid to late thirties. I set up my laboratory when I was thirty-one years old, and I was a first-year rheumatology fellow with an NIH grant, and I just saw patients and I set up my lab at the same time and hired a couple technicians in a little tiny space and got going. We're wasting in some sense the most creative years or what could be the most creative years.

Williams: Talk about being a woman in medical school at Harvard at that time.

Glimcher: Well, at that time there were 37 women out of a class of about 165. It was 21 percent, so we were in much different situation than nowadays when it's 50-50. I think there was, at that time, still some bias, some unconscious bias, but I never spent a lot of time thinking about that. My feeling has always been just do what you do best and do it and don't fret about whether there's any gender bias out there. Concentrate on what it is you really love doing and do it well.

When I was an intern, I think I want to say there were three women out of about twenty interns, and, sure, you'd go on rounds and the male attending would direct his comments to the male intern or the male resident sometimes. But, again, my response to that is just be the best you can be, and ultimately quality, I think, wins out.

Williams: Your point there being that he was not addressing the women on his team or the patient or both?

Glimcher: My point being that he was unconsciously speaking man to man. But, you know, this was now thirty years ago. I think this is much less common, in part because women make up half of the residency staff. On the other hand, if you look at women in positions of leadership at medical colleges, we're still way behind. We've got a ways to go. Hopefully, as we are training, as our pipeline is getting more robust, we will see more women in positions of leadership, but right now we're still very much in the minority.

Williams: I was impressed that you were a teaching fellow before you got your M.D. at Harvard. Maybe that was very common.

Glimcher: I think you're talking about my first year at Harvard when I actually taught. I was one of the teaching fellows in a biology course at Harvard undergrad. I did do that. I'd forgotten.

Williams: So you describe that when you went to the NIH was when you got shifted on to immunology. So what was your focus while you were studying at Harvard?

Glimcher: So actually I fell in love with immunology my first year at Harvard Medical School. At that time the medical education was organized primarily as lectures, as you know, and blocks. At the end of the first year, in the spring of the first

year, we had our immunology block, was taught by Kurt Bloch, who was a rheumatologist and allergist at the Mass General, and I became completely riveted by the idea that the immune system can recognize self tissues as self and not as foreign, and that many diseases arise when that recognition becomes impaired.

So I really kind of fell in love with immunology at that point and signed up for a one-on-one tutorial with one of the immunologists at Harvard, Emil Unanue, one of the illustrious immunologists in the country, in the world. So I did a reading course with Emil over the summer and also continued working in my dad's laboratory on skeletal biology, but it was really clear after that semester that immunology was the field I wanted to spend time in.

Williams: I'm struck by—let me put it this way. There are so many diseases that are likely to be dealt with by a study here, the knowledge of immunology, but how many people are working in autoimmunology, which—just talk about the allure of that and why.

Glimcher: Well, I can tell you from my point of view it was very alluring, and I think that the concept that your immune system all of a sudden forgets that your joint tissue is self, and thinks of it now as foreign, or your kidney or your lungs or whatever, since the immune system is so pervasive, is in many ways a startling and disturbing concept. So a lot of us, I think, got drawn into the field because of that, and I certainly did. I found a disease like systemic lupus to be utterly fascinating, and I remember thinking about where and in whose lab I would do immunology, because I spent my fourth year of medical school basically in an immunology laboratory. I went to Harvey Cantor, and I asked him whether I could join his laboratory, and I said, "Well, I really want to work on lupus, models of lupus."

And Harvey said something then which I have never forgotten, which is, the best way to understand autoimmune disease is to understand the normal immune system, and I think that's absolutely true. For many, many years it was really difficult to investigate particular diseases, particularly in the setting of human disease. Now there's a total revolution. You can really look at human tissues, and we have the genomic capabilities to look for gene associations. We're at a point now where what we call translational medicine is actually a reality. It wasn't a reality thirty, twenty, even ten years ago, and at that time the quality of basic immunology research was far higher than the quality of what we call applied research in immunology. I think that's changing, that it has changed.

Williams: What words would you use to describe your experiences at Mass General? What was that like?

Glimcher: I will probably always consider Mass General my hospital. I think where you train, where you do your internship and residency and fellowship is always in some sense your home. My father trained at the Mass General, and my son is now a fourth-year surgical resident at the Mass General. My first husband, who

was a transplant surgeon and an immunologist, trained at Mass General and was in the transplant unit there for many, many years. So even though my formal association with MGH was only for a few years, and I then when I moved over to the Quad, to the medical school, became a physician at Brigham and Women's Hospital, which is a great hospital, but the MGH will always be my home.

Williams: Talk about your coming down to NIH then. What was that like? What were the circumstances that brought you there?

Glimcher: Advice from my mentor at Harvard, Harvey Cantor. I was in his lab for a whole year, and I said, "Whose lab do you think I should go to for postdoc training?"

And he said, "Well, you probably should go to NIH. It's got the greatest collection of topnotch immunologists, other than Harvard, and it's a wonderful environment." And I think that was really true.

So I didn't really think a lot about it. My husband was also interested in training in immunology, so I went to work with Bill Paul, and my husband went to work with David Sachs. Those were three wonderful years. They were really terrific. They were terrific for a number of reasons. One was that I wasn't on call every other night, and my husband wasn't on call every other night, although he did a lot of moonlighting. I had our first child, my daughter, a couple months after I got there, and actually stayed out of work for a whole week, which is more than I did for the two sons that followed, where I literally got out of the hospital and went back to the lab.

And there was just a fabulous group of people there who were fellow postdocs and faculty, NIH. Those relationships have lasted for so many years now, just a wonderful group of people. We have so many friends, close colleagues from NIH. And the work was terrific. I had the luxury of working with more than one senior investigator, so I spent most of my time working with Bill Paul, but I also worked with Ira Green, Ethan Shevach, Ron Schwartz, Al Singer, wrote papers with all of them. It was a very, very productive time for me, and I left there feeling that I had been extremely well trained.

Williams: What was the focus of your work there?

Glimcher: The focus was trying to understand structure function relationships of MHC, major histocompatibility complex type II molecules. That was the ultimate, I think the most important output from that period of time. So with Bill we set out on a very risky project at the time, and that was to see if we could generate cell lines with mutations in MHC class-II molecules, and then ask how those mutations affected activation of T cells, and we set out on this project.

