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Oral History Project

Transcript

Henry Metzger, M.D.
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Chevy Chase, MD

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Williams: This is an American Association of Immunology [ed. Immunologists] Oral History Project interview with Dr. Henry Metzger, a scientist emeritus of the National Institutes of Health. We are in Dr. Metzger's home in Chevy Chase, Maryland. Today is Wednesday, April 25, 2012, and I am Brien Williams.

Dr. Metzger, let's start with you telling me a little bit about your own family background.

Metzger: Well, I was born in Germany in 1932, just a few weeks ago on March 23rd, so I just had my eightieth birthday. My family comes from Mainz, Germany, which is a little bit east of Frankfurt. I've been doing a little bit of genealogy, and the family, I've been able to trace them back in that general area to the mid eighteenth century, and that's sort of where my information stops.

My grandfather had a hardware store there in which my father worked. My father was one of four siblings. He had a sister who was a nurse in World War I for Germany, of course, and then, against her father's wishes, became a physician and ultimately emigrated to the United States and became a psychoanalyst. Another brother became an ophthalmologist, so I have a little bit of a physician background in my family. One other brother was also in business with my father in the hardware store.

Then partly because of my aunts coming to the United States and seeing what was going on in Germany in the 1930s, my mother finally convinced my father to emigrate, and he came over in February 1937, having gotten one affidavit from some relatives of his who had emigrated to the United States in the early twentieth century, and we followed afterwards in January 1938. So I was raised in Washington Heights in New York City. So that's sort of the background.

Williams: When did your aunt come to the [United] States?

Metzger: She came over, I think, in maybe the mid-thirties or maybe 1936, '37. I think I mentioned that in my little autobiographical thing, that she came back to visit, and I remember that visit very well because she brought with her a little Lone Ranger toy that I remember. So I must have been five years old at the time. So I was just short of six when we emigrated, came over.

Williams: So did you develop the scientific bug early in life, or what kind of a student were you in Washington Heights?

Metzger: A little bit. I think sort of the first real science I did sort of on my own. I mean, that wasn't really science, it was just sort of fooling around, was my brother had a tropical fish tank, and so I had a small microscope—I still have—tiny little thing, and I would look at little protozoa under the microscope. I enjoyed that. But, obviously, my aunt, who was probably the person I was closest to as an adult,

even more so than my parents, I must say, had a lot of influence on my going into medicine, certainly.

Williams: What did your father do when he came to the States?

Metzger: He continued to work in the hardware business, and he certainly had a lot of influence on me in terms of he was always one who was interested in how things work. He was not a very literate person in the sense he didn't read a lot, but whenever he was with friends and they would ask him about television, which was new, of course, in the early fifties, he was the one who could explain it, and loved to repair things, so on.

Williams: Your mother was a homemaker?

Metzger: She was a homemaker. At that time, she had never worked in her life in Germany, and when we came over, we didn't have a lot of resources, so she became first a seamstress, then a masseuse, and then finally an x-ray technician with a physician and actually worked at the Columbia Presbyterian Hospital, where I was training.

Williams: You mentioned a brother.

Metzger: A brother, right. He went into business, was originally going to go into engineering, but the prospects for engineers did not look so good at that time, and so he started working in a commercial laundry and recognized that that was not going to make a good career for him. So he went to Teachers College and then trained in industrial psychology and ultimately worked with various companies, sort of in executive personnel recruitment and so on. So that was his career.

Williams: Did you have other brothers or sisters?

Metzger: No, no, that's it, one brother.

Williams: Talk just very briefly about the family members that you left behind in Germany.

Metzger: Well, on my father's side, my grandmother died fairly early from complications of rheumatic disease, bacterial endocarditis, so I never knew her. My grandfather on my father's side died, I think, shortly after we left, and I forget now of what. It had nothing to do with the political disruption.

On my mother's side, my grandmother there died also, I think, of natural causes, of cancer, although I have a cousin who thinks that there may have also been some something to do with depression, and I'm just not sure exactly. But my maternal grandfather moved to Buenos Aires, where his son and his grandchildren lived, and then he came to the United States actually just shortly after the war, I think, or maybe even during the war, and lived with us in New York then.

Williams: What about your uncles?

Metzger: My uncles all came to the United States. The one uncle, tragically, thought that the Nazi period was just going to be a temporary political thing, and so he moved to Paris with his family, because he was a great fan of the French, and was imprisoned shortly. His wife thought this was the end of things and committed suicide with her children, three children and herself, turning on the oven. He was then released from prison, came over to the United States and emigrated.

It turns out that several more distant relatives probably were killed in the Holocaust. One relative, who was the wife of what was called a *Wald-und Wiesendoktor*, a sort of general practitioner, country doctor, who had led a very privileged kind of life, ended up in Theresienstadt.

It was interesting because when I was an intern and people saw my name "Metzger" and they would say, "Are you related by any chance to Lisa Metzger?"

I said, "Yes. She's a distant aunt." And they were absolutely congratulatory, because apparently she really blossomed and helped people and so on, tiny little woman, and she came to New York and read the *New York Times* every day in old age and so on. She was quite a lady.

Williams: Was your family fluent in English before you got here?

Metzger: No. My father had taken some English lessons, but, no, none of us were. Of course, at that time, my brother and I—my brother's three year's older, so he had been a little bit to school. I hadn't. But one of the last things we wanted to do was to speak German, and so we picked up the English pretty quickly, and my parents did also. There was no such thing as bilingual education at that time.

Williams: So you went to P.S.—

Metzger: 189. P.S. 189.

Williams: What was that like?

Metzger: Well, at that time the New York school system was an excellent one. City College had several Nobel [Prize] laureate students, and so it was a good education.

We lived in a rather mixed neighborhood. It wasn't all émigrés, although a lot of the people were immigrants, but I remember having a Korean classmate. Not a lot of African Americans, but a lot of Irish and American Jews. So it was a mixed neighborhood at that time. It's changed now completely. It's now largely a Salvadoran neighborhood. So I remember elementary school as being very nice.

Williams: And high school?

Metzger: High school, we lived just a few blocks away from George Washington High School, which we didn't think was good enough, or my parents didn't think was good enough for us. It was good enough for [Henry] Kissinger. [laughs] But we applied to the Bronx High School of Science, where I and my brother were able to be admitted there, so we went to that school, and that was a superb education there. It was quite a competitive environment, so I think I had sort of roughly a 90 average, which was the bottom half of the class. [laughs] It was quite a group of people there, but very, very good, and not only concentrating on science, but also on the humanities, so it was a good education.

Williams: Did you have a complicated subway commute?

Metzger: No, took the trolley car. At that time, New York in most areas was pretty safe, so even as a twelve-year-old and as a young teenager, there was no problem traveling in New York.

Williams: So you were already oriented towards the sciences by that point?

Metzger: Yes, I guess, a little bit. I mean, it was in part—I mean, there were several sort of magnet schools. There was Bronx High School of Science, Stuyvesant, DeWitt Clinton, and Music and Arts. While I was a little bit oriented toward the arts, but it was really more for a good academic background. I don't think I was that committed to science yet, particularly, although I was certainly thinking about it.

Williams: So what were the steps that took you to Rochester [Institute of Technology]?

