

**National Cancer Institute Oral History Project
Interview with Maxine Singer
conducted on July 24, 1998, by Gretchen A. Case
at Dr. Singer's office at the Carnegie Institution
in Washington, D.C.**

GC: I usually like to start by just asking about your background and how you came to the NIH, what brought you there.

MS: I came to the NIH in 1956 as a post-doctorate fellow. The thing that brought me there was a person whose name is Leon Heppel, with two p's and one l, who was one of the only people in the United States at that time who was working in the chemistry and biochemistry of nucleic acids. I came right from my Ph.D. to be his post-doc. It was not at the NCI, however. It was in an [NIH] institution that was then called Arthritis and Metabolic Diseases. It was in the Laboratory of Biochemistry.

GC: And you stayed there for quite a time.

MS: I did, because after about a year and a half, I was offered a regular research position there in that same department, the Laboratory of Biochemistry, and I took it, and I stayed there until I went to the NCI in 1975.

GC: Was that pretty typical for a post-doctoral fellow to get a permanent position?

MS: In those years it was much more common than it is now because the NIH was small and growing, and there were many opportunities. People now are astonished CI never, ever applied for a job. The Chief of the Laboratory just appeared in the doorway one morning and said, "Would you like to stay? You can have a module and be a member of this lab." But it's because the times were very, very different.

GC: How big was your lab when you arrived there?

MS: You mean the number of people in the department?

GC: Yes.

MS: Oh, boy. It must have been about eight different research groups, eight or nine research groups, of which Leon Heppel's was one.

GC: And you stayed in Heppel's [lab] the whole time you were there, until . . . ?

MS: No, because when I got my job I became an independent investigator. So I had my own lab.

GC: So at that point you were allowed to design and pursue your own research?

MS: Right.

GC: And as a post-doctoral fellow, you were supporting his research?

MS: Well, I was working on things that were problems generated in his lab, and also he was at that point collaborating a great deal with the laboratory of Severo Ochoa at New York University, so some of the things we did were in connection with that.

GC: What building were you in?

MS: In Building 10 . . . ninth floor.

GC: Did the Lab of Biochemistry take up most of that floor?

MS: No, it took up one wing of that, one small wing, the North, 9N, wing.

GC: What brought you over to NCI?

MS: I was invited by the then-Chief of the Laboratory of Biochemistry in NCI, a man by the name of Robert Goldberger, to come and join that lab. Bob Goldberger had recently become the chief of that lab, having moved from the Arthritis Institute, from a different

lab in the Arthritis Institute, to be the chief of the lab. He was in the lab in Arthritis whose chief was Christian [B.] Anfinsen. And they were at the other end of the ninth floor, and they were people who by that time I knew quite well, and Bob invited me to come over and join NCI with him.

GC: So he was just in need of he wanted to bring people with him.

MS: I think he had been hired in order to rebuild that lab, the Laboratory of Biochemistry in NCI, and so he was recruiting people, and he recruited me.

GC: That's one of the older labs at the NCI.

MS: I believe it is the oldest, in fact. It existed in the '30s. The director of the lab was a man by the name of Jesse Greenstein. You know about him already probably.

GC: A little bit.

MS: Right.

GC: Did you know him?

MS: My recollection is that I must have met him in the late '50s. But after Greenstein and I think it was the very next one, although I'm not sure it was a man by the name of Herbert [A.] Sober, who I did know and knew quite well. And Bob Goldberger replaced Sober as the chief.

So it was an old lab. It still exists. It's still the oldest lab, I guess, at NCI. It's a very unique place for NCI. So I was glad to join.

GC: How is it unique?

MS: It's one of the very few labs in NCI that's concerned with fundamental research, which is organized in academic fashion with a group of independent investigators who follow their own interests, rather than being built around a single strong, scientific leader, and then everyone in the lab following that general line of research. That's been the tradition in that lab, as it was the tradition in many parts of the NIH, but that lab has maintained that tradition, as have a few labs in what is now no longer the Arthritis Institute. I forget what it's called and also a couple of other labs sprinkled around the campus.