We decided we would use a B cell lymphoma line and would mutate it by subjecting it to treatment with a chemical mutagen, and our strategy was to treat

that population with cytolytic antibodies to one epitope of an MHC class-II molecule and then sort them positively. So you're going to kill vast majority of cells, but there should be a small population of mutant cells in there that have mutated their surface MHC class-II molecules such that they're not going to recognize that epitope, but they're going to escape death. But they will have preserved another epitope. In other words, we're looking for mutation. We're not looking for loss of that molecule; we're looking for small changes in it.

Everybody told us, "This is never going to work. This is just never going to work." I remember going through the procedure, doing the experiments, handing off the cells to the wonderful person Sue Sharrow, who ran the FACS machines, the sorting machines, and she said, "No, this is never going to work." And she did the sort and came back and said, "My god, there were some cells there." So we created a series of lines with mutations in MHC class-II molecules and began to characterize the T cell response.

And that was towards the end. That was the last year of my time there, and so when I moved back to Mass General to do my rheumatology fellowship, I was just so excited by that project that I wasn't willing to give it up. Before I left, I wrote a grant to the NIH, which I got, and so there I was with an R01. I had some funds, and I had a little teeny-eentsy lab, really teeny, and I hired a technician and combined full-time clinical work learning rheumatology with trying to keep the lab going. And I must say I had a three-year-old and a six-month-old, and a husband who was on every other night, every other weekend. So those were tough times.

Williams: Was your lab at Mass General?

Glimcher: It was. It was. That's where I was doing my clinical fellowship, and Steve Krane carved out a little corner of his lab for me, and we managed. We managed.

Williams: So did you carry on the same line of pursuit as Bill Paul or—?

Glimcher: Well, he really did not carry it on. He's a very generous guy, and he said, "Why don't you go ahead and do this." It was just at that time that molecular biology came on to the scene, and the MHC class-II genes were actually cloned. So I decided that I needed to hop on that bandwagon and get trained in molecular biology, because when I got to Harvard, I made a whole bunch more of these mutant lines in different class-II molecules, and I wanted to know where the mutations were, and I didn't see why I should let somebody else find out where the mutations were. So I did a very informal mini sabbatical in Jon Seidman's laboratory and cloned the genes and then we were able to sequence them and figure out where the mutations were. At that point, I had attracted a postdoctoral fellow who could do most of the work, so I made the transition informally while running back and forth, seeing patients, taking my rheumatology boards.

Williams: What motivated you to develop this expertise in rheumatology in particular?

Glimcher: In rheumatology?

Williams: I'm sorry. Yes.

Glimcher: I was fascinated by those diseases, scleroderma, lupus. They're just completely unsolved diseases. They're still unsolved diseases in terms of their etiology. I think we understand their pathogenesis much better, but what kicks them off is still a mystery. So, fascinating diseases, and also from a practical point of view, small field with a small number of diseases, most of it is outpatient care. Of course, you have some very, very sick patients. You can have vasculitis and so on, but very few therapeutics at that time, so that keeping up on the field, being able to continue to see patients did not require a lot of continuing clinical training. A small group of diseases, and, frankly, it almost didn't matter what connective tissue disease you had, if it was really severe, you're going to put somebody on steroids and maybe Cytoxan. Now the arsenal has grown bigger. It's totally transformed from what it was thirty years ago. But at the time that I joined it, I mean, we were giving people gold shots, and that was about it.

Williams: So your next move then was back to the Harvard Medical School itself, right?

Glimcher: Right. So I spent a year and a half at the Mass General doing my clinical rheumatology fellowship and also having a small lab. Most of the immunology at Harvard happens in the Quad, happens on Longwood Ave, and I was very eager to be right in the middle of things, so I looked for positions at the medical school, and an opportunity came up very quickly, which was space at the Harvard School of Public Health. The department then was called Cancer Biology, since has been renamed Immunology and Infectious Diseases. And it was great. It was a nice big lab, and I moved there happily.

I have to say that I didn't go looking for jobs. It was very different then, at least for me, than what people go through now as they finish their postdocs and look for jobs. I never looked anywhere else. For one thing, I knew I had to be in Boston because my husband was a surgical resident, and I wanted to be in Boston. My parents were close by and very helpful with the kids. But I didn't look for jobs. I didn't ask for a package. I just went over and interviewed with the faculty members at the School of Public Health, and they offered me the job, and I took it. I think maybe I got $40,000 as a startup package, but they were supportive and they pretty much left me alone, and I did my work, grew my lab, got more grants.

Williams: Had you had prior contact with some of the faculty at Public Health?

Glimcher: No, none at all. None at all. But it was very much a part of the immunology community there.

Williams: What was the culture like there as opposed to the medical school?

Glimcher: It was the medical school.

Williams: Okay. I'm sorry.

Glimcher: Compared to MGH? So Harvard School of Public Health is part of the medical school.

Williams: Part of the medical school, I see. Yes.

Glimcher: Yes.

Williams: But does it have a sort of different culture? Because it must have a slightly different orientation.

Glimcher: It does have a slightly different orientation, but there's a Division of Biological Sciences there with excellent, excellent group of scientists working on a variety of different problems. There are no barriers or walls between School of Public Health and the medical school or Joslin [Diabetes Center] or Beth Israel [Hospital] or Dana-Farber [Cancer Institute]. I mean, as far as I was concerned, they were just different buildings at Harvard Medical School.

I had a joint appointment at Harvard Medical School, so all the way up, so I was an assistant professor at School of Public Health and assistant professor at Harvard Medical School.

Williams: So that started a thirty-year career at Harvard, right?

Glimcher: It did. Well, I think I started the undergrad at seventeen or eighteen years old. That's a long time.

Williams: That's thirty-plus, yes.

Glimcher: I didn't leave Harvard till I was sixty last year.

Williams: So what were the highlights of your time at Harvard?