Metzger: Very different than things are nowadays. Rochester at that time, number one, had an early admissions policy, and my aunt, Aunt Emmy, the analyst, knew a physiologist at the medical school there. She had heard about the school. I didn't think I could get into Columbia [University], and I wanted to get a little bit away from the competitive rat race a little bit in New York City. So I applied to Rochester, it was the only school I applied to, got in, and that was it. Nobody took me there to look at it. Nobody took me there on Freshman Day, and that was it, very different than nowadays where the parents take you around and so on. I think that was a good experience. I really think that the idea of being able to go into a new area where you were unfamiliar with it and recognize that you could handle it, I think that was a good maturing influence.

Williams: So you were there for four years?

Metzger: Four years, yes.

Williams: And your major was?

Metzger: My major was pre-med to begin with. I had a terrible freshman year, partly—I'm not sure why. It may have been hormones. It may have been that I wasn't prepared enough. Some of it was boredom with some of the classes, which seemed to be rather rote memory. I had almost decided definitely to switch to being a German language major, because that was sort of the easy way for me, because while I didn't have a lot of German vocabulary, my German is totally uninhibited. So it seemed like a very easy route. My aunt convinced me to try one more year, and my sophomore year was very successful, and after that things went very smoothly. It's a terrific school still, I think. I haven't been back that many times, but it's a very good school.

Williams: So as a graduating senior from Rochester, what did you see your future likely to be?

Metzger: Well, I decided that I was interested in medicine. I had a pretty good idea that I wanted to go into academic medicine, but that was about it. I didn't have anything much more specific in mind. I was already thinking seriously about psychiatry, influenced by my aunt, decided against that because I think, given my personality, I wanted something a little bit more—how do I put it?—solid, that I began to be interested in hard data, and I wasn't sure I would be happy with a little bit more kind of subjective science that psychiatry is, as important a field as it is.

Williams: So why did you choose then your next step, Columbia?

Metzger: Columbia. Ah. Well, at that time, this was in 1953. This was a time when there were a lot of veterans returning from World War II, going to college and then going to graduate school. I must say at that time for those of us in pre-med in college, there was hardly a day where we didn't think about are we going to get into medical school. It was of great concern.

By the time we actually graduated, which would have been 1953, I think it was less of a problem, and so we applied to eight, nine different schools. Columbia was attractive because it was just a mile away from where my parents lived in Washington Heights, and so it would have meant I could have lived at home.

At that time, there was still the feeling—and I think it was probably true—that there was a quota for Jews, both at Columbia and at Cornell [University], not at NYU [New York University]. So I applied to all three medical schools. I think I applied to Columbia as well as Rochester and a couple of the Boston schools, and got into Columbia. I think the year that I got in must have been the year where they dropped the quota, because there were plenty of Jewish kids in the class. I remember my mother, who was at that time still a masseuse, some of her clients said, "Oh, boy, your son must be bright to have gotten into Columbia, because

they have a quota." I don't think that was really true at that time. I think Cornell still did.

So we had a rather mixed class. They still had a quota on African Americans, of course, and on women, so we only had 10 percent women in our class of 120. So the obvious economic advantage of being able to go from home, to live at home, was a big consideration, and it was an excellent school.

Williams: So the refreshment of going off to Rochester on your own, you didn't need to continue in that frame of mind.

Metzger: No, no, that's right.

Williams: You could go back and be welcomed back home and that was good for you.

Metzger: Yes, because Columbia also at that time had the reputation of being particularly oriented towards training academic physicians, and so that was a big plus for me because I knew I was headed in that direction.

Williams: So you were in the Columbia program for how long?

Metzger: Four years.

Williams: So take me through the steps of your development there.

Metzger: Well, I'm not sure what you'd like to know. It was a very rigorous program, certainly, as medical school was then. Some of the courses were kind of boring. Biochemistry was pretty unimaginative, although it was a very strong biochemistry department. But I remember having a little bit of the same feeling that I had in my freshman year in college, that you were sort of doing a lot of rote learning about lipids and so on, and the laboratory exercises were not particularly interesting. I think that's changed considerably.

One of the things that was good at Columbia was one had a very early access with patients, so I think even in our freshman year we were already in the outpatient clinic with a mentor. I think bacteriology would have been that first year, and one of the things at Columbia that was a little bit unusual was the strength of the immunology training there. Elvin Kabat was the senior person there, and so we had quite a strong academic training in microbiology in general but in immunology in particular, and I think that must have started my interest in that.

I think otherwise it was a pretty routine medical school experience, except for the first summer it was a full year-round program, which was a little bit unusual, I think. So one of the electives was to do a research elective, and that's when I did my first real research with a woman named Beatrice Seegal, who was a tiny little woman, very sharp, the wife of a very [unclear] David Seegal, who was at that

time director of Goldwater Memorial Hospital, where the new facility of Cornell is going to be going on Roosevelt Island. At that time, one didn't have bio safety hoods and so on, so one learned how to deal with keeping things sterile by just very good technique, and one learned that with her. So that was a very, very good experience. I really enjoyed that.

Williams: So then your time as a resident was strictly clinical?

Metzger: Yes, at that time. This was between the wars, between the Korean War and the Vietnam Wars, and there was still the draft, the doctors' draft, and one could get a deferment for two years of clinical training. You have internship and a year, what was then called a year of internship and a year of residency. So I had an internal medicine internship and a year of internal medicine residency. Then one had to serve in the uniformed services, and one of the uniformed services was the Public Health Service, and one of the units of the Public Health Service was the NIH [National Institutes of Health]. If one could get a position there, that was good.

I should mention, since you asked about medical school, I think one of the certainly major influences in the medical school was the head of Internal Medicine, who was Robert Loeb, whose father was Jacques Loeb, who was the great reductionist. Robert Loeb had been trained at the [Johns] Hopkins [University] and was one of the early and outstanding physicians who recognized the importance of getting laboratory data and of hard data to make clinical decisions. So that was one of the major influences in those of us who trained under him.

He was a terrific physician also with patients, but a very, very demanding person and sometimes to the point that he could almost be a little bit cruel to somebody who didn't perform well, but if you performed well, he was very, very supportive. As a house staff officer under him, he would have sunrise services before we went on the wards as intern, in which we would discuss all sorts of philosophical things. He was reading at that time something that I just read relatively recently, which was the *Essays* of Montaigne, who was a very modern kind of a thinker, and it was just a tremendous experience, all of us who trained with Loeb.

Williams: How do you spell his name?

Metzger: L-o-e-b. Since you asked that, when one presented to him, particularly as a medical student, one was very, very nervous. There was the famous incident of one of our classmates saying that "The pneumonia is in the right upper 'loeb,' Dr. 'Lobe.'" [laughs] There were several instances like that.

Williams: So you did your two years of service.

Metzger: Right.

Williams: And then?

Metzger: Then came to the NIH, and partly through Beatrice Seegal, who was my mentor in the laboratory, she had suggested that a major area in immunology that was going to be very productive was to be able to apply protein chemistry to the biology. So she was the one who suggested that there were some people at the NIH who were applying protein chemistry to immunological things. One was John Fahey, who worked on immunoglobulins. There was a lot of very good protein physical chemistry going on at the NIH.

So when I got the position to be a research associate at that time, there were two kinds of positions one could get at the NIH. One was a clinical associate, where one worked in a laboratory but also had clinical responsibilities, and the other was the research associate program where one worked strictly in the laboratory and they also had some courses, lectures, not formal courses necessarily, because many of us didn't have all that much basic science training when we came, compared to what's true now.