GC: Was it pretty easy to move between Institutes then because you were doing such basic research or was there

MS: Well, I think it was always easy to move between Institutes.

GC: Was it?

MS: Yes. It was no problem moving between Institutes.

GC: There was a lot of collaboration between Institutes?

MS; Well, in the early days the lines of communication were much more between people in the same discipline than between people in the same Institute. So in the late '50s, through all the '60s, early '70s, I knew all the biochemists at NIH, and I was much more likely to speak with them than with anybody who was not a biochemist, regardless of the Institute.

So, for example, I knew Bob Goldberger and Chris Anfinsen down at the other end of the hall. But I didn't know the people in the middle very much at all.

GC: Because they weren't biochemists?

MS: Well, Building 10 was organized so that in the middle sections people were doing clinical research mainly. So I didn't know them very well. But way down at the other end of the hall, I knew Anfinsen and all his colleagues.

GC: Did you have any occasion to be involved in clinical research at all?

MS: No, none.

GC: So, those two sides [clinical and basic research] were fairly separate?

MS: I think some people did do work that required a foot in each group, but I didn't.

GC: What was your first project when you came to NIH? What was your research interest at that time?

MS: I was interested in learning about nucleic acids. I hadn't known a great deal. In fact, nobody knew a great deal. If you put the historical setting on it, I was at the end of my first year in graduate school in 1953 when the [Watson and Crick] model for DNA came out. People had been working on the chemistry of RNA and DNA, but even the nature of inter-nucleotide bonds was still uncertain in those years. And it was, in fact, not really resolved until around '55 by Alexander Todd in England.

So people knew very little about the chemistry and less about the biochemistry of nucleic acids, and that's not what I did as a graduate student at all, but it was something that I wanted to learn about and it seemed like a good field to get into.

And Heppel had spent some time in England with two people named John Smith and Roy Markham, who were working out what then seemed like elegant and simple methods for analyzing reactions involving nucleic acids. There was a lot of chromatography, particularly paper chromatography, which allowed you to analyze very small amounts, or what we thought then were small amounts, and also developing the use of enzymes as tools for the analysis of nucleic acids.

Heppel had spent a year sabbatical with them in England and brought those techniques back and had begun to develop techniques of his own. So that was why I wanted to go there to learn that.

In the year before I came, he had been contacted by Severo Ochoa because Marianne Grunberg-Manago in Ochoa's lab had discovered the enzyme that was called polynucleotide phosphorylase. It was the first enzyme discovered that polymerized ribonucleotides. Just around the same time Arthur Kornberg described DNA polymerase I, which polymerized deoxyribonucleotides, and made DNA-like polymers. And this enzyme, polynucleotide phosphorylase, made in the test tube, RNA-like polymers. They weren't like RNA in the sense that they don't have a specified sequence of bases, but from a chemical point of view they were RNA in terms of internucleotide bonds and so forth.

And so Ochoa when, when they discovered this enzyme, realizing that Heppel was one of the only people around, if not *the* only at that point, who knew how to deal with such polymers and analyze them, contacted Heppel, and he worked on the characterization of the polymers and was doing that when I got there. And so I joined that effort.

I then began also to study the mechanism of action of the enzyme. It turned out, of course, that the enzyme does not make RNA in cells, but it was the first polymerizing enzyme, and Ochoa and Kornberg later shared Nobel Prizes for those two discoveries, even though neither one of those enzymes turned out to make either DNA or RNA, respectively, themselves.

GC: So you carried that research with you, then, to the NCI continuation of that?

MS: Oh, no. By that time I was doing very different things. I mean, that was fifteen, sixteen years later. Because I started my own lab in '58, and I moved to the NCI in '75, and by that time I had done a lot of other things. And I wasn't working on polynucleotide phosphorylase at all by then.