Glimcher: Obviously, a first-rate community of scientists and scholars, absolutely outstanding. After that many years, it feels like a family. I have many, many friends and colleagues. It is the best immunology program in the country, bar none. I headed that program for several years and was very much an integral part of running that program, I think. A lot of people say, well, Harvard's is very competitive, and there's not much collaboration. Sure, that's true, it's true at most places, but there was a lot of collaboration. The community hung together, hung together very well, and it's always fun to be part of a very strong program

and to get outstanding students and be able to collaborate with outstanding colleagues. I never thought about Harvard in a sense as something separate, because I grew up there, so I never really saw anything else.

Williams: And what kind of a balance were you able to achieve between remaining a scientist and a clinician and in the leadership roles that you assumed there? How did that work?

Glimcher: It was easy to do at Harvard, because the expectation was that Harvard Medical School and Harvard environment is training the physician scientists who are going to lead. That's Harvard's expectation, and they're very aware that it's hard to be both, it's hard to do both very well. So when I moved from MGH to the Quad, for a couple of years I did no clinical work at all. I was associated with the Division of Rheumatology. Frank Austen was then the chief of that. But I didn't really spend any time doing clinical work.

Then I started seeing patients, so I had a once-weekly clinic, and I attended on the rheumatology inpatient consult service for a couple of weeks a year and did that for years. But seven, eight, nine, ten years ago, even, I just realized that my patients deserved a full-time doctor. So I had a group of fairly sick patients, and I just didn't think it was fair for them to have me as their doctor because I'm traveling and I'm doing this so part-time. So I started transferring my sick patients over to full-time clinicians.

Then I would go into the clinic and somebody would come in with bursitis or whatever, and I would be injecting their joints. I'd think, "Why am I doing this?" How many joints do I inject? Not very many, so it just became clear to me that I should stop seeing patients, which I did. I continued to attend a couple weeks a year on the inpatient, which was great. I liked that. It kept me in the loop.

Williams: What about the taking on more and more administrative roles at Harvard? How did that work?

Glimcher: That happens naturally. When it becomes recognized that the research is going well and that you're rising through the ranks and you're female, you get asked to do a lot of administrative things, and you say no to some of them and yes to some of them, say yes to the ones you think really make a difference. So I always participated very extensively in the Executive Committee on Immunology, which runs the immunology program, and eventually became the chair of that committee for several years, at the same time I took over as chair of the Division of Biological Sciences in Harvard School of Public Health as well.

I was on many, many search committees and many other committees. I can't even remember all of them. You can look at my CV. I was on Faculty Council. I was on Larry Summers' task force for women in science and engineering. I was on the Committee of Degrees. I was on the Harvard University committee that

chooses the honorary-degree recipients every year. That was fun. It just goes on and on. Now, that was at the Harvard level, and then, of course, I was on many other committees at the national, international level.

Williams: So how do you focus with all of those various roles to play?

Glimcher: You have to be a multitasker. There's just no other way to put it. I think one has to accept that you can't be a perfectionist in everything. So, to me, the important thing to be a perfectionist in was the data. All of the data that come from the laboratory have to be beyond reproach. They have to be completely robust. A lot of other things, if you get 90 percent of the way there, 95 percent of the way there, it's good enough.

Williams: Did you bring an agenda with you? Did you have certain things at these various stages that you wanted to accomplish? What were your through-lines as an administrator?

Glimcher: I was driven by my passion for the science. That was the number-one thing for me. And mentoring, mentoring the graduate students and the postdocs in the lab. Those were the two things that drove me, and I considered all the rest to be important because it contributed to the development of junior faculty and students and postdoctoral fellows, and everybody needs to do service for the institution they're at. That's one of the responsibilities of being at an academic medical center is you do your job. You do your share of the work. But if you asked me what I was thinking about in the shower or what drove me to get up every morning, it's because I just loved what we were doing in the lab.

Williams: So these other roles did not take you away from that much?

Glimcher: Right.

Williams: Is that true?

Glimcher: I think that's very fair to say. I certainly had administrative responsibilities, but actually it made for a very varied menu, which I like. I like always being on a steep learning curve, which is one reason why we've gone from immunology to the ER stress response and skeletal biology and lipid biology. You kind of go where the science takes you to some degree. But I like being on a steep learning curve, and participating in Summers' task force on science and engineering, got a chance to meet a lot of colleagues at Harvard University. We got a chance to sit down and think through the steps that needed to be taken to make it a friendlier, better, more open place for women faculty. These experiences may be painful at the time, but they usually teach you something.

So I didn't want to be restricted to just doing my science, and it was for one of those reasons that I joined the board of Bristol-Myers Squibb as a director in 1997

as well as the Waters [Corporation] Board in 1998 and then actually joined a third board several years later, a board of a company called NDC Health, which I was only on for two years. We sold the company. It gave me a totally different perspective. How do you discover drugs? What is the world of pharmaceuticals like? What are the differences? What should the connections be between pharmaceutical companies and academia? And you see now that they're totally transformed, that I think both parties have realized that we need to work closely together to translate our discoveries from the bench to the bedside most effectively, got to work together, and it's a win-win for both sides.

Williams: And that was not happening in '97?

Glimcher: It was happening, but it was not what I would call a really robust partnership. Scientists would look to the pharmaceutical companies to give them funding, but then would just go on their merry ways and do whatever they wanted to do, and there was very little accountability back to the company. Those days are long over. Now you really work together towards a goal.

So we had a terrific relationship with Merck for over three years working on our skeletal biology portfolio and a particular one gene that we had isolated that controls adult bone mass, and it was a great interaction because we met every month. Merck scientists were in constant contact with scientists in my laboratory. We had a set of goals and milestones to reach those goals. Merck scientists created reagents for us. We created screen assays for them. We had the same goal. We wanted to identify small molecules that would target this particular protein. That's the kind of relationship that academia and pharma have nowadays or should have nowadays.

Williams: And at one point my guess would be that the academic community would have looked down on this kind of collaboration.

Glimcher: Well, I think that's right. Thirty years ago, if you went into the pharmaceutical industry instead of academia, you were kind of looked down on. It was you couldn't be a first-rate scientist if you were going to go into pharma. That is absolutely not true anymore. Some of the smartest people I know are in companies. So the field is completely transformed. I mean, there's a lot of pressure on pharma and there's a lot of pressure on academia.

Williams: You were on the Committee on Inventions, Patents, and Policy at Harvard.

Glimcher: Yes. I chaired that committee.