So I was looking for somebody who could give me some training in protein physical chemistry, and eventually ended up in a laboratory headed by Harold Edelhoch, who was a protein physical chemist working on thyroglobulin. At that time I didn't care what the protein was, because I wanted to learn the techniques of protein chemistry, so that's the laboratory that I ended up in.

Williams: This was still under the Public Health Service?

Metzger: Oh, yes, it still is. Yes. I mean, well, it's now Health and Human Services. I mean, the Public Health Service is under the Health and Human Services.

Williams: Take me then through the stages of your career at—I know this is a big question, but at NIH.

Metzger: I got the training in protein physical chemistry with Harold, but had already in the second year started applying some of that to an immunological problem. At that time there was a great interest in trying to understand autoantibodies. One of the prominent autoantibodies that was of clinical interest at that time was autoantibodies to thyroglobulin, to the thyroid proteins, because patients with Hashimoto's thyroiditis had these autoantibodies.

There was a question at that time about one of the ideas was that maybe it was the breakdown of proteins that stimulated the autoantibody production because sites on the protein that had previously been internal and sort of hidden now became exposed, and the system had not been tolerized to those hidden antigens and that that was the reason why the autoantibodies were formed.

So since I'd been working on the denatured thyroglobulin during my first year, it was sort of obvious to look for whether the antibodies in human serum and also when one immunized rabbits, whether those were against the denatured proteins. So that was a project that I worked on in Harold's lab and had the interesting experience there, which was a lesson, because in the following sense about authorship, big, big item in science research. I'd worked with a friend, a colleague, on the same level as I was, postdoctoral fellow, in the [National] Cancer Institute. We worked out this project on thyroid antibodies, and Harold, of course, was a protein physical chemist, was quite unfamiliar with some of the immunological techniques that we used, which we are no longer used now but which were prominent then. So we worked out this little project on our own.

In the meantime, of course, I had published several articles with Harold Edelhoch, a whole series, on the properties of thyroglobulin. That was a major opus of his. There were six, seven papers. So we were standing in the lunchroom one time. I was standing with Harold Edelhoch, and I said to Harold, "I'm wondering where to send this paper that this colleague of mine and I have prepared and what we should give as a title."

He said, "Well, why don't you call it *Properties of Thyroglobulin No. 6* or something like that," and he sort of assumed that he would be the senior author on that, not necessarily the first author, but the senior author. Harold is an extremely generous and nice person, so it was just the way things were done, because it was in his lab that it was done. So that taught me a lesson. [laughs] But in any case, it was fine.

In any case, I decided at that point that I did want to continue in immunology and work at a molecular level. At that time, there were relatively few immunologists or chemists interested in immunology working at the molecular level. One of them was S.J. Singer, who, with Dan Campbell, had done some beautiful work on looking at the properties of what are now called immunoglobulins or called gamma globulins, in terms of trying to understand what the valence was, how many combining sites there were per molecule and so on. There was David Pressman in Buffalo, and there was Herman Eisen, whom you'll be interviewing, Fred Karush, who died a number of years ago, but relatively few.

I was very impressed with S.J. Singer's work, and he was at Yale [University] at that time. So my wife and I were planning to go up to New Haven. He accepted me as a postdoc. My wife, who had done a year of social work training, was planning to continue that training up in New Haven, and then all of a sudden we learned that S.J. Singer was moving to La Jolla, to the new campus of the University of California, San Diego.

My wife was pregnant at that time when we learned that, and, fortunately, Catholic University was very understanding about having a pregnant woman do her graduate training there, so she was able to finish her social work training here

at Catholic University. At the end of the year, we then moved to California under a Helen Hay Whitney Fellowship which I'd won.

At that time—again, how very different things are—I had been here, I guess, a year and a half when I was offered a position at the NIH. At that time, there was no such thing as tenure track. You were offered a position, and it was a civil service position, though it was like getting a tenured position after one and a half years of postdoc. Nowadays it's very, very different.

In any case, I turned it down in the sense that I said, "I really want to go out to work with Dr. Singer for a couple of years. I have my own funding." They were willing to have me go out for a year, and I said, "I really want to go out for two years." One year was a little bit short. So I turned that down, but the offer was still good, so I did come back after two years.

The experience at La Jolla was terrific. John Singer was one of those people who immediately saw the implications of experiments, and my colleague and I, who I can talk about in a moment, often had to sort of keep the results of our experiments secret for a while so that we could interpret them, because we didn't want John to immediately tell us, "Oh, this is worth following up," or, "This is worth following up." But he was a terrific mentor, very different than Harold Edelhoch, who very much stuck to the data. It was just a very different kind of a learning experience. John Singer loved to take leaps ahead. It's important to have both kinds of training, really.

So we worked on a project there which was interesting, which grew out of a student project that Leon Wofsy, who was the other postdoc with me, had done. Leon Wofsy, who is now ninety years old, still doing very well, interesting background. His father had been a member of the Communist Party. Leon Wofsy had been a member of the Young Communist League and decided that was not really going to go anywhere, even though he was very sympathetic to some of the more liberal causes, decided to become a high school teacher in New Haven at a time when there was a political campaign during the sort of [Joseph R.] McCarthy period. He became a major issue, a name on the front pages of the New Haven newspapers, and finally was kicked out of the school system, but, fortunately, had a binding contract so they had to pay his salary for two years.

He decided to follow up and became a Ph.D. student under John Singer, so came out to La Jolla, and had worked on a student project in which one was trying to understand how come a particular inhibitor of a certain enzyme was so specific. That led to the idea of something called affinity labeling. The idea was that if a small molecule was bound to a combining site on a protein and that small molecule had a reactive group on it which could modify an amino acid side chain in that protein, one could then label that combining site, and then one could dissemble the protein and find out where in the protein that combining site was.

So at that time, one was very much interested in trying to understand what the combining site of antibodies was like. So Leon's and John's idea was to use a small antigen, a hapten, which is a small molecule which will bind to the combining site of an antibody, make a hapten that had a reactive group to it, and Leon, I think, was the one who really picked on a particular kind of a group that had been widely used, actually, by Karl Landsteiner, one of the great figures in immunochemistry.

Leon knew that there was a particular variant of this diazonium group which could be crystallized and which was in a solid form rather than a liquid form, and so one was able to construct such a hapten and label the combining sites of antibodies. That was very, very successful.

Actually at that time, a couple of other laboratories used the same approach to try and make inhibitors of certain cancer cells and so on, but, in any case, it was a very productive period in La Jolla. This was at a time when Roger Revelle was the provost of the campus. The campus only had graduate-level departments at that time: biology, physics, chemistry, and I think that was pretty much it.

We were on the oceanographic grounds, very idyllic. I don't know if you know La Jolla, but we used to have lunch on the lawn there overlooking the Pacific Ocean. I think the second year we were there had 360 days of perfect weather, which didn't interfere with the work at all. People wondered whether you could work in such a nice environment, and one could work very well.

Then I had the offer to go back to the NIH, and I didn't have a hard offer at that time anywhere else, and I really liked the NIH, so we came back. I was sort of hired as the resident immunologist in the Arthritis and Rheumatism Branch, which was basically a clinical branch. I was the only nonclinical person there. And although I missed the clinical work, I must say I decided I just wasn't bright enough to have two careers, because my research work was really at a very basic level, at the molecular level, and I wanted to pursue that, and I just didn't see the overlap.

Williams: Who made the decision for you to join that group?