GC: What would you say the working atmosphere was like at the NIH and at the NCI, and did it change over the years, how people worked together? I'm sure it changed because it got bigger.

MS: Yes. When I came, as I say, it was small. It was small and growing. And so the whole atmosphere was the kind of atmosphere you get when you have large-scale growth and a small place to begin with. People knew each other, people were in contact with each other, there was a tremendous amount of interchange. People went to seminars from one building to the next, they wrote papers together, they did research together. And, of course, it was not only logarithmic growth in the NIH, but it was logarithmic growth in the field. And so those of us who were involved in nucleic acids saw a lot of each other and talked a lot together.

It was very exciting, it was very collegial, there was no hint of competition for anything because there was no need. Resources were there for the taking if you did a decent job. And if you did a good job, it was very simple to get what you needed.

I never had any great big ambitions for enormous labs, so I never had any problem getting what I wanted, and I never had any problem with collegiality and collaboration, exchange of materials, of ideas, criticism of one another's work. The atmosphere was amazing.

At the Lab of Biochemistry in the Arthritis Institute, we had a terrific journal club which was an important part of all of our lives in those days. It was a joint journal club between the Laboratory of Biochemistry and the Laboratory of Biochemical Pharmacology, which

also, in those days, did a lot of just very fundamental work. The chief of that lab was [Herbert] Herb Tabor.

And we met every day for lunch, five days a week. It had a wonderful history. This journal club was started in the mid '40s by five people who really were instrumental in biochemistry. One was Leon [A.] Heppel, one was [Bernard L.] Bernie Horecker, who was the lab chief in the Lab of Biochemistry in Arthritis at that time, one was Herb Tabor, one was a man named Alan [H.] Mehler, and the fifth one was Arthur Kornberg, who was the chief of the Laboratory of Biochemistry in the Arthritis Institute before he moved to St. Louis, and then Bernie Horecker became the chief.

So those five guys decided to teach one another biochemistry. They all had had different kinds of training. And they started this journal club as a device for teaching themselves. And then after some years they invited post-docs and others to join.

And by the time I came, of course, Arthur was gone, Mehler was still there, and everybody in the two departments came every day for lunch. They brought a sandwich, and somebody presented some new paper for criticism.

That was probably the best biochemical education I had because it was highly critical, it was done by people who already had some knowledge, they'd been through graduate

school, they'd been doing research for awhile, and several really outstanding senior people were there every day, so you could both hear and discuss with them. And it was also a remarkable way to keep up with literature.

So I did that for nineteen years.

GC: Every day for lunch?

MS: Every day for lunch. We took holidays off, but in the beginning they hadn't even done that.

GC: So if it was Columbus Day, they still came in?

MS: If it was Christmas, they came in.

GC: Really?

MS: Yes. But by the time I came, we'd gotten lazy, so we took holidays off. So for nineteen years I did that. And I knit a lot of sweaters for my kids during those hours, too, because that was easy to do and listen at the same time.

But it was tremendous, and you wouldn't have missed it for the world. It was just great.

GC: So you kept coming when you were at NCI?

MS: No, I stopped. Actually, by that time, I think they were only meeting four days a week. And because interests began to fragment as biochemistry became less unified I mean, there was just no way by the mid-'70s to keep up with, or to hope to keep up with, the breadth of the biochemical literature. So by that time, I was reading mainly in nucleic acids.

So a group like that didn't have the kind of strength that it had at the beginning. When I went to NCI I stopped going. We tried to get something going that would be similar, but it didn't really work, so . . .

GC: The interests were just too diverse?

MS: The interests were diverse, and it turned out you had to have been brainwashed as a youth, I think, to do something like come to journal club every single day.

[Laughter]

MS: People were *horrified* that you would even think about taking an hour for that every day, but I think they didn't appreciate how tremendously rewarding it was. But it's also true, as you say, that the Lab of Biochemistry was more diversified. But, as I say, the field was diversified by then, too, so it wasn't only the people; it was just the field and . . .