Williams: Talk a little bit about the relationship of royalties and responsibility and so forth.

Glimcher: Again, this has really changed. Academia, I think, in many cases used to sort of hold off and look down upon their partners, but the 1984 Bayh-Dole Act makes it

pretty clear. We get taxpayers' money to do our research, and the government was willing to give the IP back to the universities but on the condition that we do everything we can to translate our discoveries into new therapeutics for patients.

So we need to ensure that this happens in an equitable way and that, as scientists, we participate in this as full partners. The impetus for revising our policy on that was that it hadn't been revised for many, many years. I think 1998 was the last time it had been looked at, and we wanted to make sure that we were being fair to our faculty members, to the inventors, fair to the university, and that the policy was clear and simple.

Really, it was not just the medical college and the sciences at the university; it was also Harvard Business School, the Law School. So we have representatives from almost every school at Harvard and worked together in many sessions with some help to come up with a policy that was very straightforward, easy to understand, and fair. And I think we got there. We had lots of different viewpoints, but I think we came up with a policy that everybody was comfortable with. It was also a learning experience.

Williams: Is that a policy that is widely accepted elsewhere?

Glimcher: Well, we obviously did our homework and looked at policies at other places, Stanford [University] and Yale [University] and MIT and so on and so forth, to adopt what we thought was the right mixture of them.

Williams: In a phrase, can you sort of indicate where the money went, where the money goes?

Glimcher: It gets divided between the inventors, the department, the particular school, say the School of Public Health, and the university, so the university gets—I think it's 15 percent is the number we came down to, and most of that goes to the tech transfer offices to help support them. The inventors' share goes to the inventors, and then the share that goes to the department and the school is a little more fungible so the department might say that the share they get will go back to the laboratory of the inventor, or they might not. And the school might say, well, we'll take this piece or we won't take this piece, we'll give this piece to the department. That varies between schools, departments.

Williams: What about pharma's share?

Glimcher: Well, that's different than divvying it up in the university. So that depends on the negotiations that an individual laboratory carries out with an individual pharmaceutical company. Usually the pharmaceutical company will license the invention, and for that they pay a fee. But the IP is the property of the university, so each investigator has to sign off that this intellectual property belongs to Harvard University. So an outside company can come in and say, "We're going

to license that invention," for X amount of dollars, and then you work out a deal. What are the milestones? What is going to be the sponsored research support for the laboratory? What's the percent royalties? That's a negotiation that occurs one-by-one, case-by-case basis.

Williams: So tell me, briefly talk about your scientific breakthroughs and accomplishments.

Glimcher: They've been kind of eclectic. So I started out as an immunologist and spent most of my first twenty years doing immunology. When I set up my own laboratory, we continued the work that I started with Bill Paul, trying to understand the relationship between the structure of MHC class-II molecules and T cell receptors. So what do you need to activate a T cell? And we made a whole series of class-II mutant cell lines, and we sequenced the mutants and found out where the mutations were.

At about that time, actually, the crystal structure of MHC class-II was solved, and so knowing what the key functional residues were, I think, was very helpful to the structural biologists because they made a lot of sense when you looked at the structure of the molecule. Oh, yes, that's a very key place, and that mutation abolishes function, and that mutation doesn't abolish function, and so on.

And that was fun for a while, but I actually got very intrigued, three or four years after I started my laboratory, by the regulation of gene expression, and we continued our focus on MHC class-II genes, because they're regulated during the course of an immune response by cytokines, primarily by cytokines. So you can induce the expression of MHC class-II on B lymphocytes if you treat them with interleukin-4. You can induce the expression of MHC class-II on macrophages and dendritic cells and many other cells, if you treat with interferon-gamma, another cytokine.

So we spent a few years really trying to understand why that happens and how that happens and what the regulatory regions of the genes, of what the coding that surround the coding sequence of the genes look like, and we had some successes there. I was in that field for several years, and it was fun, and then I got a little edgy and thought, hmm.

That was about the time that Tim Mosmann and Bob Coffman discovered that CD4 T helper cells were not a homogenous population but actually could be T helper 1 or T helper 2 cells. Of course, now we have multiple T helper cell populations. I was very interested in how that happened. Why does a naïve progenitor cell—why and how does it choose to become a T helper 1 cell that makes interferon-gamma or a T helper 2 cell that makes interleukin-4? Because that has huge consequences for the kinds of diseases that these different subsets are associated with and control. So in allergy, you have an abundance, an overabundance of T helper 2 cells. In many autoimmune diseases you have an overabundance of T helper 1 cells. But nobody really understood what makes a T

cell make interleukin-4 and what makes a T cell make interferon-gamma. So we set out to try to figure that out.

The first factor that we isolated was a proto-oncogene called c-maf and discovered that that controls the production of interleukin-4 in T helper 2 cells, and it's only expressed in T helper 2 cells, and so that was a big discovery, and we published that in *Cell* in 1996, maybe, something like that. But it didn't quite make complete sense because maf did not control other Th2 cytokines, and a master regulated transcription factor should control the whole program. So it didn't control IL-5 or IL-10.

Then Richard Flavell's group and, simultaneously and independently, Anuradha Ray's group identified another factor called GATA-3 that controls the whole kit and caboodle a year or so later. So a lot was being done on T helper 2 cells and figuring out more details about what other factors were involved in controlling interleukin-4, and we worked on the NFAT factors for several years and made a bunch of knockout mice that deleted these factors and so on.

We were interested in the other major subset, T helper 1 cells, and nobody knew what controlled the production of interferon-gamma, and so we tried. We wanted to crack that. I had a new postdoc in the lab who had come from Ken Murphy's lab where she had worked on T helper 1 cells, and we decided that she would go after this. She'd go after trying to figure out what this factor was. We took what I think many people thought was sort of a nutty approach. Well, she certainly thought it was a nutty approach for a while, and we decided to do it in yeast by taking a chunk of a Th1-specific promoter, which was interleukin-2, actually, and doing a reporter assay and screening through a whole library of cDNAs that we had obtained by subtracting the genes in Th2 cells from the genes in Th1 cells. So we had as a probe a Th1-like probe, and we put the library from a Th1 cell into the yeast.