Metzger: Joe Bunim, who was the head of the branch. They wanted an immunologist, and so he made the offer. I had known the group because at that time the Institute was pretty small, and so one knew pretty much everybody. When I was with Harold Edelhoch, this was the Clinical Endocrinology Branch, so this was a mixture of basic scientists and clinical people. Of course, that was a great tradition at NIH, and continues to be, that in one department you may have people who are doing both clinical work and research work as well as Ph.D.'s doing only research work. So that was that.

Then I started working on sort of continuing on the affinity labeling procedure or technique, to try and learn something about a kind of antibody for which there was much less knowledge, and that was what are called the macroglobulins, IgM. At that time, one didn't recognize the relationship between the sort of smaller antibodies, the 7S gamma globulins and the 19S IgMs and the intermediate-size IgAs. One had no idea what the relationship was, and so one didn't know whether the combining sites of the IgMs would be different than those of the smaller gamma globulins, and so that seemed like a worthwhile thing to explore.

There had been a description by a scientist about how to immunize chickens so one could get a large amount of these macroglobulins, or IgM antibodies. Well, the technique that this person had used was based upon something called hemagglutinin activity, the ability of these molecules to agglutinate red cells. Well, as it turned out because of the size of the IgMs per molecule, they're able to agglutinate a lot of cells. When I started immunizing chickens and trying to collect the IgM, it turned out they didn't produce all that much in the way of molecules, a lot of activity for a hemagglutinin, but not a lot of molecules, and I was determined to work at the molecular level and, for that, one needed a reasonable amount of activity.

In reading some of the literature on that, I decided, well, you know, there isn't all that much known about the basic structure of these proteins, so maybe I'll just do some structural work and forget about the combining site for the moment, so that the question was then, what is going to be the source of the material? That's where one had to make a big decision, because at that time there was a controversy going on about the so-called what are called paraproteins, meaning myeloma proteins or, in the case of the disease Waldenström's Macroglobulinemia, IgM.

There was some people, including John Singer and Rodney Porter, one of the great figures in immunology, who thought that the paraproteins were really [unclear], that these were abnormal proteins, and they didn't want to work on them because it would be misleading. There were others, such as Henry Kunkel at Rockefeller Institute and Frank Putnam at [University of] Illinois, who felt differently and who were the first to really recognize, particularly Frank Putnam, who never got enough credit for it, I think, that, in fact, the population of antibodies is an extraordinarily heterogeneous population, as they need to be, because they have to combine with different antigens, and that myeloma proteins are just single examples of this heterogeneous population, so that the plasma cells which produce these antibodies, if one of these kinds of plasma cells became cancerous in the sense of multiplying, they would already recognize that one cell produces one kind of antibody, so that the heterogeneity of the antibody population was due to the heterogeneity of the cells that were producing these, so that a single cell produced a single type of antibody, and that these myeloma proteins were just examples of a particular kind of antibody, but that they were normal proteins otherwise.

So I decided I believe that, and so I'm going to find out whether somebody at the NIH has a supply of a macroglobulin, work on the structure of that. A colleague in the Cancer Institute, who had actually worked with John Fahey, who I mentioned before, Bill Terry, had such a patient. He was, I think, a clinical associate at that time with Waldenström's Macroglobulin. One of the treatments for the macroglobulinemia is to plasmapherese these patients so that you take out the plasma and give back the blood, the blood cells. So he had great sacks of this protein, and I had unlimited amounts of these proteins, and I started working on that. It turned out that the original idea that this was a hexamer, we found that was really a pentamer, and so we did basically structural work on the IgM.

Then a very curious thing happened, and I'm not sure exactly that I have the order correct. But I was also beginning to continue to try and do some work on affinity labeling and had started doing some work with Michael Potter on a myeloma protein where there was some evidence that it had some antigen activity, antigen binding activity. One of them was against a small molecule, and so we thought it would be interesting. This was an IgA myeloma, one of the other classes of immunoglobulins, an IgA myeloma. So we started trying to do some affinity labeling of this particular protein.

Well, at that time, one of my postdoctoral fellows was working on that, and we decided to use as a control in the binding experiments my Waldenström's Macroglobulin, this particular one, IgM Wag. Waggenstien [phonetic] was the patient's name. We used a technique called equilibrium dialysis, where one puts the protein on one side and the small molecule on the other side of a semi-permeable membrane through which the protein can't pass but the small molecule can. And if there's a shift in the distribution of the small molecule suggesting that it was preferentially binding to the protein by shifting its concentration, one could study the binding kinetics and equilibrium binding properties of that protein.

So Bob [Robert F.] Ashman, who was a postdoctoral fellow, came back very disappointed at the experimental result. He said, "I must have had a leak in the membrane because all of the hapten is on the protein side."

I said, "Bob, it must be binding it."

It turned out that this protein, which I had just chosen for structural reason, is one of the few examples that one had at that time of a Waldenström's Macroglobulin or any kind of an IgM from any species that bound a small hapten, which then one could rigorously study, just by pure dumb luck.

So we did a lot of work on that, and that allowed us to very rigorously check the valence of the IgM, which there was some controversy about whether it was one per monomer, so to speak, so even though there were ten combining sites

potentially, that really only one was effective, and we sort of clarified that and so on and so forth.

Then we became interested in the antigen binding properties of these, quote, "paraproteins," and so that was another area that we moved into. That's still a very interesting story as to what is the source or what is the stimulus, the initial stimulus for the cells that are going to produce these myeloma proteins, and what is the role of the antigen in that. That's still an interesting area.

Shall I continue on?

Williams: Yes. Where are we about in your career, about halfway through?

Metzger: We're now in the late sixties, early seventies.

Williams: If you can—

Metzger: Move on a little bit faster?

Williams: Okay.

Metzger: So that's when there was really a major change in my career, and that is that I had the chance to take a sabbatical, but I was given a week by our scientific director to decide where I would take that sabbatical. At that time there was somebody in England, Brigitte Askonas, who had some mouse myeloma proteins that had also these antigen binding activity. I thought it would be interesting to work with her, so that's what I told him that I would be working on. Well, she decided to take a sabbatical in Switzerland at that time, so I ended up in London with not the person I was expecting to work with.

At that time, I really became interested in a problem that I thought had not really been adequately explored. At that time, Landsteiner and others had said there were really two basic issues in immunology. One was the nature of the structure of antibodies, and the other was sort of what stimulated the immune response.

But the area that I thought really had not been getting adequate attention was how does the immune response, how do antibodies work. In some cases, it was pretty obvious. They coated the virus or the bacteria and allowed that to be disposed of or to inactivate a toxin. But there were other cases where clearly, for example, in the complement system one had some sort of a biological effect. It was as if the combination of antibody and antigen lent the ability of that antibody to stimulate a biological system, and the question was how. One of the possibilities was that the antigen changed the confirmation of the antibody to allow a cell to recognize that this was an altered antibody. That was the prominent theory at that time.

So since I didn't have a direct lab to work in in London, I decided to do a literature search on that, because I was interested in that, and I began to be convinced that there was no good evidence for this, quote, "allosteric modification" of antibodies as being the way that antigens could stimulate a biological effect, and the more I read about it, the more I became convinced that something else was going on.

Then we actually, when I came back, we did some experiments to suggest that in the systems that we had where we had antigen binding of myeloma proteins that we couldn't detect any conformational change, and I decided to explore a system where we could really study the antigen, the antibody, and a biological effector system.