I think when I went to NCICI brought nucleic acid biochemistry to that Laboratory. There were some people doing some things, but they'd come from other directions. So that was, I assume, one of the reasons I was recruited, to bring that particular area of work into the lab.

GC: So as the field itself widened and expanded were there more biochemists brought into the Institute itself in general?

MS: There were more biochemists brought in, but neither of these labs that I was in expanded a great deal, which I think was the right thing to do. The new people were brought in in other situations.

GC: Was becoming a lab chief Chow did that differ from being an investigator?

MS: Well, when I went to NCI I went as a section chief, which meant very little. I mean, I was able to recruit one additional person for my section, which I did. And so I didn't have too

much administrative work. And my own group was relatively small. It was never more than six or seven people. And Dr. [Claude] Klee's group, who was the person I recruited, was also small. And Bob Goldberger really took the view that the job of the lab chief was to protect everybody in the lab from administrative issues, and he did that with great success. So at that point I hadn't done very much of that kind of work.

Then when Bob became the Scientific Director of the NIH, I became the acting lab chief, and ultimately after the wheels of the bureaucracy ground for almost a year, I became the lab chief. I mean, I was the lab chief, but I didn't have the official title except acting because of the administrative hang-ups.

And then, of course, I had to spend a fair amount of time doing administrative work because I assumed the responsibility that Bob had taken to protect everybody else from it. It was quite time consuming. I spent time doing appointments and searches, dealing with the bureaucracy in different ways. I still, of course, had a very active lab, and I probably had to spend about half the day on the average on administrative things. And that was made more difficult by the fact that there were problems in the office staff that I had to deal with that took a long time. Eventually, when that got straightened out, things got a lot easier. I had a good office staff.

GC: So you were able to still be at your bench doing . . .

MS: Oh, yes, right. Right. But certainly in those years I did less and less at the bench and relied more and more on post-docs and a very fine, very extremely skilled and thoughtful and knowledgeable person who was called the technician, but who was basically a scientist without a Ph.D., who was extremely helpful and without whom I never could have done all that.

GC: Who was that?

MS: A man named Ronald Thayer. He's now an administrator at the NCI. One of the sad things about the way that NIH works is that people who don't have a Ph.D. can't advance in the scientificCcan't advance in terms of pay, even though they become more and more competent and skilled. Ron wrote his own papers, gave his own seminars, but we could never get him appropriate raises because of the rules. And so ultimately he went into administrative work so he could get raises, which is really too bad; he doesn't like it, he never has liked it, he would have preferred to stay in the lab, but it's one of the very stupid things in the system. To take somebody highly skilled, highly knowledgeable, and waste all that, it's just ridiculous. But it happens over and over again. It's really one of the downsides of the NIH.

GC: Was that true all along, or do you think that gotC

MS: Oh, no, that's been true all along. The definition that Civil Service has for somebody who doesn't have a Ph.D. includes a certain range of ratings, and no matter how skilled they are, no matter how independently they operate, they are limited in pay. There are exceptions with only very special things like if they operate a very particular, very expensive instrument or something. But somebody who can operate six or eight or a dozen fancy instruments, and does so every day, can't get beyond a certain place. So if people want to have a better salary, they have to go into administration. It's really a very foolish waste of fantastic scientific resources, and there are many examples of that and have been forever.

GC: That's too bad.

MS: Yes.

GC: Is that true in other scientific institutions or do you think that's something particular to the NIH, the government?

MS: I think it's particular to the government. I think to some extent it may occur, but, for exampleCbut I think industry is more flexible, much more flexible, about that. Universities are not as flexible as industries, but they're probably more flexible than the NIH is.

GC: Did you also find that you had a different experience because you were a female scientist at the NIH, or did you . . . ?

MS: Actually, I never did.

GC: Really?

MS: No.

GC: That's good. Was that generally true, do you think?