I remember Susanne sitting there with hundreds of yeast plates and looking for blue colonies and white colonies. I have to say we really didn't think this was going to work. Most people had done this yeast-two-hybrid system by using very short sequences, multimerized very short little sequences, and we couldn't do that because we didn't know what the sequence was. So we had to take the whole big chunk of the reality promoter and do that. Anyway, it worked, and out came the gene that I'm probably most known for, and that is T-bet, T-box expressed in T cells, we called it, and that's the master regulator of the Th1 program.

I don't know how many hundreds of papers have been published on T-bet by our lab and other laboratories, but it turns out to be a master regulator not only for T helper cells, but actually for almost every immune cell, so it controls what we call Type-1 immunity in dendritic cells and natural killer cells and CD4 cells and CD8 cells. It's like the gift that kept on giving.

We went on to make T-bet-deficient mice and put them through a lot of different disease models, and a lot of serendipitous things happened. We discovered that if you got rid of the adaptive immune system and deleted T-bet just in the innate immune system, mice spontaneously developed aggressive ulcerative colitis that went on to colon cancer as the human disease does, and that was transmissible. And we isolated the species of bacteria that were responsible for transmission. That was at the time a very novel discovery that you could transmit a disease from mother to pup or from adult to adult just by cohabitation, so that they get infected with the microbiota. I mean, it's a whole field now of microbiota is enormous, and I don't want to say that we started that field by any means, but it was a fascinating discovery and is being carried out and work's being carried on by Wendy Garrett. She has her own lab now at Harvard. So that was, I think, probably the discovery for which we are best known.

At the same time, though, we had been looking years before that for the transcription factors that regulated MHC class-II gene expression, and we had isolated a couple factors that in cell culture experiments seemed to regulate the MHC class-II genes, but in vivo veritas, right? So at that point, the technology was such that we could make these knockout mice, so we knocked out these factors, in particular one of them which we had called X-box binding protein, because it bound to a sequence called the X-box in one of human MHC class-II genes, a really thrilling name. I wish we'd named it something different.

When we knocked it out in lymphocytes, we didn't see any effect on MHC class-II expression, so maybe in vitro it controlled those genes, but when you knocked it out in the mouse, no effect. Instead what it did was to result in an absence of antibody. There were no plasma cells, which was the terminal stage of B cell differentiation, no plasma cells. Well, I mean, that was a complete surprise. We had an animal who had normal numbers of B cells but didn't have any plasma cells, so it was the first factor shown to be required for the differentiation of the mature B cell to an antibody-producing cell, to the plasma cell. And we were sitting there scratching our heads trying to figure out how does it do it? What genes is it controlling?

Lo and behold, six months later, three laboratories independently published the discovery that XBP1 was the long-sought-after mammalian homolog of a gene in yeast called Hac1p, and Hac1p and its upstream sensor, Ire1, control what's called the unfolded protein or ER stress response in a very elegant signaling system largely discovered by Peter Walter at UCSF.

So it made sense, because this ER stress system is designed to allow a cell that's making a lot of protein to handle that load and not become overwhelmed by the fact that it's stuffed full of proteins, and if you impair that system by deleting this critical factor, the cell oftentimes cannot survive. And there is no cell in the body that makes more proteins than the plasma cell. It's just a little antibody factory churning out all these proteins. So now it made sense, and it got us very

interested in the ER stress response, which I had known absolutely nothing about. I mean, I was always flying by the seat of my pants. Nothing about the ER stress response.

Most of the work in the ER stress response had been done using pharmacological stressors and had been done in yeast, and here we had a mouse that lacked this gene, and it enabled us to ask what is the function of the ER stress response not only in B cells but in macrophages and dendritic cells and in other organ systems. So if you just make a germ-line knockout of this gene, these mice die in utero because they get apoptosis, they get death of liver cells at about mid gestation, and we circumvented that problem by making a conditional knockout because that technology had just come on line, and got interested in what other organ systems really rely on a vigorous ER stress unfolded protein response for their survival.

So what happens if we put XBP1 back in the liver, get those mice to birth? What's the next organ that fails? Well, the next organ that fails is the pancreas, because the pancreas is producing tons of digestive enzymes, and if they don't have this ER stress response, if it's impaired, then they can't handle all the load of these digestive enzyme proteins, and they die. So these little mice when they're born, they can't digest the milk in their stomachs, so they basically die of hypoglycemia. They die of starvation.

We looked at the brain and the impact on neurodegenerative diseases because those are protein-folding diseases, and, sure enough, it plays a role in amyotrophic lateral sclerosis in Huntington's disease, and we're looking at Alzheimer's disease now. And we asked what it did in macrophages and we asked what it did in other organ systems. So we were able to say in a mammalian system when is this important and why it's important in pancreatic islet cells. So these mice that have deletion of XPB1 solely in pancreatic cells, in islet cells, they get diabetes.

Then we made another very serendipitous discovery. I guess this is just an example of keeping your mind open when you get a result you don't expect. We figured that because it was so important in fetal liver, because liver again is a very highly synthetic organ that's making lots and lots of proteins, we figured it would be important in the adult liver. So we wanted to delete it selectively in adult liver, which we did, and liver looked fine. It was making synthetic proteins pretty well. There was really no significant deficiency in levels of proteins that the liver makes.

And I said to the postdoc, "Well, it's got to be doing something in liver, so let's just check every lab value in these mice," and to our astonishment, we discovered that levels of cholesterol and triglycerides were extremely low in these animals. And that resulted in a 2008 paper in *Science* showing that XBP1 controls hepatic lipogenesis by controlling the enzymes that that use fatty acids or sterols to make triglycerides in cholesterol. So mice that have no XBP1, very low levels of cholesterol.

This brought us into lipid biology, a field that I knew less than nothing about, really, less than nothing. We teamed up with a great guy at the Brigham whose field this was, and the postdoc got very interested in lipid biology, and now he has his own lab and he's really exploring this in much greater depth.

Along the way, we ended up cloning a second factor that's important in triglyceride synthesis and were able to find patients who had mutations in the second factor, had extremely high triglyceride levels. So I got invited to give a keynote address at a meeting on lipid biology. Who am I, am immunologist, talking to a group of people who actually know this subject? As I say, I'm always flying by the seat of my pants. So we don't work on it anymore, but the wonderful thing is that the postdoc who made the discovery is doing great work and has formed his career on this.

