The American Association of Immunologists
Oral History Project

Transcript

Roger M. Perlmutter, M.D., Ph.D.
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Interview conducted by
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Williams: This is an interview with Dr. Roger Perlmutter of The American Association of Immunologists Centennial Oral History Project. Dr. Perlmutter is a consultant to the biopharmaceutical industry at this present time, and he was the president of the American Association of Immunologists from 1999 to 2000 and served as an AAI Council member from '94 to '99. We are at Amgen Laboratories in South San Francisco, California. Today is Wednesday, January 23, 2013, and I am Brien Williams.

Dr. Perlmutter, thank you very much for being with us today.

Perlmutter: It's my pleasure.

Williams: Good. Let's start with you talking a little bit about your own family background.

Perlmutter: So I was actually born in Minneola, New York, on Long Island, and my family, like so many, was an immigrant family from Eastern Europe that had come over in the nineteenth century, had come through Ellis Island, and had scattered up and down the East Coast, in Connecticut and New York.

My father's family was in New York City and had been in the garment trades in one way or another. My grandparents, unfortunately, I never knew, because they died young, or relatively young, and I was the last of three children. My father was someone who was very interested in the machinery, actually, that was involved in the sewing industry and have been involved in that in New York City and had the opportunity, when I was a young boy, to move out to Colorado to represent the Singer Company and to create his own business, which was actual sewing machines and the machines that work with sewing machines, folders and other kinds of things that enable fairly complex sewing patterns. So he did that, moved out there, first by himself and then we and the family followed him, my two sisters, both older than me, and myself and my mother, of course.

So I actually grew up in Colorado, and Colorado is what feels like home to me, though, of course, since I was seven years old or so when I left, I remember Long Island fairly well, but my life in Colorado in the western suburbs of Denver, what is now really the western suburbs but at the time was a much more rural environment. I was kind of a boy on horseback. I mean, it really was a time when the city was expanding a lot.

My father's business was expanding a lot. He had the opportunity to catalyze the development of some important companies. At that time the company that would be Samsonite was interested in devices that could be used to sew luggage, the Shwayder Brothers at the time, and similarly something that became Jerry Mountain Sports. Jerry Cunningham in Boulder had come back from the Army after World War II, having grown up in Colorado, understanding extreme conditions and wanting to produce a line of garments that would be lightweight down that one could use in the out of doors and created that whole down-parka

industry. But to do that, he needed sewing equipment that could actually sew those things, which was just the kind of stuff that my father liked to do, and so my father created a business that did this.

During my early years, when I wasn't in school and doing other things, I was working in the shop. So I learned to be a pretty good sewing machine mechanic as an early teenager, thirteen, fourteen, fifteen, and my father used to always send me out to jobs to fix sewing machines, which would surprise the clients quite a bit when I would show up, a beardless youth, to do this. [laughs] But I liked those machines and I've always liked working with tools, still do, and so that was a lot of fun.

I attended public schools, Lakewood Junior High School, which is now gone, and Lakewood High School. Sometime during my junior year it became fairly clear to me that I actually wasn't doing very much. The schools were not terrible, but I didn't have a lot of interest in what was going on there and I didn't find it terribly challenging. At the time, I thought very much that I might grow up to be a writer. I mean, I was interested in that.

So sometime during my junior year I decided, well, there really was not much point in staying around in high school. Maybe I should just try to go to college. So I applied to three colleges, to Reed College in Portland, Oregon, to Harvard, and to Bard College Annandale in Hudson, New York. I didn't actually know anything about these colleges at all, and neither of my parents really had been to college. My father had gone briefly for a year, but the [Great] Depression intervened and etc., so it didn't work.

So Harvard said, "Well, you know, you should wait and apply later." And Bard accepted me and Reed accepted me, and I decided to go to Reed because I liked the picture on the cover of the annual report. It was a picture of a dog, you know. It was terrific.

Anyway, so I went to Reed. I arrived there sixteen years old, first time ever. I'd never seen the campus, I'd never been to Portland, Oregon; just arrived there. As I've said in some other contexts, it's the measure of an education is the extent to which it changes one. I got a pretty darn good education, because it changed me completely. So I arrived at Reed College, imagining that I wanted to be a writer, perhaps I wanted to be a poet. It was extremely romantic. I had all these poems that I'd produced and pasted up on the walls. They were dreadful.

And while I was there, my interest in physical things and in working with tools gradually translated into an interest in science, and I moved progressively through the curriculum from literature to philosophy to science, soft and hard, so that by the time I graduated, I was more chemist and physicist than I was anything else, and that was my real interest.

At the same time, though, I had become interested in the idea of biomedical research, even though I really didn't understand what was involved in it. There was no background in that in my family, certainly. My sisters had gone to college and my eldest sister had pursued graduate work, but I really had no idea of what it meant to be a researcher or that one could actually make a living doing that.

It happened for whatever reason that I had applied to medical schools, and there was an interviewer who came from Washington University in St. Louis who was really a terrific, terrific guy, a cardiologist, but a man with broad interests. I began talking with him about some work that I was thinking about in the physics department, which had to do with the way in which snowflakes formed. This is of some interest, because, as we know, every snowflake is different one from the other, and yet they're symmetrical, and how do you form these very different symmetrical structures. There is actually a mathematics behind it, which is sort of interesting.

He thought that was pretty interesting, too, and we hit it off right away. I suspect for one reason or another that that interview having gone as well as it did resulted in my being admitted to Washington University in St. Louis, another place that I had never visited and knew absolutely nothing about and had no sense of what the middle of the country was like, certainly what it was like to live in a southern state, no sense at all.

I went there with the idea in mind that I would get a medical degree, but almost immediately, within minutes of stepping into the door of the place, I realized that that actually wasn't what I had wanted. I mean, what I really had thought about was medical research, and I had done an undergraduate thesis. All Reed College students have to prepare an undergraduate thesis. I was nominally in the biology department. Reed was then and is now a fairly structured and strict place. It is very liberal with respect to the environment for students, but it has a very strict curriculum with comparatively few electives.

I had decided, based on some reading, that phthalate plasticizers, which are used to make plastics flexible and are included in virtually all the plastic materials that we use, but in particular they're used, for example, in blood bags and things like that to give them their flexibility, that these were items of interest because of the risk that they would contaminate biological preparations, like blood. This was something that I had read about in *Nature* or something like this, and I thought, well, I can look at this problem, because I can synthesize these compounds, I can mark them radioactively, and I can follow their movement through an organism. And I thought that would be a great thesis, which would combine both synthetic chemistry and biology.

And the Reed faculty said, "No way. No way." And I still actually don't know why they said, "No way," because it was actually an interesting problem back then, and it's still a matter of great interest, because the phthalate plasticizers have

this characteristic of being weakly active at estrogen receptors. They have activity at nuclear hormone receptors, and there is grave concern about the behavior of these compounds, which are ubiquitous at this point. All of us, if you were to measure, have these plasticizers in us. There was concern about the effects of these molecules. There is concern now about the effects of these molecules on human behavior, on sexuality, on weight gain, all kinds of things. But I thought it was a pretty great project, but they would not have none of it.

Instead, I was given to a different area and was told that I should work with Laurens Ruben in the area of immunology. Now, Larry Ruben is an interesting man, and he had been an embryologist by training. At the time it was spectacular to take Larry Ruben's embryology course, because he was one of these people who could draw simultaneously with each hand. So he would stand at the side of the blackboard, in those days, with two different colors of chalk, and he would draw development. So here's the blastocyst, he would draw with the right and left hand at the same time, different—I mean, it was quite astonishing to watch.

He, having been an embryologist for a number of years, which was an area of enormous interest, decided that he wanted to pursue those studies into immunology, which was related because the issue of tissue specification and how one could distinguish self from non-self was something that was important in embryological terms. So he had done a sabbatical with Dick Dutton at San Diego. This was in the very early days of trying to understand the distinctions between T lymphocytes and B lymphocytes, and the T lymphocytes and B lymphocytes could, in fact, cooperate to give rise to more potent immune responses. He came back from that and said, "Well, what we're going to do is we're going to look in amphibians to see if we can identify the same kind of phenomena in amphibians, and we'll do that in salamanders and urodeles and in true frogs and this sort of thing, and this is a perfectly reasonable kind of thing for someone with a strong background in embryology who understands amphibians very well, has worked upon them a lot, and is working at a small private liberal arts college and can't afford the kind of enormous investment, even then, in mammalian studies.

I, on the other hand, had no interest in these amphibians, did not want to study amphibian immunology, and was really interested in even then, though I couldn't have articulated it this way, I was really interested in that interface between synthetic organic chemistry and biology, even molecular biology, though that wasn't the term that was used then.

So I, again, referred back to the literature and said, well, there's a big concern about barbiturates, which are used as seizure medications; still are. They're sedatives, of course, but they're barbiturates, because someone had reported again in *Nature* that they behaved as immune suppressants, and I felt like that was something in a very simple way that I could study in a mammalian context.

To that point, I think almost no one in the biology department at Reed College studied mammals. Zero. I mean, maybe there was somebody who had gone and done a field study of voles or something, but really there was none of this. But I arranged to have a room configured with a few cages and to ship in rats and some mice, and I took care of them, and I would immunize them, and then I dosed them with barbiturates and with barbituric acid, which is a parent compound that doesn't have a sedative effect. Looking back on it, these studies were not in any way informed by a real understanding of pharmacology. There was no attempt really to understand what the exposure would be and to translate how that might relate to human exposures.

I decided that I needed some help from people outside of Reed, and, fortunately, the Oregon Health Sciences Center had a pharmacologist named John Gabarelle [phonetic], whom I just called up and said, "This is what I'm trying to do. Can you advise me?" He was very gracious and agreed, and that was helpful in terms of some of the understanding of the fundamental compounds that we were using.

Then I was able to work with chemists from the chemistry department at Reed to actually assay some of the materials that came out in the urine in these animals so that we knew a little bit about what we were doing. Anyway, the results of the experiment were that these barbiturates had no effect on the ability of the animals to respond to model antigens and, as near as I could tell, didn't behave as immune suppressants at all. A negative result, but in the meantime I got interested in the whole area and prepared that material and wrote it up and learned quite a bit about it.