MS: No, I don't think it was generally true. I don't think it was generally true at all, but it was true for me. I think it's a complicated thing. First of all, I think that women scientists had a much better deal on average at the NIH than [at] universities. When I went to the NIH, if I had decided to apply for a job in a university, I would have had a lot of trouble because by the time I would have finished my post-doc, it was still a time that women weren't getting jobs in academic places, not independent jobsCnot *not* getting them at all, but very rarely getting them.

But the NIH was a much better atmosphere for that, which is not to say it was perfect. So a lot of women had difficulties and a substantial percentage of those difficulties were because they were women; it's perfectly clear. But I didn't.

I think it was partly the timing. It was when thoughtful people were beginning to realize how stupid this situation was. And there were enough women scientists around in academia and at the NIH so that people recognized that there were people making great contributions who were not getting appropriate pay or recognition or whatever. So intelligent and very thoughtful people of liberal persuasions were already sort of aware of that, and I think that was true of the lab chief, Bernie Horecker, and of my mentor, Leon Heppel. So there was that very special circumstance at a window of time.

But it was before there were very large numbers of women coming into the field, which in a way exacerbated the problem, so the problem became worse for awhile than it was when there were so few of us around.

GC: When there were more women coming?

MS: When more women came in it became more of an issue because it was just more visible, people were more frequently faced with having to make decisions about women scientists. I think that made it harder in a way. And also because women began to be

aware that they ought to be demanding more. That riled some people. So I think I was just lucky. I was in a window of time when things were a bit easier because people were realizing how dumb the situation was, but it hadn't yet grown to a proportion where you had new difficulties, backlashes, or whatever you get when you have more numbers. So I think there was that involved.

I think it was also true that because of my own academic history I never thought it was an issue, so there was nothing in my behavior or demeanor or anything which would have reminded anybody that it was a problem. You see what I mean?

GC: I think so.

MS: I had very good luck in my academic training with respect to this, so that by the time I got through with my Ph.D., I had never been aware that there were problems.

GC: Okay.

MS: I never even knew it. I was beginning to hear about things, but for a whole variety of reasons, I just never was aware of it. So by the time I came to the NIH, I was not someone who in the back of her head had the notion, "I'm going to have a problem when I want to get a job." I just didn't think about that because it didn't occur to me. I was very

naive, but I'm happy I was naive because it was not something that presented any challenge in my mind, and therefore never would have surfaced even in subtle ways with people who had to deal with me.

GC: Right.

MS: But that was just luck, *just luck*, because of my own academic history. So I think that probably played a role.

And beside being well trained, because I'd had very good training, and beside being reasonably smart, it must have been clear to people also that I was a well-organized kind of person. I got things done. That was already clear. So I think all those things added together.

And, in fact, I should add, it wasn't just the lab chief, Horecker, and Heppel, but also the leadership of the Scientific Director of the Arthritis Institute at that time was a man named Hans Stetten, who also eventually became Scientific Director of the NIH. He's a very great man. And he also carried no prejudices with him. His wife was a scientist, an independent scientist. So he too would not have objected.

But then again, it was just lucky coming upon people like that and having those be the people making the decisions. But that was in the Arthritis Institute. And I don't think the situation was the same in a lot of other places, even at the NIH.

GC: Really?

MS: No, because, I mean, I knew women who were not getting jobs, not getting promotions, not getting this or that. The first time I really ran into a problem and was aware of it was after a couple of years being independent I had not been able to recruit a post-doc. And I was getting interested in different things, and I wanted to have a couple post-docs. So I went to see the then-lab chief, who was a man named [William B.] Bill Jakoby, and asked him about this. He said, "I've been waiting for you to come in and ask me about this." He said, "Because I have been pointing all kinds of post-doc applicants to you since you became independent but the post-docs don't want to work with a woman." So that was actually the first time I met it [prejudice].

GC: There were male post-docs?