Williams: What's his name?

Glimcher: Ann-Hwee Lee, and he's here. He came to Weill Cornell where he's an assistant professor. He was an assistant professor at Harvard.

Williams: What about your postdoc with the T-bet discovery?

Glimcher: Susanne Szabo. She decided to go to Novartis. She's at Novartis.

Williams: So, briefly, what are you working on now?

Glimcher: We continue to work on the ER stress response. When I moved here from Harvard and took on the role of dean, I knew that I would only be able to spend a small percentage of my time in my lab, so I cut down the size of the lab dramatically, and only a handful of people came with me here to Weill Cornell. We had to pick and choose what we were going to work on, and we choose to focus on the role of the ER stress response in other diseases, because that was yielding us surprises all along the way. So we're studying the function of ER stress in cancer and have some very interesting data on its role in breast cancer stem cells and initiating cells in breast cancer.

We're also looking at its function in the host immune response to cancer, and we're finding, again, some dramatic effects of XBP1 in the immune system in the studying of, in this case, ovarian cancer. We're looking at its function and continuing our work on its function in macrophages, so that's one group.

We also began a few years ago to look at HIV infection. I got involved with the Ragon Institute of the Mass General, and we have some very interesting data on the control of HIV infection by a number of different things, and we're continuing to work on that for a while. The other major area is skeletal biology, which we haven't touched on.

Probably the best example of serendipity was our segue into this field of skeletal biology. Actually, we were looking for the factor that controlled Th1 differentiation, which turned out to be T-bet, but actually before we found T-bet, another postdoc in the lab had done a screen looking for that factor, and he turned up a factor that at that time was called KRC. Somebody else had isolated it from a thymic library, wasn't sure what it did. Anyway, we turned up with this factor which is now known as Schnurri-3. We thought, well, this is really it. It's only expressed in high levels in T helper-1 cells and not T helper-2 cells. This is going to be the factor. So we knocked it out and looked as hard as we could into every single immune parameter in those mice and didn't find anything. There was a little decrease in interleukin-2 expression so it did something in the immune system.

I was sitting in my office one day talking to the postdoc and the graduate student who were working on this, and I said, "You know, we have so much in vitro data that this factor is important in the immune system. There's got to be something it's doing." So I said, "You looked at everything, right, the lymph nodes and the thymus and the bone marrow?"

And the graduate student, Marc Wein, said, "You know, the funny thing is we're having a hard time getting the bone marrow out."

I said, "Why?"

He said, "Well, I don't know. The bones seem to be occluded. There doesn't seem to be much marrow in them."

I said, "Well, tell you what. Why don't you walk down the street, take the mice with you, and go to my dad's lab at Children's Hospital and take an x-ray of the mice." I'm a rheumatologist, you know, bones and joints.

They kind of looked at each other, like, "We'll humor her." So they go down the street. They take an x-ray of these mice. Unbelievably elevated bone mass. The bones looked normal, but there was just a heck of a lot of bone. It was amazing phenotype, very dramatic phenotype, and that was the beginning of our interest in skeletal biology. I shouldn't say it's the beginning. Over the years, as we had generated a series of knockout mice that were deficient in various transcription factors, we had occasionally come up with a skeletal phenotype, because, you know, transcription factors are promiscuous; they don't just do one thing. So mice that lacked c-Maf, for example, not only didn't have any IL-4, but they were runted and they were also blind because they failed to develop the lens, of all things. So they were runted.

So I worked with my dad, and we showed that they had hypochondrodysplasia. They had impaired development of cartilage, and that's why they were runted,

and that had been the same for another factor that we had cloned called mXBP1 or ATF2. We deleted that, and we found that those mice were runted, and that was for somewhat different reason. And we also had deleted each of the NFAT transcription factors, and when we deleted one of them, the mice developed osteoarthritis and chondrosarcomas. So we studied that with my dad.

So we had dabbled in the field, but we're not skeletal biologists. Then we got this absolutely blow-away phenotype that had just enormous implications for a disease that's more common than any other disease in the world, and that's osteoporosis, low bone mass, particularly in women. I thought, you know what? I'm a little tired of immunology. Skeletal biology is in many ways a simpler field. It's also quite a barren field compared to immunology, not that many scientists working in it, and much less known. It's a little bit simpler because there are fewer cell types in the skeletal system. I mean, you have the cell that resorbs bone, that's the osteoclast, and the cells that lays down bone, that's the osteoblast. Then you have the cartilage cell, the chondrocyte. Finally, you have the osteocyte, which is the fully differentiated osteoblast that secretes matrix proteins.

So I thought, you know, let's really pursue this. And we had a lot of interest from pharmaceutical companies because of its obvious therapeutic implications. The mice were otherwise completely healthy. So we knew. We'd had mice for two years there, no other problems, healthy mice, haven't any other issues in other organ systems. They just had a lot of bone, and it was good bone. It was normal morphogenesis of bone, normal joint spaces, just a heck of a lot of bone, and they were impervious to age-related bone loss.

So we had this wonderful agreement with Merck, and that allowed us to really expand and become a bone lab as well, and we were working on more than just Schnurri-3. We isolated a bunch of other factors that were important in the osteoblast or the osteoclast, and it became a very robust part of the laboratory that I called my bone team.

So we're continuing that work, because I really want to find a small molecule that targets Schnurri-3. I think it is the best target around right now to increase bone mass. So most of the current therapeutics for osteoporosis target the osteoclast, and they halt bone resorption. The problem with that is the two processes are usually coupled in vivo, so if you decrease bone resorption, ultimately you're going to decrease bone formation, and what you really want to do is lay down more bone. You don't want to just stop resorbing bone. You want to lay down new bone, not just for osteoporosis, but inflammatory arthritis where you have bony erosions. You want to heal those erosions.

In cancer where you have metastases to bone, painful lytic lesions, you don't want to just halt that; you want to fill in those lesions with new bone. So the gold standard, the pot at the end of the rainbow now in this field is find agents that increase anabolic bone formation. So we're continuing those studies in the

laboratory as well. So we're determined that we're going to—I think we've finally figured out how Schnurri-3 actually works to increase bone mass in the osteoblast, and now we have to find a small molecule that targets it, which we're doing.