So when I got to Washington University School of Medicine, which is this enormous place—I'd gone to a small school with 1,200 students, and here's Washington University with thousands and thousands of people on staff, a giant hospital, Barnes Hospital, almost unmanageably large—I had this background at this point in immunology. I was more or less interested in everything, and I had this background in immunology. And I quickly surveyed all the people who worked in immunology at Washington University, and there was one person really whose interests, it seemed, overlapped with the kinds of things that I might know about, and that was Joe Davie. Joe was also a physician scientist. He'd trained at Washington University, and he'd spent quite a bit of time at the Laboratory of Immunology with Bill Paul, another former president of AAI.

So Joe then had come back as an associate professor in pathology, he was a pathologist by training, and I went to see him. I had a copy of my thesis, and I went to see him and I said I was interested in immunology, and I gave him my thesis. He actually read it, and he said, "You know, you really should be in the physician scientist training program, the Medical Sciences Training Program. You should be in the M.D./Ph.D. program here," which I knew nothing about. I had actually not thought of it.

At that time, the M.D./Ph.D. programs around the country were just starting up, the Medical Scientist Training Programs, the MSTP programs, where federal money was provided—still is—to leading academic medical centers to train physician scientists in a relatively short period of time, so they would obtain an M.D. degree and a Ph.D. degree more or less simultaneously. So that sounded like a good idea to me, and I applied to transfer from the traditional M.D. program into the M.D./Ph.D. program and was accepted into that program, which had the further benefit of paying my tuition and providing a stipend, which enabled my parents to retire. So it was all perfect, right?

So I began then working with Joe Davie in his laboratory, and stayed with him through my Ph.D. degree, and it was a fantastic experience. It was terrific, and it was exactly the kind of thing that I was interested in doing and introduced me to the whole idea of being a researcher as one's career, which I had not thought about, really, at all before. I really hadn't. I reflect on this. I really hadn't.

Williams: So when you went to Washington, you were as much prepared to have a clinical career as—

Perlmutter: I was prepared then to get medical training and be a medical practitioner, and the only doctor I ever knew is my family physician in Colorado.

Williams: So that was your focus going there?

Perlmutter: Yes. I imagined that I would go to medical school.

Williams: Even though what you were doing really was interesting research?

Perlmutter: Yes, absolutely. And even though the tradition at Reed—I mean, Reed was then and is now a quirky place in many respects, but Reed trains an astonishingly high percentage of faculty members at major academic centers, and it is within the top three schools in terms of number of students pursuing Ph.D. degrees, just by its tiny size, because students who go to Reed, that tends to be what they want to do. So despite all that, you know, I didn't really see myself as pursuing a research career. I didn't imagine that that's what I would be doing.

At any rate, the experience of working at Washington University was terrific both from a basic research point of view, but also from a clinical point of view. It was then and is now a superb clinical environment. The access to patients is terrific, because they have a major catchment area throughout the Midwest, and they have a very, very distinguished clinical faculty, and they had a tradition which was embodied in the words of Carl Moore, one of the very distinguished chairs of medicine at Washington University, and the man who revealed one of the fundamental explanations for the disease called idiopathic thrombocytopenia purpura, which is an autoimmune disease caused by people making antibodies to their own platelets. He demonstrated this by actually transferring blood from

such a patient into himself and showing that his platelets disappeared. I mean, it was quite amazing.

Anyway, Carl Moore, the great Carl Vernon Moore, famously said that basic science was much too important to be left to the basic scientists, all right, so that clinicians had to be involved in basic research, and that idea that clinical practitioners at the bench side would be people who were skilled in basic research was something that was viewed as essential at Washington University, maybe more so than just about any other place.

David Kipnis, who was then the chair of the Department of Medicine and an extremely distinguished diabetologist, had spent his training at Washington University with Carl and Gerty Cori, the Nobel laureate, in working on fundamental issues in metabolic regulation, so trying to understand glucose utilization, glucose uptake, and how you controlled fatty acid synthesis, very, very important basic biochemistry, and he took that back to his clinical practice as a diabetologist and as a distinguished physician and was a fantastic role model in that way, as were many others.

Phil Majerus, who was a biochemist in his own laboratory, who actually discovered or clarified the mechanism of action of aspirin, that aspirin irreversibly acetylates an enzyme called cyclooxygenase, and that was critical in terms of prostanoid synthesis. Yet there he was, a distinguished clinical hematologist on the wards practicing medicine. So many examples.

And another example, and an important one, was Roy Vagelos, who during that first year at Washington University was my professor of biochemistry. Roy Vagelos transformed the institution completely. Roy was a real visionary in terms of thinking about how one should view the basic sciences in a medical school environment. He was chairman of the Department of Biochemistry, he was a very distinguished biochemist—still is—working at the NIH [National Institutes of Health], had been the first to characterize fatty acid synthase, and he was a very, very substantive scientist, member of the National Academy but also an MGH-trained physician.

Roy had the view that the sciences, all of the individual disciplines in the medical school environment, including biochemistry and microbiology in particular, but also physiology and anatomy, were all coming together, and there ought to be a Division of Biology and Biomedical Sciences that would include all of this and permit students to take courses in any of these different areas. This, I think, was the first Division of Biology and Biomedical Sciences that was created in a medical school environment. It's now commonplace, but this was back in 1973 when he was advocating this, and he was a powerful advocate.

He persuaded the institution to change in this way and then sort of abruptly and astonishingly left to become the head of research at Merck, a job that I

subsequently held twenty-some years later. But Roy and I were friendly then and have remained friendly ever since, and he has been a driving force in thinking about the application of basic research to the discovery and development of important new medicines. Full stop, there's no question, he's been incredibly important.

So at Washington University I had the opportunity to delve into everything, and I loved all of it, and I found myself in a situation where there were days when I thought, you know, I really like clinical practice, and this is what I ought to be doing, and other days when I thought, you know, this work in the laboratory is fantastic and fantastically exciting. And it was fantastic, I mean, all of it was.

I'm sure there were plenty of moments when I was unhappy about one thing or another, but with the benefit of time, looking back, it seems it was a paradise because—well, St. Louis is no paradise, as I think everyone would agree with. [laughs] But the opportunity to pursue scientific questions so broadly in so many different areas was terrific, and there was a cohesiveness to the institution and a desire to advance medical practice that was so palpable, more so there really than any place that I have been since, I think. It was really quite extraordinary.

Williams: So it must have narrowed your focus or focused your focus as you went through the graduate program, correct?

Perlmutter: Well, the business of pursuing graduate work inevitably means that you must become extremely narrow, and as I always said to my graduate students thereafter, in one particular incredibly narrow area as a graduate student, you become the world's expert. There are only a few other people in the world who would know as much about that particular area as you would.

So the expectation is—again, as I would say to my graduate students, "My expectation is that we come to your oral defense of your thesis, I can keep asking you questions forever. There's no bottom. You're just impossibly deep in that one little area. You have to have enough breadth to know what you're doing, but you're just impossibly deep in that one area," which gives you a lot of self-confidence. I mean, the fact that you're impossibly deep in that area is not that important, actually, except that it gives you the confidence to actually master an area. Subsequently, the success of the people who get graduate degrees is based on their ability to take that skill and apply it to other things. Those who stay in the same area where they pursued their Ph.D. degree rarely succeed in doing anything important, in my view. And I think a review of the careers of great scientists would say that that was true, in fact.

At any rate, at the time when I was doing research, a fundamental question quite different from anything that I had thought about before was an attempt to understand how it was possible for a human being or, in fact, any mammal to make antibodies directed against anything. This was something that had been

observed, in essence, for a hundred years, that it was possible to make chemical substituents via organic synthesis that had never before been produced in nature. And to immunize animals with these, you had to play some tricks to do that because you had to derivatize the protein with these chemical substituents, but when you did that, you could produce antibodies directed against these chemicals never before seen in nature. Now, how did that work? Because at first pass you would say, gee, the genetic information must be there to encode an immune response to something that's never before existed. How do you do that?

Since it seemed clear from studies where people had attempted to identify individual antibody-producing cells that there were billions, potentially many billions of different antibodies that could be made, how could you possibly have enough genetic information to encode all those different antibodies? So a priori, I mean, you would say it can't be the case that there's a gene for every single antibody, that's just not possible, because we're not going to have enough genes no matter what. Even at the time, we thought we had a lot more genes than it turns out that we do, but it just didn't seem plausible. So how could you make that work?

The antibody problem was one of *the* fundamental problems in immunology and really one of the fundamental problems in molecular biology. Solving the antibody problem, which occurred in my lifetime and to which I contributed just a tiny little bit, not very much, was a really very important accomplishment, and many, many members of the AAI and presidents of AAI contributed to that. It was an extremely important set of problems, and those were the problems that I focused attention on when I was a Ph.D. student.

What happened, though—and this is very illuminating; not the only field where this happened—at the time when I began studying in 1973, let's say, when I began studying those things, we had powerful tools of protein biochemistry that permitted you to separate proteins based on size and charge, and you could begin to analyze different antibodies based on differences in size and charge. Those tools were not and probably would never have been adequate to solve this problem.

Similarly, the genetic tools that we could use which took advantage of trying to look at specific markers of inheritance—because if there were genes for antibodies, then you ought to be able to show they're inherited, so we should be able to cross animals and follow those genes going from one place to another, and that would tell us to a first approximation how many genes there were if we did our crosses right. Those tools would not have been powerful enough either.

What happened, though, was that in the mid-1970s it became possible to sequence DNA, and it was extremely clear to me, extremely clear to me as a Ph.D. student, that from the time that the initial publication from Gilbert, came out, Maxam-Gilbert sequencing, and thereafter Sanger sequencing, nearly the same time, it

became clear to me that this was going to be the way that we would understand the molecular basis of immune function.