MS: Male and female. Because women had a very bad reputation as bosses: they were difficult to get along with, they were finicky. And I have every reason to believe everything Bill Jakoby said to me. He said, "No matter what I tell them about you and no

matter how I show them how exciting the work is, they just won't do it." So it took awhile.

And then, of course, once I had the first post-doc, then that post-doc could tell future applicants that I wasn't an ogre. [Laughter] Then things were easier. But that was the first time it really surfaced for me . . . which was interesting, right?

GC: Yes, it's interesting that's the first time you came up against that problem.

MS: Yes, first time it ever surfaced. But I had a really wonderful time there, and they were just terrific in giving me independence and letting me do what I wanted to do. In those years, between early 1959, the beginning of 1959, through the middle of 1964, I was essentially pregnant all the time. And yet it never was an issue, never a problem.

GC: They just worked around it?

MS: Nobody bothered with it, nobody objected, it didn't get in anybody else's way, which was really nice.

GC: That's great.

MS: Yes. And part of the reason was because Marnie Stetten had had, I think, three kids. Celia Tabor, Herb Tabor's wife, was also a scientist in biochemical pharmacology, a member of our great journal club, and she had had four kids. So there were people around who had experienced this. It wasn't so unusual. But that was really, again, just luck. I could have come across other people. They might have had a very different attitude.

Everybody had seen that with people older than I was and realized that it wasn't an issue.

GC: So they just weren't worried about it.

MS: So they just didn't worry about it, right.

GC: Great.

MS: Yes. I was very lucky.

GC: It sounds like you had a lot of support in a lot of different ways.

MS: Oh, yes.

GC: That was one of my questions, was how easy it was to get resources in terms of money and people andC

MS: The only problem I ever had was getting people, post-docs. I had a technician, that was fine, but getting the post-docs was a hurdle to get over. And once I got over that, then really I had what I wanted.

I never had big ambitions to have a very big lab because I wanted to stay at the bench and didn't want to manage a lot of people, but I wanted a couple, two or three. And I had a big household to manage besides. So I don't know what would have happened if I'd wanted more. But I had what I wanted.

GC: So when you were at the NCI, what did you have? You said youC

MS: When I went to the NCI, I had somewhat more resources. That was '75 by that time. My kids were not infants anymore. I had more space, I had more positions for post-docs. And I guess at the maximum I must have had five or six people in the lab besides myself.

GC: That's fairly small.

MS: It was small, right. But all of the groups in the Laboratory of Biochemistry were that way.

GC: Oh, really?

MS: Yes. And I had something like 650 square feet of space, but there was only one person in the department who had more than that. He had about 800. So we all had relatively small space and small groups, and if you wanted to have a bigger group, you really had to go elsewhere. We lost a couple of terrific people including while I was Lab Chief, people who moved on because their ambitions were to have larger groups. They were great scientists, but we could not, given the philosophy of the laboratory, accommodate that. So we were happy to give them a good start, and then they went elsewhere.

But I was very happy with that because I really just was much more comfortable working that way. I think you're much more in touch.

I'm concerned about the size of groups today. I think it's a very different kind of culture, and I'm glad I'm not part of it.

GC: It's typically much bigger now, isn't it?

MS: Yes, typically it's much bigger. And I'm not sure that's great for science or for anything.

GC: Because it cuts back on the connections between

MS: Well, if you think about it, one of the consequences is that a lot of people do many years of post-doctoral fellowships. In my time, you spent four years getting a degree. If you didn't get a degree in four years, it meant you weren't going to get a degree, because that was part of the challenge. You had a lot of very careful mentoring from your professor so that the choice of problem was something you could do in a reasonable amount of time so that you could get it done.

The same thing with a post-doc. Most people did one two-year post-doc. And again, it meant good mentoring, on a different level, but good mentoring.

Nowadays people have large groups, they have graduate students who stay for six, seven, sometimes eight years. That means that they're not getting good mentoring. And part of the reason they're not getting good mentoring is they're in a very huge group.

The post-docs stay for a long time, partly because they're not getting good mentoring but partly because the jobs are scarce.