That's how I decided to use the IgE system. There were already lots of people working, very good people, working on the complement system. This was a system that I thought was ripe for picking because one could get an antigen, one could get the right kind of an antibody, because there were people who had been able to work out a system where one could get substantial amounts of those antibodies, and one could collect mass cells in reasonable amounts from animals. So one had an intact system, one needed a little bit of calcium, and one could study it. That's how I got into the IgE system, and basically I did that until the end of my research career, working on that system.

Williams: So at the point where you left your active research activities, were you on the cusp of something, or what was the status of your research?

Metzger: No. As a matter of fact, it was almost the opposite, in the sense that I had developed an idea about how the system works, and the idea was a relatively simple one, not totally unprecedented, but we were certainly within the group that was thinking in these terms. That is, that basically what the antigen did was to allow two molecules of antibody to aggregate, and it was the recognition of, by whatever system one was looking at, the complement system or, in the case of mass cells, the mass cells with a surface-bound antibody, that the cell recognized that the two molecules had gotten together. That was the critical signal, and then was the question of, well, what does that do?

It turns out that we had an idea about that, what it would allow the system to do was to allow an enzyme that was already associated with the molecule that was binding the antibody, the receptor, to cross-modify the other receptor, to modify, to phosphorylate through kinase activity the other receptor. So that by aggregation, one was, in a sense, catalyzing a covalent modification of a critical molecule on the cell surface, and then the rest of the cellular machinery recognized that. That's what it turns out, I think, is basically correct.

So we started working on that, trying to identify the kinase, which actually another group had already come with some pretty good evidence for what that

kinase was, and trying to work out the details. I actually then did something that we spoke about a little bit before, working with a biophysicist, Byron Goldstein and his group in trying to actually develop some mathematical models for how this was working.

Really, at that time I was seventy years old and decided that to really stay interested in working at a good, interesting level, I would really have to modify my research quite a bit, to take a somewhat different approach, a much more mathematical biophysical approach. I thought as long as I'm healthy in between that age of seventy and eighty is an important decade, and I'd like the flexibility of not having to spend the whole year with training postdocs and so on, and so I decided this would be a good time to retire. I had sort of felt satisfied that I thought I had solved the main problem that I was interested in, and I decided this was a good time to retire. But I've continued to be interested in organizational matters, which I guess we'll get to, and love the NIH, and so I still do some organizational things with the NIH and yet have the flexibility.

Williams: Did you pass your science on to others, then, and their continuing that line of pursuit?

Metzger: Yes, one of my trainees, who is one of the great success stories, this was a young man who had been in the Stay In School Program. He's of Puerto Rican ancestry. He's the first one to, I think, maybe even have a high school education. He trained in the lab and then actually got a master's degree and a doctoral degree, became a postdoctoral fellow with me and is now a major contributor, and he's continued on that work.

Williams: By name?

Metzger: Juan Rivera.

Williams: Good. You spent a half century at the NIH or pretty close to it.

Metzger: Yes, basically came in '59.

Williams: So what words would come to mind to describe that experience?

Metzger: Well, I obviously voted with my feet. The NIH is an extraordinary place. I think the combination of being able to interact with very solid basic scientists and clinicians at the same time is an unusual experience. It's not as unusual perhaps as it used to be. It was unique, really, at that time, the fact that the clinicians were willing to talk with the basic scientists and the Ph.D.'s were willing to tolerate clinicians who had not had basic kinds of science. I mean, the fact that Harold Edelhoch, who was a protein physical chemist was willing to take me on as a trainee, even though I'd never had even a basic physical chemistry course was sort of part of it. The whole atmosphere of the intermixture of basic science and

clinical work was really very special, and I think that's continued. Plus the fact that unlike in academia where people to some extent have to scrap in order to get their funding and maybe be a little bit more possessive of their resources, that was not true at the NIH and I think is still not true. So it was very good collaboration, sharing of resources, and so on, so that was nice.

Then, of course, in later years, the idea that if one's work went well, even though one was being reviewed quadrennially, and the reviews initially were perhaps not that rigorous and one depended on what resources one got more on the scientific director, and later years the Boards of Scientific Counselors, the outside peer reviewers, have much more influence, even though the review became more rigorous, still, if one's work went well, one didn't have to sweat.

I don't think I ever, during the years that I had the lab, really was concerned about presenting to the peer reviewers. One prepared, but it was nice to talk about one's work to people who were not specialists in your area. That's not true for people on the outside. Even Nobel laureates sweat as to whether their grant is going to be supported and may have to revise it and have to give much more detail about their future plans, whereas the reviews of the intramural scientists are much more focused on what they have done rather than focusing on what they're going to do in great detail. I must say, in my own experience, very often we switched projects practically from one month to another without having to get permission from somebody and justify it and so on. So that was a terrific way and a wonderful way of doing research, so that still continues to be true, maybe a little bit less so, but it's basically still true.

Williams: Were there other cultural changes as time went by?

Metzger: Yes. I mean, one change, which is the way science has changed, when I worked in Harold Edelhoch's lab, I was the one postdoctoral fellow, there was one technician, and there was Harold. He had a desk here. I had a desk here. He was a great cigar smoker. At that time, one could smoke in the labs. One could smoke in the auditorium during lectures. I had constant contact with him during all the hours of the day. That's changed. It changed when I became an independent investigator. I had a little office, very small. We moved from the laboratory.

Nowadays research is done much more in teams, and depending upon the investigator, the investigator, depending on the size of the team, may interact with some of the fellows maybe only once a week, very different than the kind of everyday experience I had. So that's changed. It's much more team science and maybe having a hierarchy of postdoctoral fellows, senior postdoctoral fellows, having staff scientists who are supervising the younger trainees and so on. I mean, that's been true at the NIH and it certainly is true in academia.

Again, when I was with John Singer, there were one other postdoc, a technician, and myself, and we saw John every day, talked every day, had lunch every day, and so on. That's no longer true, and particularly for larger groups. I must say in the institute in which I grew up, in quotes, the "Arthritis Institute," the tradition there was to have a small lab and intense close relationship between the senior person and the trainee. So that wasn't always true in every institute, and the Arthritis Institute was one of the more academically oriented institutes, so it was a terrific experience.

Williams: Just as a footnote, what was the title of your group that you led?

Metzger: I think the section on chemical immunology.

Williams: How dependent is the NIH, has the NIH been, on the director, the leadership?

Metzger: I think that probably varies. I'm sorry. Now, are you talking about the leadership of the NIH or the leadership within the lab or the department or the institute?

Williams: No, the overall direction from the director.

Metzger: Oh, I think very, very little. I think the resources of the institutes depends a lot on the director, although much less than in most other federal agencies. It's a very, very heterogeneous group, so that the resources of the director of the NIH are much less in terms of resources that are available to him than the director of an individual institute. So in that sense, no, the director didn't have a lot of influence on us at all.

Williams: One thing that intrigued me in reading Harold Varmus' book was the proliferation of institutes in his time.

Metzger: Yes.

Williams: Was that a good thing, in your opinion?

Metzger: Well, we faced that, and those of us in the old Arthritis Institute, when the possibility was raised that the Institute would be divided into two institutes, we wondered whether that was a good thing. I'm not sure it was a good thing. As it turns out, I think the facts will show that it didn't lead to more funding ultimately, and it did lead to more administrators, no question about it.