I recall as a young graduate student saying to some faculty members that they should just stop everything they were doing and convert entirely to this, because this was clearly a revolutionary technology that was going to supply a lot of information and could be done much more readily than the protein biochemistry that everyone else was doing. That seems so obvious now, but it was not so obvious then. And I was not so persuasive, because not one of them changed, and they were completely blown away, completely, and their fields of inquiry just completely supplanted by the advent of molecular immunology, the molecular biologists who were applying their skills to important immunological problems. The best of them, of course, were people who gravitated to the area because they were interested fundamentally in immunology.

I was absolutely convinced that this was something that would be powerful and needed to be approached, but in the meantime I had clinical work to do. So, having completed my graduate work, I went on and did clinical rotations, and then I was an intern at Mass General Hospital. And while I was doing those things, the antibody problem was solved. [laughs]

So all of that stuff got done, but I was convinced that that was the right approach, and, in particular, I was extremely interested in the work that was being done at California Institute of Technology under Leroy Hood. Now, I had first been exposed to Lee Hood at Reed College, not because of anything that was taught at Reed, but because of my time spent in the library reading things of interest, and I had read some papers by Lee on multi-gene families and expansion and contraction of multi-gene families, which was an area of enormous interest for Lee, and I thought this was very powerful thinking. To me, he had seized on something extremely important that could help to explain the tempo of evolution.

In fact, when I went from Reed to Washington University, I sat down with Joe Davie, and I had decided that I wanted to pursue my Ph.D. with him, and I said, "Joe, there really are only three fundamental problems that are important in biology."

The first is, what is development. How do you start with a single cell and generate us? The complexity of that process of controlling the developmental axis and positioning, how you do that, that's a very important biological problem. The second is what is evolution. How is the tempo of that controlled? We understand selection is merciless and all that sort of thing, but how does that actually work? My thoughts influenced a lot by having read, as a nineteen-year-old, the things that Lee Hood had written. And the third one is how does the brain work, which might seem like a smaller question, but it's pretty substantive question about how you actually encode within the central nervous system an

image of yourself and empathy, how do we understand that, how do we manage to project into the lives of others, all this sort of stuff.

So Joe looked at me, and, you know, there's this twenty-year-old kid who said this stuff, and he said, "You know, let's just solve one of 'em." [laughs] I knew then that he was the right kind of guy for me. But, of course, you ended up working on a very narrow question, but a question that was related a lot to problems in development and evolution, which have remained of great interest to me ever since.

So while I was at Mass General, I said, "Gee, I should be thinking about where I go from here, and it would be nice to have an opportunity to pursue additional research in molecular biology, because I really feel like this is fundamental to doing any kind of biology research going forward." And I talked with a number of people. I was convinced I couldn't stay at that time at Mass General. I talked with a number of people, and I actually had been interested in some work that was being done at UCSF, where there was very important work being done in molecular biology. I ended up going to UCSF for a clinical residency there, but it turned out it didn't work out.

I had also written to Lee Hood, and Lee, in his very informal way, had just said, "Okay, why don't you come down and we'll talk. Meet me at the corner of Wilson and San Pasquale Saturday afternoon at one p.m., and we'll talk."

So I showed up at the corner of Wilson and San Pasquale on a Saturday afternoon, having gotten the time off from the coronary care unit (CCU), where I was the resident in charge at UCSF, and there was nobody there at the corner of Wilson and San Pasquale. [laughs] I kind of wandered around. It was really right on the campus of Caltech, and finally I decided it must be one of these buildings.

I went in there, and there was Lee, you know, in his shorts and his plaid shirt, working away at some manuscript, and we spent a couple of great hours talking about where science was. In particular, he was just over the moon about the microchemical instrumentation work that he was doing that created this facility for moving smoothly back and forth between protein sequencing, where he had trained when he was a graduate student at Caltech, working with Bill Dreyer, and DNA synthesis and ultimately DNA sequencing.

And I decided that was for me. So there I was in the CCU at UCSF, and I took advantage of some of the work that I had done while a graduate student. I called Joe and asked him if I could use that as the basis for a grant application and use the molecular biology skills that I felt I would acquire at Caltech, and I put that together and wrote a grant to the NIH, which was funded. Inconceivable in these days, but there I was.

I arrived at Caltech then in 1981 with my own funding and ready to work in Lee's laboratory, which was the most informal place that you could possibly imagine. It was, as many have said, creative chaos. [laughs] There was no structure or organization to the place at all, but it was a spectacular environment, again, because of the quality of thinking that goes on—did then, does now—at Caltech.

I, of course, was unusual in being a clinically trained physician working in an environment that was really much more on the math/physics side. So I ended up being the clinical consult for everybody, including the president of Caltech, who would call me up and ask me about clinical problems. So I kind of was an advisor. I was also moonlighting in emergency rooms in Los Angeles at the time. So it was an interesting period, but it was a wonderful place to be, and Lee's lab was a terrific place to be, and included a lot of people who went on and did important things in immunology and continued to do important things in immunology.

During that period, the molecular definition of the structure of the mouse major histocompatibility locus was performed. A lot of work was done on the structure of the antibody loci, which I contributed to a little bit. And, in addition, Mark Davis, who had come from that laboratory, identified the T cell receptor genes, and then that work was continued in Lee's lab as well. So a lot of really important work was done at that time. It was terrific preparation for me and enabled me to go on and start my own laboratory.

So I could have stayed at Caltech forever. I would have been happy to stay at Caltech forever, loved the place then, love it now, but by then I had a significant other. In fact, I'd met her at Reed when I was sixteen years old, and we had gone to medical school together, and although we had been apart a lot and together a lot, but we were really together. So my wife, Joan, and I were living together in Los Angeles. She was a Robert Wood Johnson scholar in epidemiology at UCLA, clinically trained. She decided she wanted to do an infectious disease fellowship, and she had three places that she thought about where she could an infectious disease fellowship: Harvard, Case Western, and University of Washington in Seattle.

So we thought about it. At the time I said, "Well, look, I've already been to Harvard. I don't want to go back. And Cleveland falls off the bottom of places of my list of places where I want to live, so let's not go there. So that sounds like Seattle."

Seattle is a terrific place for clinical infectious disease, terrific. So she was accepted into the fellowship program there, and I figured, well, since I'm going to Seattle, I probably should get a job, right? I'm going to be there anyway. So that was in 1984, 1983 really, when that process started. I looked at a number of potential opportunities, but it was really the Division of Medical Genetics then, unusual in that there were not really very many medical schools that had

significant Divisions of Medical Genetics. But Arno Motulsky, one of the great giants of medical genetics, had established the division there, along with George Stamatoyannopoulos, and Arno and George decided that I would be a great addition as a junior faculty member, and I wrote grants to fund that.

But in the meantime, the Howard Hughes Medical Institute became interested in me for whatever reason. I'm not sure why. George Cahill, who was then responsible for running the much smaller Howard Hughes Medical Institute, at the time quite a small operation, called me up and said, "Why don't you fly up to San Francisco." I was still at Caltech. "Why don't you fly up to San Francisco, and we'll meet at the airport."

So I said, "Okay."

George, who was laconic, he said, "Well, you won't have any trouble finding me. I'm six-foot-one and I'm blond and I'm kind of haggard-looking." There was George Cahill, someone who came from the Center for Clinical Research in metabolism in Boston, really a very important person in medical research, and, sure enough, he was sitting in a cafeteria, whatever it was, at San Francisco International Airport, and we sat down and had a cup of coffee.

And he said, "You should join the Hughes Institute." I didn't know anything about the Hughes Institute, but it sounded good to me.

So, in fact, they appointed me to the Hughes Institute, and that meant that although I had a primary appointment in the Division of Medical Genetics in the Department of Medicine at the University of Washington, I ended up funded by the Hughes Institute, which was a very good deal, and also had an appointment ultimately in the Department of Biochemistry as well.

Williams: Then you also had other grants.

Perlmutter: And I had other grants, too, which I developed before any of that happened. So it was really a terrific thing, because I had not expected—you know, was just following my wife. I wasn't actually expecting this, but it ended up a terrific environment. In particular, the other Hughes investigators were very important to me.

So Edwin Krebs, the late Edwin Krebs, Nobel laureate, who was not a Nobel laureate at the time, but Ed had been at Washington University. He, too, had studied with Carl and Gerty Cori, and Ed was responsible, in trying to understand the regulation of metabolism, he and Eddie Fischer had identified a posttranslational modification called phosphorylation, which took place on certain enzymes and changed their activity. It's probably the case about 30 percent of the biochemists in the world now work on things that Ed discovered. I mean, he's just a remarkable man. So he was a very important influence because he was

right next door, and for a while actually we shared an office. Just a wonderful man, really, really remarkable, and extremely humble and such good stories, which I could tell for hours about Ed Krebs and his life, but they're part of a different historical memoir. [laughs]

Also, Richard Palmiter, I had known Richard Palmiter's work since he was a graduate student at Stanford with Bob Schimke. Richard Palmiter is really special. Richard is an enormously incisive scientist and just fantastic. He had done these experiments working with Ralph Brinster at the University of Pennsylvania in which they had transferred DNA into the male pronucleus of a fertilized mouse egg and then adoptively transferred that egg into a pseudo-pregnant foster mother and created transgenic mice that had those genes incorporated and that expressed them.

Richard is all wheat and no chaff. This guy is really special. He and I became very close intellectual colleagues. We shared joint lab meetings. We never published a paper together, but we talked almost every day. He had just remarkable insight into biological systems and was able to think through experimental design in a very special way, and he had done that when he was in Schimke's lab and had had first characterized the nature of the translational apparatus that produces protein on messenger RNA by making antibodies directed against ovalbumin and actually immunoprecipitating ribosomes on chicken ovalbumin RNA, and he could characterize the RNA species.

This is a remarkable set of first-author papers published in the 1970s by then postdoctoral fellow Richard Palmiter, and that I had become familiar with in the course of my interest in molecular biology when I was a graduate student. So he was a legend, as far as I was concerned, and proved to be an astonishingly good experimentalist. Richard's view was very clear and quite different from mine. His attitude was that he was a pretty good experimentalist, and as long as he was, he was going to do experiments himself, right? So if you went to Richard's lab and said, "Gee, Richard, could I borrow some EcoR1 restriction enzyme?" Richard would get up, he would take his micro pipette, he would pipette out 5 lambdas of that for you, right, because he did the experiments himself.