So you have people who stay in training for as much as ten, twelve years. Okay? We used to think, and I still think it's true, that the most productive, creative part of a

scientist's career is when they're young. And nowadays, when people are young they're not independent.

GC: They're still a post-doctoral, working for someone else.

MS: That's right. So while they may apply their creativity to the problem that the senior person has outlined or set the parameters of in some way, fewer and fewer young people have a chance to see their own vision and go after it, which may be a completely different problem than any mentor they have is doing. And it is typically through young, independent people that science has really progressed. There are dozens, hundreds of stories of young people who did one great thing in their life, and they did it when they were young. And we're losing that time.

That's one of the big problems I see with the large groups and the length of stay in training. And I object to it at the NIH and I object to it elsewhere. And I'm proud to say that the Laboratory of Biochemistry tries very hard to be different because of its tradition.

They try not to keep post-docs a long time. They almost never hire anybody as an independent scientist who's been a post-doc in the lab in order to be sure that they have independence, because very often it's hard to separate that. But that laboratory is totally atypical for NIH. It's not unique; there are a couple of other labs like that. But it's not typical. And increasingly, it's even atypical of university situations.

Anyway, I was very happy with a small group. But I had changed fields also by the time I went to NCI. The field I was in was certainly something that was of more interest in general at NCI than what I'd done before.

GC: So what was that field like?

MS: By the end of the '60s, I really thought I needed to do something different. I didn't have a lot of good ideas, and what I was doing felt like it was getting stale. So I went on sabbatical, which the Arthritis Institute very generously provided for me. I was working on nucleic acids in bacteria, and I went to learn how to do animal cell tissue culture and work with DNA viruses, which happened to be tumor viruses.

So I spent a year, '71, '72, learning that. And when I came back I essentially dropped everything I'd been doing and worked on DNA viruses. And I was working on that when I was recruited to go to NCI. I worked on a virus called Simian Virus 40 and animal cell tissue culture . . . and nucleic acid chemistry. So that's what I brought to NCI.

GC: SV-40 was something that a lot of people at the NCI were working on from different angles.

MS: Absolutely. That's right. It was one of the model systems that people all over the world were working on at that point. And my particular interest was in the interaction between the viral genome and the host cell genome and the acquisition by the viral genome of host DNA sequences into its own genome, which will tell you why I was so interested and intrigued by all the early recombinant DNA work. Basically I was working on self-replicating DNA molecules, which carried with them the DNA of another thing, namely the host cell. So I was interested in that.

[End Side A]

[Begin Side B]

GC: I talked to several people who worked on SV-40 at the NCI. Would you [have been] in contact with other laboratories that were working on that model?

MS: Sure.

GC: Was there anyone in particular or any other lab you remember working with?

MS: Well, I talked a lot and workedCdidn't actually collaborateCbut I talked a lot and actually I went to Malcolm Martin=s lab to do some experiments because I was worried about

contamination in my lab. Malcolm Martin was in Allergies and Infectious Diseases. And he was interested mainly in polyoma which is a cousin of SV-40; it affects mice, not monkeys.

Boy, I haven't thought about this in a long time. Who else would I have interacted with at the NIH in those days?

GC: Did you do anything with Robert Huebner's lab?

MS: No, nothing, nothing. I was really taking a complete CI came at it as a biochemist, not as a virologist. I learned some virology, obviously, but I really came at it as a biochemist and as a nucleic acid structure and enzymology person, which Huebner and the other virologists really were not.

GC: Right.

MS: Malcolm was closer to being interested in such things, although he is a virologist. But he's also a good biochemist and interested in those things.

I'm trying to think. . . . The people who come to mind that I interacted with were mainly not at NIH; Dan Nathans at [Johns] Hopkins, Ernest Winocour at the Weizmann Institute, which is where I went to do my sabbatical, and where I learned all this stuff.

GC: In Israel?