Williams: There are some, I guess, institutes that are more subject to political pressure.

Metzger: Yes.

Williams: Did you as a scientist feel any direct political pressures from—

Metzger: Zero. Zero. No. I mean, well, my own career, as an example, I was, in quotes, the "Arthritis Institute." Okay? Arthritis, musculoskeletal, and then ultimately skin diseases, none of my work was related to that. It was very basic work, trying to understand the fundamentals of the immune system at a molecular level and then really something related much more to allergy. The reason I went into that was not because I was particularly interested in allergy—I, fortunately, don't have any allergies—but because it allowed me to explore some fundamental questions, and so I worked on something that was really much more appropriate for the National Institute of Allergy and Infectious Diseases. Nobody gave me any problems about that.

Williams: Were you able to interact with people in that institute too?

Metzger: Oh, yes. Oh, no problem, collaborated directly and had very good conversations and meetings with people. One other person who contributed a lot in this field was in the Dental Institute, another one in the Heart and Lung Institute, which is related a little bit more to asthma, and certainly Allergy and Infectious Disease and the Cancer Institute. So immunologists have metastasized to all the institutes. [laughs]

Williams: The NIH itself fosters that kind of—

Metzger: The intramural program, yes.

Williams: Talk about that for a moment.

Metzger: I met up with this concern when I became scientific director, when the intramural program divided up along with the extramural portions of the two institutes. And you understand—

Williams: Explain it.

Metzger: Okay. Well, about roughly 90 percent of the funds of the NIH, in fact, more than 90 percent now, is in the form of grants or other kinds of funds that are spent outside of Bethesda and outside of the Rocky Mountain Spotted Fever Laboratory and a few other areas of sort of in-house research, only 10 percent, or even less, 9 percent is spent within the so-called intramural program.

The director of an institute and the Congress decides how the funds of the institute are going to be spent, but that largely refers to what areas are going to get the major amount of support, and that depends a lot sometimes on the consumer groups, on the people with certain diseases, whether it's cystic fibrosis or the diabetes constituency and the arthritis constituency, and so on. The constituencies for diseases that are less prominent, either for not philosophical but psychological reasons or public health reasons, they may get less support. Now, polio got a lot of support because the President [Franklin D. Roosevelt] had it and children were

affected by it, but it wasn't the most prominent public health problem by any means.

But intramurally we really don't feel that very much at all. So apparently that is changing a little bit, that there is a little bit more concern that people in the intramural program work on the mission of the institute. As I was starting to say, I had that problem when the institutes were divided up, and one of the people who I very much wanted to keep within our new institute was an electron microscopist who worked on the detailed molecular structure of viruses.

Some of the Boards of Scientific Counselors gave me a little grief on that. They appreciated his work, it was magnificent work, but they said, "What's the relationship of that to arthritis?" Well, we tried to make the case that this was one area sort of where the light was where one could begin to understand how macromolecules interact with each another, which is one of the major difficult research challenges, and the fact that it happened to be on viruses for the moment meant that one could develop the techniques to study this, to begin to study macromolecular interactions on systems like I was studying in cell biology and so on. So we were able to keep him, and he's still in NIAMS. So in that sense there was a little bit of pressure, and that may vary from institute to institute. I don't know enough about how true that still is.

Williams: So 90 percent of the funding is in the form of grants to extramurals.

Metzger: Yes, not just grants, but programmatic, various ways to the extramural, yes, some of which are individual grants, some of which are other mechanisms that are used.

Williams: What is the interplay between the intramural and the extramural—

Metzger: Interesting that you ask that. At the moment, still very little. In fact, there really is almost a dividing line between them in that, for example, surprisingly, never quite understood that, intramural people are rarely asked to serve on the panels that peer-review the grants, even though the people who are the least competitors are the extramural people, because it's always been kept quite separate.

The one area now that is being explored very actively is whether there is some way by which the unique clinical resources of the intramural program can be of service to the extramural program where it's very difficult to do clinical research because of the expense of clinical research and they don't have the mechanism that we have. All the patients that we see here clinically get totally free care. We don't accept third-party payments. They can't do that on the outside. In fact, when I was scientific director, we tried to do that in our own clinical program by trying to see whether we could recruit or identify somebody in the outside program who would be interested in using some of our clinical resources, the patients we could gather and so on and so forth. That's being actively pursued now. There's the possibility to interact with colleagues in the extramural

program, so that's possible, and to some extent that goes on. I'm sure that varies a lot by institute.

Williams: I suppose you keep in touch with what's going on extramurally.

Metzger: Oh, yes, of course.

Williams: Primarily through publications, right?

Metzger: Publications and meetings.

Williams: Right. That leads me to another side question here. Looking at your 250 publications and all of your appearances in various organizations and whatnot, was there a lot of distraction to your work? I mean, you've got the research here, but then you've got all these other activities you're doing. I'm amazed that you fit it into a twenty-four-hour cycle.

Metzger: Well, it's certainly—I mean, there are some scientists who come to the NIH, and one of the other advantages of the intramural program is that although sometimes there's a little pressure put on, but basically you're evaluated on your research, and if you don't want to do any teaching, any administrative work, if you want trainees, you are expected to be a good mentor, a good trainer, but you can spend all your time doing research. You don't have to sit on any committees and so on and so forth.

I happen to be interested in organizations and the role of organizations in organizing a complex society, and so I'm very tolerant of doing committee work and so on. So I did not find that a distraction, I found that interesting, and so I've done a lot of that. I did that starting in high school, being involved in student government and college and so on, so forth.

Williams: So it's probably that—

Metzger: Probably. You know, maybe I could have been more productive spending more time on my research, but it was part of my career. I enjoyed that and still enjoy it.

Williams: One tangent of that interest, I guess, was your association with the AAI.

Metzger: Yes.

Williams: So talk about how you became involved in it.

Metzger: Well, I became involved with it because the current—I think he may not have been president at that time, Baruj Benacerraf, who was the Nobel laureate who recently died, who at that time was at the NIH, he was at the head of the department that [William E.] Bill Paul, who you've just interviewed, is in, the

laboratory of Immunology and NIAID. He asked me whether I would be willing to serve as secretary-treasurer because at that time Sheldon Dray, who was an immunologist who had been secretary-treasurer who was at the NIH, moved to Illinois, and they needed somebody. It's an elected position for which there's only one nominee, and so I said, "Sure, I'll try it," and that's how I got involved with the organization.

At that time, the organization was much smaller. The editor was elsewhere, and there was a secretary, Blanche Reines, who was, I mean, a secretary in the usual sense of the word, and me. That was it. That was the organization at that time.

Williams: Where were you located or was it just—

Metzger: I was located at the NIH. The AAI was one of the six organizations in the Federation of American Societies of Experimental Biology, FASEB, and right up on the [Rockville] Pike. I think we were the sixth organization to join FASEB, and so there was a small office there.

Williams: So you remained in that post, I think, for eighteen years.

Metzger: Either sixteen or eighteen, yes.

Williams: So what changes occurred in the organization over that period?

Metzger: Well, it grew a lot at that time. I forget now how many members there were when I first became an officer there, but it grew substantially, the journal grew substantially, and the field became bigger, got into a little bit more of public affairs. That was an area that there really was no activity in. The Council began to meet twice a year instead of once a year. The Council became more interested in educational activities, also trying to improve the diversity of the people going into immunology, had been very successful in many of the fields, and that—

Williams: Can I ask again, what was that last comment?