He so much did the experiments himself that he insisted on drawing his own figures using a Leroy pen, which is one of these pens that has an ink pod and a needle in it. He would draw his own figures for all of his manuscripts—for all I know he still does—using a Leroy pen. He did all of this stuff himself. He was so admirable in so many ways.

So the challenge, of course, with Richard Palmiter, there's nobody like him, but the challenge there is that it's very difficult for him to participate in the overall activities in an academic medical center, because people would say, "Richard, would you join us in this program project grant?"

And he would say, “No, I don’t think so. No, actually, I’m busy working.”

“Richard, would you be willing to review this?”

“No. When I can’t do these experiments anymore, then I’ll review stuff.” He wouldn’t serve on any study sections, wouldn’t do any of that kind of work, because he felt like, “This is what I can do,” and it’s hard to argue with him. He was incredibly successful. I think he’s gotten a little bit more liberal now in his attitudes. But at any rate, we had a very close interaction there.

While I was there at the University of Washington, within months it became clear that there was a need to develop a more robust community in immunology. There were a number of people in different departments, in Department of Pediatrics, in Microbiology Department, and Department of Medicine, who were interested in immunology, but there really wasn’t a central focus. And I wanted to work to develop that central focus, and that led in a fairly short period of time, after the dean had done some searching for someone to come in and build it, that led the dean to ask me if I would be willing to take over and build a new Department of Immunology, which was one of the first, maybe the first, Department of Immunology ever at an academic medical center.

The argument that I made was that immunology at that point had acquired its own set of tools and questions that were so distinctive that it really needed its own separate home. There was an interface between immunology, of course, and biochemistry, of course, and microbiology, of course, other parts of the academic medical center, particularly clinically. But the language of immunology had become so specialized and so recondite, and the questions that were addressed were individually profound and had their own characteristics, and to me that meant that the only way to successfully build a strong immunology program was to give it departmental status.

We could spend a lot of time talking about what departments mean. Departments are things that faculty members care about, certainly much more than students do, but it was an opportunity to focus a lot of resources that came through the university, through the dean’s tax on clinical revenue, a little bit from the state, and a little bit from the Howard Hughes Medical Institute because Howard Hughes, though they had taken the position that if you were a Howard Hughes investigator, you shouldn’t have significant administrative responsibilities, when I told them that I was considering this, they were willing to continue to support me as a Hughes investigator and have me be chairman of the Department of Immunology as well, because at that time they said—Max Cowan was then the head of the Hughes Institute, and I had known Max as a student, because he was the chairman of the Department of Anatomy at Washington University when I was there. And Max said, “Well, you know, it’s a small little department. There’s not much work to it. You can go ahead and do this.”

So I did both of these things at the same time, beginning—I guess that was 1989 when we began to build the Department of Immunology, and over a period then of a half-dozen years built a very substantive program in immunology at the University of Washington, were able to attract luminaries like Mike Bevan, for example, from Scripps, who has done enormously important work, both before and after he arrived at the University of Washington. Pam Fink, who's now the editor of *The Journal of Immunology*, his wife, also joined us at the time. Sasha Rudensky, who has since left and is the head of the program at Memorial Sloan-Kettering [Cancer Center], made very, very important contributions to understanding of antigen presentation in MHC.

So it was a chance to bring together a lot of gifted scientists who did really, really important work, and that work goes on to this day, and the department is very much a going concern at the University of Washington. I'm very proud of what the group was able to achieve there in bringing that together, and I think it's become an important part of the University of Washington.

So, in a way, I make this point only to—I guess, distinct from Richard Palmiter, who was so focused on his own activity in the lab and the experiments that he himself did and the figures that he himself drew, I saw myself as someone who could facilitate the work of others. To me, I said, at the time, you're only as good as your colleagues are, always, always, always. I had had the privilege of working at institutions where I'd had superb colleagues that meant the world to me, and I wanted to have the opportunity to try and build those kinds of programs myself at the University of Washington. So that was a lot of what drove me.

Because I was interested in building something larger than myself and trying to build a large organization, there were others in academic medicine who thought that it would be a good idea for me to take on a larger administrative responsibility, and I was asked to consider a number of those kinds of jobs. I, of course, was, first of all, a Hughes investigator at the University of Washington, which is a terrific academic institution, a great academic medical center. I was chairman of a department that I'd established and had the privilege of recruiting its members, and it went from zero to three hundred or so people in a fairly short period of time, counting students and postdoctoral fellows, built a graduate program, obtained a training grant in immunology, did all of this work.

I wasn't so easy to move. Why would I move, actually? I could see my boat from my office window. What was I going to move to? And I really did not have any interest in being a dean because I didn't want to be drawn away from research more than I was. I could argue to myself with some rationalization, I think, that the work that I was doing in building the Department of Immunology and contributing to the executive faculty at the University of Washington and participating in the deliberations about the clinical activities at the university, and even still I continued to see patients at the university for a few years, and then I stopped, that all of those things contributed to my own research program and

informed my research program in that I was able to stay close to research questions, and, indeed, my own laboratory was extremely productive and we did terrific work.

Williams: How close to that work were you?

Perlmutter: I was very close to that work. Not as close as Richard Palmiter. I was not actually doing the experiments, but I had wonderful graduate students at the time and postdoctoral fellows, and they have gone on to do important work in universities and in industry.

My first graduate student, whom I shared with Edmund Krebs, Jamey Marth, is a chaired professor at the University of California, Santa Barbara now, and he was really the person who introduced the Cre-Lox system for recombination applied particularly in the setting of transgenic animals, in order to be able to manipulate genes in transgenic animals and to be able ultimately to control the deletion of genetic elements in an entire genome. Jamey was the first to do that and has also done enormously important work in glycobiology.

So Richard and I used to talk about this, that in general what you hoped for in your career was that you'd reproduce yourself one time, because otherwise it's a problem. [laughs] If you keep reproducing yourself many times, there just won't be enough funding available. There's an exponential problem here. So I think Richard certainly reproduced himself many times, and I think I did as well. But I've been privileged to work with really great people, and we did important work understanding signal transduction and lymphocytes. That was the problem that I settled on.

When I left Caltech, I said, we have these receptors, we've been characterizing their structure, so how does the inside of the cell know that the receptor has been engaged? How does that happen? And having Ed Krebs around was terrific for that purpose, because Ed had spent his entire career working on metabolic regulation and, in essence, what turned out to be signal transduction, which, as it happened, employed similar kinds of mechanisms for lymphocyte receptors as for receptors for traditional growth factors. They involved protein phosphorylation that worked in a different way, because lymphocyte cell surface receptors have to recruit membrane-associated kinases to actually engage in the signal transduction process as opposed to being covalently linked to those kinases as in the case of growth factor receptors.

But it was a terrific time for me from an experimental point of view, a lot of really great work was done that was very revealing, and we learned a lot in that process. So I was close to that work, and that's what I was doing.

Williams: What about teaching at Washington? Were you doing very much of that?

Perlmutter: I did an enormous amount of teaching, because I wanted to protect my junior faculty. So what we taught in the Department of Immunology, we taught an undergraduate immunology course, we taught immunology to the medical students, and, in addition, I taught biochemistry to the medical students. Then we had our upper-division courses in immunology, as well as other teaching that I would do within the School of Medicine in the upper-division courses, including in the Department of Medicine.

So I did more teaching than anybody else in the department, but I felt that was my responsibility, after all. I mean, you need to protect junior faculty so they have time to write grants and build their programs, etc., and later they would take on those responsibilities, and they did. But for a period of time, I was teaching much of the undergraduate immunology course. The immunology to medical students, I taught all of it, and also the biochemistry molecular biology section, which included DNA replication and a lot of very interesting topics but that were pretty far afield from immunology.

So I did a lot of teaching in that period, and it was a very good environment. What was missing from that environment, I didn't really know what was missing, but I knew that, to me, it again seemed like there was a lot of running room at the interface between synthetic organic chemistry and molecular biology, and we weren't exploiting that. In faithful mimicry of Lee Hood, I had set up an instrumentation facility that included the capability to do peptide synthesis and oligonucleotide synthesis and some chemical analysis.

That group, which included two synthetic chemists who were graduates of the University of Washington chemistry program, was capable of making some compounds, and the work that we had done on protein phosphorylation suggested that it would possible to make inhibitors of these enzymes and that they would have an effect on lymphocyte activation. I had the view, thinking about immunological disease, that if you could just turn down the thermostat a little bit so that signal transduction was not so facile from cell surface receptors to the interior, that you could have an ameliorative effect on autoimmune disease.

So we started out with a set of compounds that Alex Levitzki in Israel had made, which were very, very simple compounds designed to inhibit the epidermal growth factor receptor, and tried to modify those through synthetic chemistry in a way that would affect these lymphocyte-specific protein phosphorylation events, which had been discovered by people in my lab. So we were playing the methyl, ethyl, propyl, butyl game at a very low level, because we were not medicinal chemists and had really no idea what this was all about.

We also began some work which was designed to explore mechanisms of signaling in lymphocytes, and this was work in which we tried to bring together receptors on the surfaces of cells or a receptor and something on the inside, using a small molecule to link the two together, so this would be a small molecule that

could bind to two different structures and would pull them together, because there was reason to believe from work of others but we carried it a bit further, there was reason to believe that some of these receptors really kind of behaved as kind of proximity detectors, and if you could bring two signaling elements into proximity, that they would catalyze the signal transduction event, even if there was no ligand present, even if the outside of the cell didn't see anything, if you could just juxtapose things on the inside.

So that was interesting work. Mike Farrar, who's now a professor in Minnesota, began this work, and I challenged Mike. I said, "Look, we want to have a compound that could do this in a whole animal environment, and so we need something that's really not toxic." So what do you think about when you think about things that are not toxic? We think about antibiotics. If you want to kill yourself with penicillin, if you're not allergic, you have to smother yourself in it, right? It's really not toxic. Things that bind to prokaryotic sequences, you know, are highly specific. "So let's look. Why don't you go and look and see if there are any antibiotics out there that nobody has bothered to pay attention to, that have a perfect axis of symmetry that are dimeric and have two identical arms."