Williams: How many years off do you imagine that will be?

Glimcher: Well, we've done a couple of screens and gotten some candidates, and I think it's—who knows? Who knows? I'm hopeful that we can find a small molecule sometime in the next couple of years and send it on its way.

Williams: What other results of your work should laypeople know about in terms of their self-interest?

Glimcher: We've used genetic models in mice to look at a lot of different diseases, so when you think of what does Type 1 immunity do, it does a lot of things. You need vigorous Type 1 immunity to combat cancers. You need it to fight off infectious diseases. You need vigorous Type 2 immunity in the setting of infection with parasites and worms, for example, and for optimal antibody responses.

So when you have a transcription factor like T-bet, for example, and you delete it and you essentially abrogate Type 1 immunity, you can show what impact does that have on disease X, Y, and Z. So if you ablate T-bet, you're protected against Type 1 diabetes. You're protected against systemic lupus. You're, however, much more susceptible to asthma. So we showed that if you deleted it in T-bet, you get spontaneous asthma that looks very much like the human disease because it's accompanied not only by airway hyper resistance but also by chronic remodeling of the airways.

We looked at a lot of diseases, looked at a lot of infectious diseases. We've looked at a lot of tumors. If you delete T-bet, you are susceptible to prostate cancer and so on and so forth. We showed that patients who have hypomorphic mutations in XBP1 have a higher risk of developing Crohn's disease and ulcerative colitis. So you can go from mouse to human.

I think the central problem is lineage commitment. What makes one cell be a liver cell and another cell be a pancreas cell, another cell be a lymphocyte? Or what makes a cell be one kind of lymphocyte and not another kind of lymphocyte? That is at the level of gene expression, because we all have the same complement of DNA, but each cell expresses, transcribes, and translates only some of those genes, and the reason for that are these regulatory proteins called transcription factors that turn gene expression off and on, and we have been dedicated to finding what those factors are.

Williams: You were president of the AAI from '03 to '04. What memories, critical things come to mind from that period?

Glimcher: It's a group of very devoted people, and we've been really fortunate to have Michele Hogan be the executive director of the AAI for so many years. She's just done a really superb job at making that community run, making that organization vibrant and alive. The councillors, it's an honor to be elected as a councillor to AAI, and that group of people really work hard together and try to expand the community of immunologists, make *The Journal of Immunology* outstanding, and organize the yearly AAI-FASEB [Federation of American Societies for Experimental Biology] meeting.

The president of AAI should use it as a bully pulpit to speak out on issues that are important to science. I decided when I was president that I wanted to do something concrete that would level the playing field for women. The idea I came up with was a program that would provide some technical assistance to postdoctoral fellows who are primary caregivers. Having raised three children myself, I know how difficult it is to do everything. It's tough. It's really tough. Sometimes you're lucky and you have a spouse whose schedule is more flexible. In my case I had a spouse who was a surgeon, so his schedule was totally inflexible, and it's not easy to do all those things at once.

When I was a postdoc at NIH and our daughter was born just shortly after I got there, my day was constricted. Drop her off at daycare and pick her up, and I didn't really have time to sit around and chat with the other postdocs. I mean, the male postdocs would sit around they would talk, you know, they'd exchange ideas. They'd go down for lunch. I saw the cafeteria at NIH maybe two times in the three years I was there. I didn't have time to do that. I had to do my experiments. I would bring a little paper bag from home with lunch and eat it at my desk, because I knew I had to pick up my daughter at five o'clock at daycare. So I'd drop her off, go into work, come back. I could work on the weekends sometimes, but it wasn't easy.

So when I started my own lab, I wanted to try to make it easier for the young women that I was training who had children. Now, it's not gender-specific. I mean, if it happens that the male, the husband's the primary caregiver, then—that is the case not very often. So I found that by giving my female postdocs who had kids technicians, full-time technical help, it really leveled the playing field. Not that they shouldn't themselves do experiments and work hard; they absolutely should. But at least when they have to leave at five o'clock or six o'clock, they're not being penalized because they can't be there till ten o'clock at night and they can't come in and spend all weekend there. And I saw how helpful that was.

So many of my female postdocs have gone on to do well. Terri Laufer is a professor at U of Penn. Kerri Mowen is at Scripps. I could list a lot of successful female postdocs who have said to me it really made the difference to have this helping hand. And the men in the lab didn't resent it at all. They understood.

Williams: Functionally, how did it work?

Glimcher: Hired a technician. I would pay the money. My lab was well funded, I was able to do it, and I was able to say, "You can hire a technician."

Williams: But as president of AAI, what, you just promoted this idea or what?

Glimcher: So I promoted this idea, and I convinced the NIH to fund a pilot program, the NIAID [National Institute of Allergy and Infectious Diseases], actually, Tony Fauci, to fund a program where if the PI had an R01, could apply for a supplement of $50,000 for a year to provide a technician for a primary caregiver. That program was called PCTAS, Primary Caregiver Technical Assistance Supplement. It was a small program. Unfortunately, I mean, as always, money is always an issue at NIH.

But over the years I got letters from the women that had been chosen and saying this made an enormous difference, because many labs don't have the funds to be able to do that, and I didn't—I wanted it to be available to all. Now, that program, unfortunately, because of the budgetary constraints, is no longer in existence. I tried, but unsuccessfully, to get other institutes at the NIH to pick it up. I pushed very hard for that program at Harvard as part of Summers' task force women on women in science and engineering. But I would love to be able to do that here at Weill Cornell. I'd love to have the resources here to make that a college-driven program, because I think it makes a huge difference at that stage in your career. You're thinking, "Can I do this? Can I stay competitive, be on the cutting-edge of science and raise a family?" And, in the case of a physician, also keep my hand in the clinical pool as well?

Williams: Funding, of course, was a big issue during your time as president under the Bush administration.

Glimcher: Less so. Less so.

Williams: Less so than now?

Glimcher: Oh, less so than now, yes. So when I first went on study section the late eighties, early nineties, very bad time, very demoralizing. The funding pay lines were way down, and then, of course, [William J.] Clinton came in and we had the doubling of the budget. That continued some into [George W.] Bush's years. So it was reasonable. Funding was reasonably robust until, I don't know, around the last five years. Then the ARRA [American Recovery and Reinvestment Act] program, of course, under [Barack] Obama gave people a boost.