Metzger: Well, one of the concerns of the NIH and the scientific community in general is that there are certain population groups that are not well represented in the sciences, and where this particularly has some impact is in the area of health disparities, where there's no question that there are some major health disparities between African Americans and other groups, and one would like to get people to work in this area. It would be helpful to have more African Americans working in that area, but it's not an area where at the moment there's a good strong pipeline.

Williams: As an American immunologist, how important was it to be a member of the AAI?

Metzger: Well, it was just sort of expected. I mean, I don't think the organization really promoted the research that much. Of course, it held a meeting, but there were other meetings, other than the annual meeting, to which people went. Immunology in many ways is a laboratory field where the focus is really, used to be, on the individual laboratory and now is more on collaborative laboratories, but where the organization itself has some influence and more so now than it used to be, but not a major thing.

For example, one area where the organization did have some help both at the international and domestic level, but where in point of fact the major thrust came from an independent group, and that was in the area of nomenclature. As one began to get more and more molecules identified so that they're now in the hundreds of surface molecules that have been identified, the question of how to name them in some rigorous way and so on, the organization helped there a little bit, but it was more an independent group that really started the nomenclature thing.

Of course, having a journal and an organization to run the journal was important, but a lot of immunological research is published not in the AAI's journal, but in independent journals like *Nature* and *Science* and *Journal of Experimental Medicine* and so on.

So politically as a lobbying force through FASEB and independently in terms of trying to get the Congress to recognize the importance of scientific research, that's important. I think, as I said, the educational, the immunology course has been useful for many people, but more and more, of course, universities are offering immunology courses and so on.

Williams: What were the highlights of your year as president?

Metzger: I don't know that there were a lot. [laughs] I think the year that I was president, but I'd have to look, I think it coincided pretty much with our having the International Congress of Immunology during that time. So that was certainly a major challenge to have a good Congress. That worked out well.

Williams: Where was that held?

Metzger: I think that was in San Francisco.

There were some discussions particularly as to how we could interact more with the clinical immunologists, whether that should be a separate group and so on. That was only partially resolved, and there really now is a fairly strong independent clinical immunology group. So I don't know that there were any major highlights, I must say.

There was a period, but I think this may have been a little bit later, where the organization decided that they would no longer participate with all of the other FASEB societies in one big annual meeting, but would have a separate meeting either by itself or with one or two other societies, and that was certainly a change that occurred more or less during that time.

Williams: I notice increased numbers of women are active in the group.

Metzger: Yes.

Williams: Talk about gender—

Metzger: Well, I think, in general that's been the trend in the biological sciences. There was a time when the lack of diversity among research trainees was the gender diversity. It wasn't that we were discriminating against women; there were just no candidates. Nobody came around looking for a job. That's changed dramatically. I mean, whereas when I mentioned to you when I went to medical school, 10 percent of the students were women, it's now over 50 percent. So there's just a lot more women going into particularly the biological sciences, which may be a little bit more conducive to pursuing a research career than maybe some of the other sciences, which may in some ways be more time demanding, not necessarily more intellectually demanding, but more time demanding. So I think there is a predominance of women scientists in the biological sciences and so on.

I have two sons who are very, very much involved with their families. They do the laundry and do housekeeping, which I never did, and yet when the kids, the grandchildren, were young, it was the wife, even though they were professionals, the wife who took them to the pediatrician. We have special considerations for women at the NIH in terms of how long they can be on a tenure track and so on, and there is now a move to perhaps allow people to even work part-time if they're rearing children or having a parent who needs care and so on. So some accommodations are being made.

Williams: Did you remain active in the AAI after your presidential year?

Metzger: Not really, not very much. No, not really that much.

Williams: You did come back for the Achievement Award?

Metzger: Yes, but I'm not sure that I served on any committees and so on.

Williams: To sum up, looking back, do you feel you made the right choices at critical moments in your career?

Metzger: Yes. I mean, one of the questions that comes up is if you are going to pursue a career in basic molecular research, wouldn't it have been better to take a Ph.D. rather than an M.D., even though one may be interested in medical things? I never regretted that I—there's no question that there were certain kinds of training experiences that I missed, but I think the human being is the most interesting organism, and to learn one organism in real depth at the social, psychological, physical level, I wouldn't have given that up for the world. I think that so enriches one's life, I must say, and not only the research. It certainly has helped me keep a focus on what kinds of problems I was interested in, so I never regretted that. That doesn't mean that one has to do it that way. There certainly is a lot more emphasis now on people getting combined degrees, Ph.D./M.D.'s. My mentor, Harold Edelhoch, when I raised that possibility with him of taking a second Ph.D. degree, said, "Well, you can do it. It helps you get your first job, and after that, it's what you do." So I never did.

Williams: Were there some wrong turns you took in your career or dead ends or unproductive lines of inquiry, particularly?

Metzger: [laughs] It's terrible to say this, I don't want to be immodest, but I don't think so. I don't think that there was any particular—I mean, there are lots of experiments that failed, but I don't think they failed because they were foolish to do necessarily. So I don't think so. There's been a lot of talk about doing science in different ways. The fox and the hedgehog, are you familiar with that? Well, the hedgehog says, "Hey, this is an interesting place," and digs and digs and digs and digs and never leaves that place, and so has a very narrow kind of approach and therefore comes up with a lot of interesting data, but it's very narrow.

Then there's the fox, who says, "Hey, this is an interesting area," and digs a little bit and says, "Interesting. Oh, there's another area," and so on. There are a lot of people who do that kind of research, and sometimes they have a greater sense of perspective and so can recognize whole new areas that those of us who were digging in the same hole all the time don't see.

I certainly have been more the hedgehog than the fox. I think the Nobel laureates tend to be foxes, with few exceptions, including the some of the ones who've worked out a particular technique, like the ultracentrifuge and electrophoresis, people got Nobel Prizes for that. But I didn't regret that. It's one way of doing science. They're both good ways of doing science, and it's good to be aware of what the foxes find as interesting, but it's also important to have some people who really work in-depth in certain areas. So I never regretted that, really, but some people would say that was a deficiency.

Williams: So at no period in your career did you run with the foxes?

Metzger: Not really, no. I thought I was working on a pretty major problem, and that is how do antibodies work, how does the immune system work. So in that sense it

was a broad conceptual problem, but I approached it by doing an in-depth exploration of one system.

Williams: So if you had to do it over again, would you—

Metzger: Absolutely, yes, yes. Every time we have a five-year reunion for medical school, we're always sent a questionnaire and being asked if you had to do it all over again, would you do it the same way, and I must say, absolutely, yes I never regretted either the medical school or the clinical training, even though I never used that again. I did regret not seeing patients, but had to make a decision, and I think it was the right decision. So certainly the NIH was a terrific place to work.

Williams: Looking back, can you describe some of your happiest moments in your work?

Metzger: In my work?

Williams: Yes.

Metzger: Oh, yes, yes. Well, I think I described that in my autobiographical piece. There was one particular experiment where somebody had published a technique by which one could separate easily molecules that tended to be more lipid soluble or that had more lipid-like properties than more aqueous-like properties. When we were studying the subunits of this receptor molecule, that was sort of a long story. Initially, the receptor that we focused on, which is a cell surface protein that binds the antibody and which, when aggregated by the antibody combining with a multi-valent antigen, is the thing that aggregates and triggers the whole explosive cellular response, we began to recognize that it wasn't only the antibody binding component that was part of the receptor, but that there were two additional subunits which we discovered which had very different properties.