Right away, it took a while, but he found such a compound called coumermycin, which has a molecular weight of about 1200, it's dimeric, and it actually penetrates cells for reasons that are mysterious, and the binding site for it was actually known. We stand on the shoulders of giants. It enabled us to see further. We knew where it bound, and we could take that little piece that it bound to from a topoisomerase and insert it into whatever receptor structure we wanted. Then this homodimeric agent, when introduced into cells, would link together anything that had those tags on it. And we could show doing that that we could, in fact, get signal transduction to work just by linking two things together with this small molecule, which we would add in a dish, and subsequently attempts were made to do it in whole animals. Since that time, a lot of people have gone on to use the coumermycin method for a lot of different things. It was kind of cute and sort of fun.

But in all of that, really what I was doing was trying to apply synthetic organic chemistry and really pharmacology to the manipulation of immune function and more generally biological function, and because of that, I became involved with the biopharmaceutical industry, and I was asked to serve on the scientific advisory board of Abbott, and at the same time, I became a member of the scientific advisory board at Bristol-Myers Squibb, and became quite involved in their programs.

A number of pharmaceutical companies, and in particular Merck, had contacted me and asked me if I would be willing to join them, and I didn't really think that I wanted to do that. But then there was Roy Vagelos, who had gone to Merck and had risen up through that organization and had become the chief executive officer at Merck. So I had the opportunity to go there and talk to Roy and think about

whether that would be a good thing. I had a very close friend, still a close friend, who was chairman of the Department of Biochemistry at the University of Washington, Ben Shapiro, who decided to go to Merck, and he had terrific stories about the kind of work that they were doing there.

What impressed me about the work that I was seeing in my role as a scientific advisory board member—and this was particularly the work that I was seeing at Abbott—was the power that came from having a dedicated group of really skilled chemists who could tear a system apart by making organic molecules as probes, and it was extremely revealing how well that had been done at Abbott in a couple of different areas. One was using a combination of medicinal chemistry tools but, more importantly, genetic tools to understand the macrolide antibiotics, fantastic work that was done at Abbott, and also they had really done wonderful work on nicotinic receptor, nicotinic acetylcholine receptor subtypes, and making very specific probes for each one of them and defining the subtypes and their action. That works goes on still around the world.

That just seemed very powerful to me, and I came very close to accepting a position as head of the Merck Research Laboratories organization in West Point, Pennsylvania, but things just didn't work out quite right. Two years later Merck came back to me and said, "Well, would you consider instead running the laboratory in Rahway, New Jersey?" which is a bigger laboratory and had been sort of the flagship laboratory of Merck for a long period of time. It was the original facility that George W. Merck had first established in the 1930s.

I agonized over that for an embarrassingly long period of time because I had a great job, Hughes investigator, chairman of the department that I founded, you know, the privilege of being an academic which is a wonderful thing and a wonderful life, pursuing research questions of great interest to me with a great team. Seattle's a wonderful place to live. But at the end of the day, I decided if I'm going to do this, if I'm going to try to apply synthetic organic chemistry to these important questions, if I'm really interested in the idea of trying to discover new drugs, I can't do it as a scientific advisory board member, and I certainly can't do it as a member of the university community because there's just not enough chemistry.

So at the University of Washington, there were three synthetic chemists of some skill, but naturally they wanted to do things that were chemically interesting and that were relevant to their own research programs. So it was not possible, really, to say to them, "Hey, how would you like to do synthetic chemistry in service of biology?" because that's not what they do. On the other hand, that's exactly what a great pharmaceutical company did and does.

So I finally decided that I would try, I would do it, and I moved to Merck then. I agreed in 1996, but in that usual academic sort of way said, "Well, okay, I'll agree to come, but I won't come till 1997." [laughs] I have this whole laboratory, got

to wind it down, there are grants, there are graduate students, there's all this sort of thing.

Of course, I misperceived completely, misperceived completely what the environment was in an industrial research laboratory. For some reason, people had told me that it was pretty much like being in an academic center and sort of the same thing, and while it's true that the skills translate to some extent, it is actually a very different animal. It's a different animal because you have alignment, or should, you have common goals, you have incentives, and if there's one thing that you learn in a business environment, it is that incentives are powerful, and you drive behavior with incentives.

Now, in a university setting, each university faculty member views themself more or less as an artist in a garret and they are pursuing their own research ideas and chance favors the prepared mind, and that's an important aspect. That freedom is an important aspect of what they do.

Clark Kerr, the president of the University of California system, famously said that a university is a collection of two thousand entrepreneurs with a common grievance in parking, and that's right. I mean, it is famously like herding cats. It's very difficult to bring them together. It's very difficult to gain alignment. No one can agree on what the central issues are. They're not supposed to; they are seekers of contradiction. This does not work well in a corporate environment, because in an industry laboratory, you're actually trying to get something done, and at the end of a day, you really need to get drugs across the finish line, and they have to make a difference for people, and if you do don't that, why are you there? I mean, there's no point.

So it's a really very, very different environment, and I've talked about it in different ways for various audiences. One of the interesting things that I found over the years in running large industrial laboratories was that it was so difficult to work with my academic colleagues, not because we didn't share the same interests—we did, and they remain great friends, and I love academic life and academic medicine—but for an academician pursuing a research question, academicians often focus on the outliers in any dataset. So if you're an academician, particularly for junior faculty member building their career, they are extremely interested in aspects of a dataset that are perplexing, inexplicable, provocative, and highly reproducible. I can say, speaking as a drug-development professional, that the last thing in the world that I want to see is something that's perplexing, inexplicable, provocative, and highly reproducible. That is a nightmare for me.

What I want is something that works exactly the way I thought it would every time, because biology is really complicated. The human organism is incredibly complicated, and if I spend my life trying to pursue all these little observations, I'm never going to get anything done. So when I work with my academic

colleagues and we'll look at a dataset, I'm interested in the central tendency; they're interested in the outliers. So we're misaligned right from the beginning. Our goals are totally divergent.

Looking at the outliers, you discover unusual things. Careers can be made from this, if you have good taste. I'm not interested in careers. I want to make drugs. It's a different, totally different mindset. There were many, myself included, who wondered whether it was possible to run a basic research laboratory that was actually goal oriented, I mean, where you have objectives. You say, well, this year we're going to do the following things, so this is what we're going to discover.

What do you mean, this is what you're going to discover? I mean, chance favors the prepared mind, doesn't it? You don't know what you're going to discover. You go out and do stuff, and you make observations and then that—no. We are going to perform explicit tests of hypotheses which are directed at actually getting this mechanism validated, let's say in a preclinical species, and creating a compound that meets pharmaceutical requirements that we can actually test in people, right? That's what we want to do, and we're going to set goals and we're going to measure ourselves against those goals. And if we make progress against those goals, then we do better, right, and we'll be rewarded for it, however that is.

It's not financial remuneration. People, particularly scientists, are rewarded by the appreciation of their peers. You get a gold star. It's Napoleon pinning a medal on his lieutenant and saying, "It is with such baubles that men are led." It's being recognized that's so important. If you can gain with your group a shared view of reality and become aligned with respect to the goals and agree on a set of metrics, then you can drive these programs forward, and if you're thoughtful about it, you should be able to make some progress. That is easy for me to say now. It took a while for me to understand that in the environment of pharmaceutical company. What is it we're actually trying to do here?

Part of it, of course, is going from an academic department, which has independent investigators, and each lab has ten or fifteen people in it, perhaps, and they're pursuing their research questions, and your job really as a department chair is just to make sure that they're aware of resources that are available to assist in the process and to try and ask questions that will help people grow and work together. You go into an industry laboratory—the Merck Research Laboratory Rahway site was probably eleven or twelve hundred people at that site at the time. In fairly short order, I had responsibility for all of basic research and all of preclinical development, so that was about ten thousand people. That's a lot of people. At the time, I was running research sites not only in Rahway and West Point, but in Montreal, in Chebre [phonetic], in France, in Madrid, in Terlings Park in England, and the facility in Japan. So just going around to all of these sites, to nine international sites and raising a flag once a year took some time.

But the goal was still how do you get everybody aligned and how, in particular, do you get people to work across sites. So I would make the observation that humans are tribal by nature, and much of my career certainly in the last twenty years has been spent trying to defeat tribalism, because left to their own devices, humans will close ranks against their brethren, always, on the narrowest of differences. How many times have I sat in my office and had an investigator come in from the laboratory and say to me, "You know, those people over there, they don't know what the hell they're doing," articulating a point of view from his little or her little group that had closed ranks against the other people over there, perfectly good people doing good work, important work, but because these people were pharmacologists, let's say, and these people were biochemists or synthetic chemists, no, they couldn't align.

The best experiments were always—these human experiments—were always to say to the person who came in complaining, "Great. Go over there and fix them," reassign that person to that new area. Two weeks later they would come back and say, "You know, those people over *there*, they don't know what the hell they're doing." You could watch these experiments and tribal affiliation take place over very short time intervals without any sense of cognitive dissidence at all. It was quite amazing.

So a lot of what has to be done to bring these things forward and be successful in a biopharmaceutical environment leading a research organization is to get people to actually share the same view of what the problem is, how it's to be addressed, and to have trust and respect for one another in pursuing those questions. It's never perfect. You always have complaints. But to the extent that you can do that and provide a structure in which people can work, it's inspirational. A lot more work gets done. People see that more work gets done. It's exciting. You make progress.

And for people in the biopharmaceutical industry, there's one thing that they want. They almost never get it, it happens so rarely. The one thing they want, they want to make a drug. Most scientists spend their entire career in the pharmaceutical industry without ever being within shouting distance of a drug. Not even close. They work for thirty years in the industry on three or four or five mechanisms, none of which have any value. They work for a decade testing compounds, none of which prove to have any utility at all. Compounds that you lavish affection on, that you place on a pedestal of adoration, humiliate you by proving to be toxic in some animal species, and you're inevitably faced with the fact that, well, it's only toxic in this one species, not in the others. And you perform this sort of zoo experiment when you test twenty different species, and it's only toxic in the one. See, it's just toxic in rats. It's not toxic in dogs or mice or etc. So are people more like rats? Aren't there some people who are kind of like rats? What am I going to do with that? Inevitably, you can't go forward unless you can prove that people aren't like rats, which you can just about never do. So most people spend their entire careers in the industry not even being close,

but they want it so much, because that's why they got into it. And if you can give them the opportunity to more often contribute to producing a successful drug, it's a powerful incentive and everyone can get aligned behind that.