Williams: You said that government was driving research more and more.

Glimcher: No.

Williams: Well, this was from one of your presidential messages, I think.

Glimcher: What do you mean, "government was driving"?

Williams: Well, they were deciding where money should be allocated. I guess it started with the AIDS research. But you had some issues with the NIH Roadmap Initiative. Do you recall that?

Glimcher: I think we should leave that out.

Williams: Okay. What about biodefense research? That's one area where—

Glimcher: Well, I want to say that Tony Fauci has been a truly remarkable director of an institute at NIH, and Tony has always been a big believer in basic research. Yes, there's a big AIDS budget and, yes, there's a big budget on biodefense. I was a recipient, I was a PI of a biodefense program project grant, actually, and we did a lot of basic research on the host and on the pathogen. So I think Tony has done as good a job as anybody possibly could do in seeing that the funds—and recognizing that the biggest discoveries come from basic research. That's where they come from, and so if you are thinking about biodefense, you're thinking about HIV, you've got to understand the virus, you've got to understand the host's response to that virus. The way that the funds at NIAID have been distributed, I think, reflect the belief that we need to continue to support investigator-initiated research.

Williams: So looking back on that year, that was a good experience for you?

Glimcher: It was. I still remember the week of the meeting, the AAI meeting, which was in Washington, booked from morning till night. Every day was scripted. Actually, I brought my mom with me because my daughter was living in Washington, D.C., and I brought my mom with me because she wanted to hear my presidential address, and so it was a very fun week.

Williams: What were the themes of your presidential address?

Glimcher: Well, it was a combination of one's own work and what you think you've accomplished as president. So I talked about my own work, talked about that, and then I talked about this PCTAS program and how I hoped it was just the beginning of more programs to come and that universities and colleges would pick this up and really use resources to try to fund it, because I think it's a crucial inflection point for young women. It's where biology meets career.

Williams: So, big picture, where do you see immunology going today and how promising is the future?

Glimcher: Immunology has grown by leaps and bounds in the last couple of decades. It's almost inconceivable when one thinks that it wasn't all that long ago that we didn't know there were different kinds of lymphocytes, like T cells and B cells. The pace of discovery has been phenomenal. I think it has moved at least as fast, and probably faster, than any other field.

The possibilities are enormous for harnessing the immune system in many of these diseases. Look what's happening in cancer immunotherapy, which people have worked on for years and years, and all of a sudden it's really taking hold. We're learning how to manipulate the immune system, the host immune system, to actually go after tumors. Look at the number of different T helper subsets there are and the different functions each of them subsume, the function of cytokines in so many different diseases, and the interplay between the immune system and other organ systems. So metabolism and immunity, immunity and neurologic disease. It's clear that microglia and inflammation are very important in Alzheimer's disease. In obesity, macrophages are important in obesity, and eosinophils are too. So it's a fabulous field. It's a fabulous field.

Williams: If you had it to do over in the steps you've taken, would you do anything vastly different, or no?

Glimcher: I don't think so. No. I've always been a risk taker. That's how I've approached science is to always try to do something new, make new discoveries, not just confirm and extend. I suppose if I had to do it again, I'd maybe take even more risks. [laughs]

Williams: With risks come potential disappointments, too, and how do you—

Glimcher: Plenty of disappointments. Most experiments don't work, you know. You have lots of ideas. It's easy to have ideas. Not all of them are going to work, and you've got to be willing to say, "I was wrong about that." When you get an unexpected outcome, hey, what is this telling me? I've got to forget what I thought was happening and think about it again. When you get an unexpected result, sometimes you want to pursue it and sometimes you don't. You have to stay focused to some degree, right? You've got to create a body of work. You want to make a contribution that's very solid in a given field.

But there are times when you want to follow your nose, as we did for the discovery of Schnurri-3. We made a lot of other serendipitous discoveries that we explored and published papers on but then didn't proceed. I mean, we discovered the NFATC1 was critical in the development of cardiac valves, one of the most common human congenital abnormality, and that was great. We explored it and we wrote it up and then we gave the animals to the people interested in developmental cardiology, because we weren't going to pursue that. c-MAF was critical in the formation of the lens because it controls crystallin genes. Now, who would have thought that? Not something that we personally were going to

continue with, but you make all your reagents available to other investigators so they can pursue it.

Williams: You've talked about balancing career and family and what a challenge that is. What kind of recreational activities do you indulge in? What's the fun side of your life?

Glimcher: Like what hobbies do I have other than—you know, I'll tell you, when the kids were young and at home, I had very few recreational hobbies, because every spare minute I had was spent with them. I used to do a lot of acting when I was in college and high school and even a little bit in medical school, but that's not something that you can really do once you start your career. [laughs] I'm a very vigorous believer in exercise, so I run and I do the elliptical and I really am pretty religious about exercising. Love the opera, the theater. I love to garden. I think probably the only thing I miss about Boston is that I don't have a garden anymore. We had a big house out in the suburbs. I like to travel.

Williams: Are we leaving any important thing unsaid here for the historical record?

Glimcher: I would only say that I hate to see women sacrifice the chance to have children if they want to have children because they think that it will negatively impact their careers, and I think a number of women do that. It's fine if you don't want to have kids, great, definitely going to make your life easier. But if you do want to have them, you should go ahead and have them. My three children are really the lights of my life, and my grandson now.

Williams: What are your three children doing?

Glimcher: My daughter is a lawyer at the FDA [Food and Drug Administration], and she is the mother of the most perfect little boy in the world. He's almost two years old. My older son, Hugh, is a fourth-year surgical resident at the Mass General, wants to be a cardiothoracic surgeon. And my younger son, Jake, who's twenty-five, graduated from Harvard and shocked us all by becoming a first lieutenant in the Marine Corps, and he is back from Afghanistan, thank god, where he commanded a fleet of light armored reconnaissance vehicles in southern Helmand Province, leading to many sleepless nights. But he's back safely, and he will probably go into business or law. I think he's not going to make the military a career, but I have to admit that it was unbelievable experience for him, and I can say that now that he's back from Afghanistan.

Williams: Thank you so much.

[End of interview]