We used this technique of separating these molecules along with some dyes that had either a purple color or a yellow color, depending upon the environment, and were able to separate out the more aqueous subunit from the more lipid soluble in a more colorful way. That was very dramatic. That was extraordinary.

And then, of course, being able to actually affinity-label a myeloma protein, that was exciting, because for the first time, since it was a homogeneous protein, one could really identify which residue in the combining site was modified. And then working out the valence of the IgM. So there were a lot of eureka moments, yes.

Williams: What do you see as the road ahead for immunology?

Metzger: Oh, unlimited. I think immunology is really at the forefront of being able to understand at the molecular level and at the system level a very complicated integrated system, and we're just beginning to do that in other areas of cell biology. I think there are probably more markers on different kinds of immune

cells than almost on any other kind of cell. Now, the system is not as complicated as the neurological systems, but I think many of the techniques that have been developed in immunology in terms of imaging techniques and so on being very widely used now throughout cell biology.

So I think we have a long way to go. As I said, I think we're just beginning to recognize the true complexity of biological systems. For example, I mentioned the word "kinase," enzymes that modify and phosphorylate proteins. Well, we had no idea of how many kinases there are. Now we know, I think, there are hundreds of them. But there are not 10,000, okay? So we have some idea about how many there are. We have some idea of how many different kinds of lymphocytes there are. It's not an infinite amount, but it's a very large amount. The whole immune system consists of, I don't know, I guess twenty different kinds of cells, different kinds of cells and how they interact, and so on, we may need to set some limits, but the complexity is enormous. Working that out in detail is a major challenge, so I'm not worried that people are going to be lacking things to find out in the immune system.

Williams: So for trainees you would recommend a career in this path?

Metzger: We were just talking about this yesterday at a meeting of the foundation that I'm associated with. The majority of the trainees are not going to end up in research. That's by definition. I mean, nowadays, trainee groups are eight or ten in a group per investigator. They turn over every two or three years. It's just not going to be enough money to train all those people.

But I think there is a major source or need for scientifically trained people in all sorts of other professions, including the Congress. There are very few scientists in Congress. Our society is faced with major problems that require not only a scientific background but a background that is used to taking data seriously. So, scientifically trained people, physicists, chemists, biologists, not only for their specific discipline, but for the way they treat information is important in tech transfer, in pharmaceutical industry, in legal matters and so on.

So I think there's a lot of opportunity for people who've had a good solid training in research, but who won't necessarily have a research career. Some will. Some will feel that they need to make more money in order to pay off their debts, some because they're interested in patent law or legal things and so on.

The whole area of medical care, which is moving in very different directions, whole ethical problems related to genetic information and so on, so that people who are used to thinking about those things have lots of opportunities there. So I think the training is a great opportunity, but they won't necessarily all use that training for research.

Williams: What about a growing dependence upon scientists from other countries? Do we have our own supply sufficient for—

Metzger: No. No, no, no, we don't. I think I've seen the number that half of the Ph.D.'s being trained nowadays are from other countries, and we are really lacking in that. On the other hand, we certainly have—I mean, I don't think that's necessarily a problem. It's nice to have people from other countries, other cultures.

In the book club I belong to, we just read a book called—I think it's called *Exceptional People*, which is very positive about the fact that we are a country of immigrants, because it's been one of the great strengths of this country to have that kind of cultural diversity. So I think as long as we have people who are willing to be trained here and also to stay here, I think is a good thing.

Then I think we have a lot of things to offer the world so that even those people who we train here, the fact that they're going to have a fairly intimate familiarity with the way things are done in the United States, I think is a good thing. Some good things, some things we do well, and some of the things I'm interested in like organizations, I think we do very well in terms of how to organize our society. Other things we do less well.

Williams: What do scientists do to have fun?

Metzger: Oh, that varies.

Williams: What have been some of your outside pursuits?

Metzger: Outside pursuits. Well, I was going to say some scientists have fun doing science and not much else, and that's fine. There are one or two scientists who are in their nineties who continue to work at the NIH—you mentioned Michael Heidelberger—and they like nothing more than doing their science. There are others, many scientists, into music and spend much more time there.

I do running, hiking, cooking, reading, so I don't have another major hobby other than sort of a little bit the running, did some fairly serious running late in life, as my daughter is a physical fitness person, started me running. So I started running when I was sixty-five, but I don't do marathons anymore. [laughs]

Williams: I was going to ask you about your children. Have any of them followed in your footsteps?

Metzger: Not directly. Our oldest son is a gerontological psychiatrist up in Boston. The other son is a lawyer, litigation lawyer. The third child is a physical fitness person. So we have very good coverage in our old age. [laughs]

Williams: One thing I didn't ask you about, and I don't know whether you want to talk about it much, but I guess in your *Eureka!* [*And Other Pleasures*] piece you talked about political activities in the sixties and seventies.

Metzger: Yes. I mean, political activities, I did a little bit of that when I was in college. I was associated with the newspaper, and during the McCarthy period wrote some strong editorials about that.

Then what happened during the sixties here was after the assassination of Martin Luther King [Jr.], and the riots here in Washington [D.C.], we very quickly established a local chapter of the Medical Committee for Human Rights. Medical Committee for Human Rights was started by some Boston physicians who wanted to be sure some of their children who were participating in the civil rights marches in the South had adequate medical coverage for anything from being beaten or having blisters or having a psychiatric break, and so on. But also, during the riots here, we provided medical coverage. So that really was nonpartisan. It wasn't really political.

Then that sort of became transformed into providing medical coverage for some of the demonstrations during the Vietnam War. So we were involved in that. In fact, the headquarters for the local chapter was in our basement down here for a while. And there was a short time where there was some question about what would we be allowed to do at the NIH. We invited Dr. [Benjamin] Spock to speak, and there was some question about whether that was appropriate, had some posters up and so on and so forth, but it wasn't a major thing.

Then the Medical Committee for Human Rights became more and more focused on the idea of medical care being a human right and that that is something that the society as a whole, the government, should provide to the population at large. At that time, this was just around the time that we were leaving for the sabbatical in the early seventies, it became clear that that became a major political issue and was going to be solved or not solved by the political process. It's still not being solved, but it's in the appropriate place where the decisions should be made, by the Congress and by the President and by the [U.S.] Supreme Court and so on. So I didn't feel that the Medical Committee for the Human Rights was going to really influence that in a dramatic way. So I left that organization, didn't continue to participate.

Williams: Are we leaving anything unsaid?

Metzger: Certainly one of the aspects of having a successful career in science is having a supportive spouse, because certainly during the most active years, both when we were living here and when we were living a little closer to the NIH, I would usually be home for dinner but often go back to the lab after dinner, so a lot of the childrearing and the housekeeping and so on, the laundry and so on, was done by my wife, who had her own career but only worked part-time.

At that time, I mentioned to you that when she wanted to pursue her training, all of a sudden the rug was pulled out from under her because instead of going to New Haven where she could continue her training, we went to La Jolla. There was never any question about who was going to decide whether we were going to stay or move. It was the man's career. So that's strange now. But certainly having a very loving and supporting wife has been a big help, no question about it.

Williams: Very good. Thank you, Dr. Metzger.

Metzger: Thank you.

[End of interview]