So, to me, I fairly early on established a pretty simple set of guiding principles, and I brought those guiding principles with me from Merck to Amgen, where I went after I'd been at Merck for five years, and they were just these. I said, look, what are we going to do? We're going to focus on grievous illness. That may seem simple. You say, of course, you're a pharmaceutical company. What else are you going to do?" But it's amazing how often people lose their way and end up spending all their time trying to make modest improvements in existing therapies, trying to take a drug that's given three times a day and give it once a day. Well, those are good things. They, too, serve, who do that. But, you know, we're going to focus on grievous illness and try and make some real progress here. So that's the first thing.

The second thing we're going to do is we're really going to focus on the task, not the tool. So if you're sitting in a traditional pharmaceutical company—this was true before; it's not true any longer. Well, it's not as much true. But if you're sitting in a traditional pharmaceutical company, if you and I were to go and visit a traditional pharmaceutical company, certainly in the mid-nineties, we would walk around the campus and eventually somebody would walk up to us and say, "You know, biologists don't make drugs. Chemists make drugs." And that's really focusing on the tool, right?

So you say, what is the target that I can approach for this disease that I can address with a potent orally by available, once daily, highly selective molecule that I can manufacture in Singapore and put in a blister pack? What is that target? To me, that's not the question. The question is, what is the target? Let's not talk about how we have to address it. I don't really care about that, because if I have a target that's really worthwhile and can affect some horrible disease, I don't care if you have to approach it with a cell-based therapy or protein or an infectious therapy. I don't care what it is. First show me the target. They're so rare. They're so unusual.

For all of the antibiotics that we have, and there are many hundreds of them, there are only about six targets, because there really aren't very many things that you can do to kill bacteria or stop them from growing where the reversion rate for bacteria isn't so fast that they just quickly are no longer sensitive. I mean, it's just so rare, and it always has to be something that involves many components, cell wall synthesis, protein synthesis. Those are the only places you can get away with it.

So it's very difficult to find targets. That's just one example. It's even worse when you talk about targets in the human being rather than in the bacteria. So let's focus on the task, not the tool. We worry about tools later. If you're going

to do that right, though, that means that you have to bring together everyone with their different background, chemical engineers, on the one hand, physiologists on the other, and get them to speak a common language. I guess if I'm proud of anything that I've done over the years in industry, it's that. It's bringing together people to do that. Let's speak with a common language and understand what we're trying to do.

The third guiding principle was do the experiment in people, and that really has two parts. The first part is to do an experiment. Scientists, amazingly, lose track of the scientific method pretty easily. Actually, they go rogue pretty easily, and they end up doing studies where they just accumulate information, but data is not understanding. In order to actually understand what's going on in a human physiologic process, we actually have to study humans, right? I've argued that human beings are an appropriate object for study for a human therapeutics company.

My experience running an animal health unit was if the experimental subject is a chicken and the patient is a chicken, it works really well, but if the experimental subject is a chicken and the patient is a human, that's not so good. So you really have to get to the point fairly quickly where you can safely do a study in humans, and you have an ethical responsibility to actually show you can do that safely, but you need to get there quickly, because the human organism is really quite a bit different from other organisms.

When you do that, you have another ethical responsibility, and that is to actually do an experiment, because so often what happened in the industry years ago was, "Hmm. I have this compound and it seems to work in this rabbit model when the compound reaches concentrations of 100 nanomolar in the blood. So let's take it into humans at 100 nanomolar and see what happens." Well, that's not really an experiment. What you're doing is collecting observations that are associated with a certain drug concentration in the human population, but if it doesn't work—and it almost never does, right? Almost never do you put a compound into people and say, "Ah, look at that. It works." It never works. Probability of success is so low that you're just about never going to succeed.

So what you need to do is actually demonstrate that you test the hypothesis, that you hit the relevant target in the relevant tissue, did what you said you were going to do molecularly, and then it didn't work, and then, you know, job well done. You can take that target and move it aside, because it's not important for that disease process. If you can't do that experiment, I will not take that drug into people. I just will not do it, because, to me, there's an ethical concern. You don't use people as guinea pigs unless you can actually get something out of it, right? And you have that responsibility. So to me that was extremely important.

And the last guiding principle relevant to these others was to integrate the efforts of everyone, not just the scientists, but the people who come from the commercial

side, the legal side. Everyone has to get together in order to—I refer to it as a seamless integration process. If I don't have the right intellectual property attorneys working with me, we can never characterize what we've done. We just can't. So if I can't get them, if they're not in the room, I don't know what I'm doing.

Similarly, I found from my experience as a physician that patients didn't tell me the truth. It wasn't anything bad on their part. It was only good things. It was because they need to feel better. So the experience is this. This happened to me when I was on the Bristol-Myers Scientific Advisory Board. The experience was, well, Bristol-Myers was interested in the question, having developed the first angiotensin converting enzyme inhibitor, was there reason to make angiotensin receptor blockers? They would do the same thing in principle, so was there a reason?

So I was asked to lead this discussion, and I gathered together all my learned academic cardiology colleagues, and we had a good discussion. At the end of this discussion, which was held in Princeton, one of the vice presidents in the sales organization got up and said, "Dr. Perlmutter, that was really fascinating. I learned an enormous amount from that. Thank you very much. But I think you kind of missed the point, because it's really all about the cough."

Now, angiotensin converting enzyme inhibitors have a mechanism-based adverse effect: they make you cough. We know how that works. And we academic practitioners always say, "Well, you know, so you're going to cough for a little while. It'll be okay."

What actually happens is I go in to my patient and I said, "Well, Mr. Johnson, how are you doing on your new ACE inhibitor?"

"Great, doc. It's really great. It's making a big difference for me. I feel like I've got a lot more energy. I can do a lot more."

What really happened was he took one pill, started coughing, and he flushed the rest down the toilet. That's what happened. But he doesn't want me to feel badly that I prescribed this drug for him that didn't work, so he tells me that it's actually working. That's what happens.

I said, well, you know, if I'm going to actually make drugs that make a meaningful difference for people, I'd better know what the sales force knows. It's all about the cough, right? If I don't know that, I'm not doing anything. So that's just an example of how you have to integrate the information from all sources.

So those are the guiding principles that I learned, hard-won lessons, even though they sound simple, while I was at Merck that I brought to Amgen and that proved

to be, I think, in retrospect, a pretty successful set of guiding principles for building that organization.

Williams: So when you went to Merck, you were attracted there because it sounds like you felt they would have the opportunity for you to continue your own research to some degree.

Perlmutter: Yes, you're right.

Williams: But it sounds like…

Perlmutter: You're absolutely right, but that pretty much fell by the wayside. In fact, I made the argument, not unfairly, that when I went to Merck that I wanted to have my own lab and that I needed to do that because the business of testing hypotheses is not a natural habit of mind for humans, and that if I wasn't doing it all the time, that I would sort of lose my edge and that I wouldn't be able to contribute to the research direction of the laboratory. So I needed to have my own lab. I actually had a number of postdoctoral fellows who moved with me from the University of Washington to Rahway, New Jersey. That was a big step. So we continued the laboratory with postdoctoral fellows, and we continued to publish papers, and that lasted for a little while. But fairly quickly it became clear that that really wasn't going to work.

Williams: So this, then, called upon a whole different skill set for you?

Perlmutter: Absolutely, right. At this point I had to really say, well, I'm no longer going to be publishing papers. That's not what I'll do. I really am in the business of trying to bring people together to discover drugs, and that's what I need to try and do.

Williams: And you were comfortable with that transition?

Perlmutter: I wasn't completely comfortable with it. I'm never comfortable with it completely. When people ask me what do I miss in the work that I have done over the last twenty years, I miss scholarship. That's the thing that we started with in the beginning. In one particular area, you're impossibly deep, and it gives you a sense of confidence and understanding, not to mention friends all around the world, and great, great puzzles to toy with. Scholarship is powerful. It's wonderful to be able to read the literature. I try to keep up as much as I can, but faced with the voluminous literature on the one hand and with a lot of administratively responsibilities on the other, it's not so straightforward. So I missed scholarship and I missed having the time to just think deeply about problems. Probably, bulk flow being what it is, it moves away from that towards these more general responsibilities, I'll probably never get back to it. It's unfortunate. It just is.

Williams: So what lured you away from Merck to Amgen?

Perlmutter: Well, as in all such cases, there has to be a push and a pull. The push was that it became very clear that I was completely not aligned with Ray Gilmartin, who was the CEO of the company. Ray and I had a number of occasions to interact. It wasn't a hostile interaction at all, but I was sort of an angry young man at the time, and my hair was completely on fire, that everything needed to change. If the place was going to be successful, a lot needed to be done. And he was much more cautious. He said, "Work with me. I hear what you're saying. We can solve these problems together." But then it wasn't happening, and so I felt like it was time to leave. My feeling was that I could either go back to a university setting, which I thought very much about doing, and I looked at a couple of deanships, or potentially I could go to another company.

As it happened, I had gotten a number of calls from Amgen. I wasn't interested in Amgen, because I felt it was too small to have any real impact. But Amgen had on its board David Baltimore, and David, a distinguished molecular immunologist, no one more distinguished, Nobel laureate. David called me up and said, "You know, you really ought to look at this." I'd known David for many, many years at that point. And he said, "You ought to look at this because I think it's an unusual opportunity."

Based on his recommendation, I said, "Okay, I'll go out and look," and I went to Amgen, and it took me about thirty seconds to realize that there was a great opportunity because Amgen was big enough, as it turned out, had sufficient resources to actually be able to mount a credible research effort, but on the other hand, it didn't have the rigor and discipline of a great pharmaceutical company. I felt like I'd been an apprentice for five years, I'd learned how that was done, and I could bring that rigor and discipline.

My goal was to bring to Amgen the rigor and discipline of a great pharmaceutical company without destroying the ebullience and risk-taking environment and the very West Coast attitude of Amgen. Again, I think in some significant measure, I succeeded. Yes, it was a spectacular period for the eleven years I was at Amgen. We grew stupendously by any measure, from an organization that had less than 7,000 employees when I joined—remember, I was supervising 10,000 at Merck, so less than 7,000 employees—to 20,000 by the time I left. The company had only two drugs at the time when I joined and ten when I left and had increased its revenue by fivefold, so it was really a giant, giant change. That was a great experience, to be able to be with the company and help to grow the company in that way.

Williams: So how much of that accomplishment is really due to your having come?

Perlmutter: Not much, I mean, to be honest. I'm sure I don't have the right perspective on it. What I think I was able to do was to bring together a group of very talented people and to give them a set of goals that they found inspirational, and they did

all the work. I didn't do any of it. I didn't discover any of those drugs. My name is not on any of those patents. I didn't write any of the documents. I corrected spelling and grammar in some cases. I didn't do any of the regulatory filings. I did defend some of them with the FDA, but I didn't write any of them. So I wasn't responsible for that work, but I had the opportunity to bring the group together and to applaud their progress and to make some decisions about which things would go forward and which things wouldn't, and that helped.

Williams: How would you characterize the people, the scientific people that you were working with in both these settings as compared to your colleagues and postdocs and whatnot in the academic setting?

Perlmutter: I think they are very different in attitude. Their training is identical, of course. Everyone trains in academic centers. They all trained in the same kinds of labs. But people who come to industry are people who really like the idea of working in teams and being part of some larger structure. People in the academic environment, first of all, most of them don't have much experience with that. That's why chemists make that transition a little bit more easily. That's number one.

Number two, they're really very focused on individual accomplishment. Again, there is the issue of a body of work associated with your name, and the idea that these careerist aspirations are a very important part of the socialization process in an academic center. So people are trained in that way, and those who do well in an academic center typically have those kinds of attitudes and really don't like what goes on in the pharmaceutical company because how do you distinguish yourself in that sort of environment, where you recognize, if you're smart—and people who have been trained in the sciences typically are—you recognize within minutes that you don't have the skills necessary to advance a drug, and you're not going to have them because there are too many different fields. You can't know them all. You may be an extremely gifted immunologist, but what you know about material science is modest, and you're never going to be somebody who actually works out the formulation for a new drug. You're lucky to be able to spell it. You don't know what that is. You have no idea what the underlying physical chemical principles are behind that, and you can't learn them. You don't have time. You're too busy doing your own work.

So you have to take pleasure in the fact that you're working with other people who do have those skills. That's at least previously. I think it's changing a little bit in academic life. But that's a very different kind of attitude, and it's the only attitude that enables you to succeed in the biopharmaceutical industry.

Williams: So it's my understanding you rode out what we might call a phase of the history of Amgen, because by the time you left, things were not quite as vigorous as before. Would that be right?

Perlmutter: No, I don't think that's fair. I think it's, if anything, more vigorous. So Amgen's story is this. I was present at the creation. It was really started with Lee Hood and the original identification of both the erythropoietin protein sequence from a small sample, taking advantage of the protein chemical expertise that existed in the Hood laboratory, and the linkage with phosphoramidite synthesis, which Marv Caruthers had developed in Boulder, made it possible for Fu Kuen Lin, who was one of the first scientists at Amgen, to clone the erythropoietin gene. And from the founding of the company, Amgen, in 1980 until the launch of the first drug, which was in 1989, I guess, that's a pretty quick time to go from, you know, an idea to actually having a drug.

Indeed, when the company was started, they had no idea what they were going to do. The business plan included all kinds of things. The company was started really by Bill Bowes, a venture capitalist, a wonderful man, and Bill started many companies, as he points out. His view was this sophisticated. This is Bill talking. It was this sophisticated. He said, "Back in 1980, I figured that the world probably had room for three biotechnology companies, and there were only two. So I decided I would start the third, because, you know, why not?" There was Genentech and there was Biogen, so he started the third, which was Amgen.

And Amgen became the most successful earliest. Both Biogen and Genentech suffered, and eventually Genentech had to sign a pact with Roche that ended up with them being acquired. Biogen struggled for a long time. But Amgen was immediately successful with erythropoietin, which was something the Fu Kuen Lin had been asked not to work on. It was completely outside the business plan. And not only were they successful with that, but two years later, they were able to launch G-CSF. So two successful drugs, astonishing, and they just skyrocketed, and there was money pouring in over the transom to do all kinds of things. Then they didn't register another drug for ten years.

So when I joined the company, hadn't registered a drug in ten years. Not only that, in the prior year they hadn't even introduced a single new molecule into clinical trials, zero. That was the state. When I sat down and spoke to the heads of research, each one of them told me the same things, the same two things. They said, "Number one, I'm not qualified to do my job, and, number two, I don't want the damn job anyway."

Well, that was pretty easy. Now we had to start at the beginning. So it involved recruiting a whole new team across the board in research and ultimately in development as well. Over that period of time then, the company was enormously successful. Not everything worked, some things didn't work, but we were able to register a terrific series of drugs. And by the time I left the company, we had a giant pipeline, arguably—as always, everyone has the best pipeline in the industry. It certainly was something that was viewed as being enormously valuable.

When I left the company, Kevin Sharer and I, the CEO, had decided, unbeknownst to everyone else, that it was time for a generational change. We'd been there for a long time. He basically became CEO, and I came in as one of the first recruits, and it was time. And we'd both had the privilege of recruiting and grooming our successors. So we decided that we were going to do something that was extremely unusual in American business, which was to orchestrate an orderly transition in leadership. Almost never happens, right? But we were going to get that done.

So nobody else knew it, we for a long time knew it, and we would go and give our presentations to the company and to everybody else, winking at each other that we knew we weren't going to be there. Then we announced, together, that we were going to leave in December of 2011, and we were both gone.

So the company's moving along by itself. When I look at the company now, and, fair balance, I am a consultant to the company still, though I'm not an employee, I told them, "Well, look, if I've done my job right, then you don't need me."

And the response of the company was, "Right, we don't need you, but we'd like to have you around anyway. You're kind of a nice guy. So keep your email address, and every now and then we'll ask you questions."

I said, "Fine." So I do a little bit of work for them, not much.

But my view of it at this point is that the drugs that are in mid- and late-stage development now at Amgen will be Amgen's best drugs. They're extraordinary. And I feel privileged to have been able to catalyze that work and to bring it to the point where now they can get it across the finish line. I take nothing away from them, though. They're the ones who are going to get it registered, not me, and it's terrific. It's exactly what you want. I had a wonderful run for eleven years, and now they're going to go on and do better, so it's a great period then.

Williams: So then what are your next steps?

Perlmutter: What are mine going forward?

Williams: Yes.

Perlmutter: Well, that's an interesting question. So it's been now ten months or so, eleven months maybe now, since I stepped back from Amgen, and I had thought—Brien, if you had asked me at the time, I would have said in a few months I'm going to find another company that I can really sink my teeth into, and that's probably what I'm going to do. But I took the position saying, you know, for the first time since I was a teenager, I actually am keeping my own calendar, right? This is an unusual experience, so I am going to look at everything.

I am fundamentally interested in drug discovery and development. I want to translate important observations in basic research into meaningful interventions that make a difference for sick people. That's what I want to do. I don't care whether I do that in a university setting, in a not-for-profit institute, in a small company, for-profit large company, I don't care where it is. Wherever I can find the biggest lever, that's what I want to do. Now, that's a pretty broad canvas. I mean, that opens up a lot of possibilities. So during the past now almost a year, I've worn out a lot of shoe leather, because I also don't have a geographical preference. U.S., Europe, I mean, I'd look at Asia, Latin America, maybe, but I'm willing to look anywhere.

So I am very involved in board work, but board work is a little bit different. There, of course, you're a consultant, and all this consulting work is you can offer your best advice, but somebody else has got to do the heavy lifting. I like doing the heavy lifting. That's more important to me.

So I haven't found exactly the right company, but I have looked at a number, and I have no doubt that at some point, I'll say this is where I really want to try for the next decade or so to try and make a difference in this process of bringing important new drugs to patients who need them.

Williams: Let's talk a little bit about the Association. Would you consider your presidency there as being an activist or not?

Perlmutter: You know, I wasn't an activist president. At the time, it was a pretty good time for immunologists and immunology. The Association was actually in quite good shape. My predecessors had left it so. The funding situation for immunologists, both within the academic environment, most of them, and also for those within industry was not too bad. Things had improved substantially at that period, and so because of the doubling of the NIH budget and because of really the bubble in biotechnology, there were lots of opportunities and lots of horizons, and things looked pretty good.

There were also some early interventions in biotechnology in the immunology space that suggested that you actually were going to make these translations from basic science to clinical intervention. New companies had sprung up that did that. So it was a fairly optimistic time.

Williams: But you said in one of your presidential—no, I guess this is when you went on the Council, which was, of course, six years earlier—

Perlmutter: Yes, that's right.

Williams: So I guess the times then were a little bit different.

Perlmutter: Yes, they were, indeed. That was a time when Harold Varmus had first become head of the NIH, and he talked to everyone about that there's flat budgeting or worse that were coming forward, and that was going to be a very serious problem. At the time, we were looking at pay lines that were going to do very, very low numbers, although now it's even worse.

Williams: Any particular memorable experiences while you were president?

Perlmutter: We have within the American Association of Immunologists, there's a very standard format for the way in which Council meetings are held and the things that one usually does. There's certain activities that the AAI takes on with respect to running the immunology course, with respect to running the international meeting, international congress every year, trying to work on Capitol Hill to lobby, in a very small way, to lobby Congress to improve funding for research, this sort of thing.

At that time, Bob Rich was deeply involved in the advocacy for AAI in the congressional scene. He was working with an AAI staff member, Pat White, who was terrific. Michele Hogan was, of course, in place as the executive director, and she had everything very much under control. And I was a little bit unusual, because during the period when I had been a councilor I had moved from being an academic to being someone who was pretty significantly involved in the pharmaceutical industry and more significantly over time. So I had a different approach to each one of the tasks that the Association undertook. My ability to influence lobbying, for example, was different by virtue of the fact that I had corporate lobbyists who were involved on a different side, but I had other ways to gain access to Congress, and I had other meetings with senators and congressmen. Similarly, my perspective on what immunology could do scientifically was changed by my experience of working in the industry.

Williams: So you brought a sort of different perspective to the position.

Perlmutter: Yes, and also I think because of the fact that I was involved in managing very, very large budgets, and I was used to that kind of financial management, the way in which the Association budget was run was very transparent to me. It was very straightforward. That wasn't always the case for Council members and presidents who had difficulty with those things because they didn't have much experience with it.

Williams: Has there always been a contingent from big pharma or from the business side of the industry in the organization?

Perlmutter: Not at all. Not at all.

Williams: So you were sort of a rare bird.

Perlmutter: I was a rare bird in that case, yes. It was very unusual. I mean, the most unusual, of course, was Roy Vagelos leaving to go to Merck, and Phil Majerus said to him, "You know, they're going to make you sell brushes and combs." That was so unusual. After that, other people made that transition. I was not in any sense a pioneer there, but I was unusual among immunologists, and certainly that hadn't been done before.

Williams: One thing that loomed very large during the time you were the head of the AAI, which we now never think about, was the Y2K phenomenon. Did that have immunology really worried at the time?

Perlmutter: No, I don't think so. I mean, I think it was something we joked about. I mean, there were some who believed that the whole world was going to grind to a halt, but I don't think we felt that way.

Williams: Talking about current trainees, what advice would you give them in terms of the field in general and maybe the various directions to go in.

Perlmutter: Yes, that's a great question. To me, one of the most important things about immunology as a field has been the receptivity of immunologists to adopt whatever technology was necessary in order to answer their very profound questions. Immunologists, shockingly, have been among the first to actually put to use important biophysical techniques. Many of the important advances in protein biochemistry, for example, were made by people studying antibodies, in part, of course, because antibodies are relatively abundant and have interesting characteristics, and they're relatively stable. But in part it's because people who gravitate to that field were willing to say, okay, we'll adopt these techniques, so we'll learn to do this.

For a long time, as in the early days of molecular biology, of course, I knew every gene that had been identified and every exon-intron structure that had been determined, and so much of it came from immunological studies, because immunologists were quick to bring those kinds of tools and apply them. Immunologists were enormously quick to apply gene manipulation, gene manipulation techniques, whole animal gene manipulation techniques. They really pioneered the development of isogenic animals and the sharing of tissues between genetically identical animals, which enabled you to use them as furry test tubes. All of that work was done by immunologists, in part because it was profoundly question-driven, but in part also because immunology sat then, and sits now, at the interface between conventional disciplines. That's where all the interesting work is going on.

I would say to young trainees, that's where you want to be. Immunology is a great place to start, but all of the interesting work is always going on at the interface between conventional disciplines. As you look around you, you'll see that that's where you want to be. Currently, there's an enormous amount of

interesting work at the interface between, for example, computation and biochemistry, genetics, or traditional chemistry, just as there is still a lot of running room at the interface between chemistry and biology, as I've always said. So these are great places to work.

Right now, certainly my sense is from my academic colleagues and the time that I spend at universities that people are somewhat dispirited, and there's good reason for them to be. If you have a situation where investigators don't get their first R01 grant until they're forty-seven years old, when they only spend a few years in the system before they're no longer funded, this is not a great circumstance. It can't change quickly, because we are faced with, around the globe, very difficult financial challenges that make it impossible to allocate more money for this kind of research. So there's no doubt that this is a difficult place to be.

On the other hand, I would say that you have to follow your heart. And for people who see themselves as wanting to contribute to understanding of how biology works, I mean, this is a voyage of self-discovery in the most profound way, in a literary way. This is man's greatest adventure, and this autognosis, this self-knowledge that comes from understanding in molecular detail the function of an immunological system—because immunology sits at that interface between us as us and the outside world which colonizes us—that's a very powerful place to be in biology. And if you have a passion to understand that, there are opportunities still in academics, in government, and in the biopharmaceutical industry to explore those kinds of questions and make a real contribution.

Williams: Do you have a vision of what the field will be like in ten years?

Perlmutter: What you say in general about such questions—what they taught me in C-Suite school is that you never respond to a hypothetical, but what you say in general about these questions is that you always achieve less than you imagine in two years and much more than you imagine in ten. The progress in the near to median term never seems like it's as great as it should be, but you look back after ten years and say, "Wow, look at what has happened."

Ed Krebs said to me at one point that because of methodologic constraints, that at the time when he was an assistant professor, it was a perfectly reasonable Ph.D. thesis for a student to have addressed the question, what is the amino acid composition of a protein, and to have answered that question over the course of their thesis, and they would answer it by taking the protein and hydrolyzing it and then feeding the hydrolysate to yeast mutants that were dependent upon exogenous amino acids and then weigh the yeast. So you could say, well, if it required alanine, then here's how much alanine it must have had, because here's how much the yeast had. The error bars were enormous, etc., but they determined, sort of, the amino acid composition of the protein. That same experiment which can be done by a machine in a few hours now. It takes no time.

Similarly, when I look back on my experience—and Ed was a little bit older than I am now when he told me this story, but when I look back on my experience, the problem of understanding antibody diversity, which perplexed everybody for half a century or more, I mean, you can figure that one out now in a couple of weeks, less, for a few thousand dollars, because the sequencing machine can quickly show you the difference between germline DNA and DNA in a B lymphocyte population. True, there's some other background that had to come, but, frankly, we had that background for a long time.

So technology drives science to a very significant extent, and the pace of technology advancement is only increasing. The DNA sequencing is, of course, famously—the pace of improvement has exceeded Moore's Law with respect to semiconductors, but that's true also with respect to all aspects of measurement and purification. In general, when you can measure things, you can make progress. You don't get what you expect; you get what you inspect. And if you can look at it and measure it and understand exactly what you're seeing, it's possible to pose questions that have real salience, and those questions drive you to further discoveries. So when I look at the future for the next ten years, I would say that technology is going to produce advances in our understanding of immune regulation that are unimaginable now, because it's so powerful.

Williams: What's the interface between technology and technological development and the scientific field?

Perlmutter: Well, the interface is closer now than ever before and more challenging than ever before, at the same time. The reason that's true is that biologists who think biologically, in the past anyway, didn't have the computational skill, the mathematical skill, to understand the engineering of tools that they had to use. When the only thing you were using was size-exclusion chromatography, that without too much statistical mechanics, you can get to. I mean, that, people can understand that.

But when you get to surface plasmon resonance, most people who use a surface plasmon resonance instrument to do experiments don't really understand what they're measuring, and that creates all kinds of problems. So what that drives you to is the situation in which those who are posing the scientific questions must actually work with technologists in larger teams in order to actually get high-quality datasets. I don't think that's going to change. I think increasing specialization requires that there be more and more specialists, and the team-based approaches with be more and more important even in academic life.

Williams: And that's between manufacturers and the academic community as well as others?

Perlmutter: I'm not sure what that means, exactly. I would say all the discovery, well, with a few exceptions—really, most of the discoveries, the important fundament

discoveries are made in academic centers. They're not made in biotechnology companies or pharmaceutical companies, for the most part. When I was at Merck, I used to say that we can be proud of—we've introduced more new molecular entities than any other company, and we've never discovered any, not one thing. Yes, we discovered new molecular entities, but they worked on targets that other people had worked on in academic life, and that's generally true. The understanding of the machine, how does the human organism work, by and large, I mean, the vast majority of that work is done within the not-for-profit sector. The technologies necessary to drive that, many of those are invented in industry to work on some other problem, and then are adapted in university setting.

Williams: I've been asking everyone this question. What do you do for fun? What are your outside pursuits besides science?

Perlmutter: Well, I have a lot. I was for many, many years on the periphery of the music industry, and that, again, is part of my college experience. Los Angeles actually was sort of a second home to me long before I went to Caltech because I had spent a lot of time in recording studios, and though I play neither wisely nor well, I play often. [laughs] So having had a lot of friends in the industry who actually were talented, that made it possible for me to sit in. So I continue to do that quite a bit, and those friendships endure, and I'm still fairly active in…

Williams: Any particular instrument?

Perlmutter: You know, I play a lot of instruments, but I usually play keyboards. But I've played a lot of instruments.

Williams: Now, it sounds like at least in Seattle you were a sailor.

Perlmutter: Yes, I used to sail a lot. In fact, I taught it at one point for sailing dinghies in particular, but that requires an enormous amount of effort. In Seattle I had a beautiful pocket sloop, a 26-foot wooden boat, William Garden designed, built at the Edison Boatbuilding School, Port Orford cedar and copper fastenings, and just to varnish the toe-rails on the boat would take me like sixteen hours of rocking on the boat, cutting in, and that's just for three coats. We're not talking about Bristol condition here. It's too much work. It's impossible. So though I've enjoyed it in the past, I haven't done it for years.

Williams: So it's mainly music.

Perlmutter: It's mainly music.

Williams: Are we leaving anything important unsaid at this point, or have we pretty well covered things?

Perlmutter: I feel as if I've given perhaps short shrift to immunology as immunology in the American Association of Immunologist and I've described mainly my own odyssey through the academic setting and through the corporate setting, and I can't remedy that really, except to say that I arrived at immunology unexpectedly. It was because of the introduction of Larry Ruben in the Department of Biology, and it wasn't something that I necessarily wanted to do. But I feel that I've been so privileged to have been introduced to immunologists and immunological ways of thinking and to have worked with immunologists, because, as a group, immunologists both have in a really quite remarkable way focused on critically important questions that address issues germane to development and evolution and have also been in a position to apply tools that enable them to solve these problems and to advance the cause of fundamental research.

There are few other areas where the same thing has transpired. It's been my privilege to be involved in it, and it's been my privilege to be involved in the American Association of Immunologists as a result.

Williams: Thanks a lot.

Perlmutter: Thank you.

Williams: Great.

[End of interview]