MS: Yes. Also, Paul Berg at Stanford, who was by then working on SV-40; those are the people that I interacted with.

GC: So people at other institutions entirely?

MS: Yes. Also, by that time I was very much involved in using restriction endonucleases. They had been discovered in '70, '71. The first paper was by a man by the name of Hamilton Smith at Hopkins, and the first really elegant distributionCfirst elegant . . . not distribution . . . what's the word I want? [Laughs] My aging head . . . *demonstration* of the utility of them was actually with SV-40, and it was done by Dan Nathans and Hamilton Smith at Hopkins.

I learned about that work [in] the summer of '71, just a couple weeks before I left for the year in Israel. So I brought that news, and in Israel one of the things the lab I was in did

was begin to use those enzymes to study the host DNA sequences that had been incorporated into SV-40, which they had discovered in the meantime.

I was actually able to make a contribution to the study of these things they had discovered because I'd just heard about this just before I came. So by the time I went to NCI in '75 I came back from Israel in the summer of '72 to the Arthritis Institute, having changed fields by the time I got to NCI, I was very much involved in DNA chemistry and restriction endonucleases and things of that sort.

And, of course, all of that just sort of merged with the recombinant DNA stuff and so forth.

The first recombinant DNA experiment, successful one, really successful one, was announced at a Gordon Conference in June of 1973, and I was the co-chairman of that conference. So I knew about everything from the beginning, and I was putting these techniques to use. That was another thing I could bring to the NCI, was all that technology. So I interacted a lot with people who were doing that.

GC: Was that kind of outside interaction encouraged at the NCI or at the NIH, to be working with other institutions, and . . . ?

MS: I must tell you, I was never aware of whether it was encouraged or discouraged, because it went on all the time and nobody seemed to have any problem with it. I mean, I never, *never* had anybody say

GC: Well, I was assuming it *would* be encouraged, that that would be a part of being part of the scientific community.

MS: Right. I mean, that's what I assumed. I just assumed that was normal operating procedure. So if you interpret that as encouraging it, fine.

GC: Okay.

MS: But I wasn't aware of any particular actions on the part of people to do that. Certainly they made it easy for you to go to meetings and go and do seminars and stuff, and eventually that got much harder when the bureaucracy got very heavy handed. But in '75 or so, it wasn't bad.

And then we recruited to the lab, for example, a man whose name is Martin Rosenberg, who is one of those people who ultimately left because he wanted to have a big group. But while he was there, I collaborated with him. Actually, I collaborated with him before

he joined the lab. By the time he joined the lab, he was doing different things, and I was, too. But we did some work together, which was a great deal of fun.

GC: What was your favorite thing about working at the NCI or at the NIH?

MS: I didn't really distinguish a lot between working at the NCI or working at Arthritis. I think if the situation hadn't been to my liking at the NCI, I would have done something else.

But I liked the collegiality, I liked the fact that I still didn't have to spend a lot of time preparing grant applications, I liked my colleagues a lot. Dr. Klee, who I had recruited to come to NCI when I formed my section, is now the Lab Chief. She became the Lab Chief when I left. She's a really marvelous scientist and a wonderful colleague. She had been my first post-doc, in fact.

GC: She was the one who finally came?

MS: She didn't have much choice. She came from abroad and she was looking for a place, and it worked out very well. She and I are now very close friends as well as close colleagues.

You know, we had kids the same age, just a lot in common. It was terrific and it is terrific still.

But getting back to outside activities CI attended the '73 Gordon Conference where the announcement of the first recombinant DNA experiment began the whole public debate about recombinant DNA experiments. I was very much a part of that because I was co-chairman of that conference, so I was one of the people who made the matter public and asked the National Academy of Sciences to undertake investigation of people's concerns about those experiments.

I was one of the organizers of the Asilomar Conference in '75. And I would say from '73 to, oh, '83 or '84, I spent an enormous amount of time on recombinant DNA issues, both within the NIH and without. And it's important that the NCI was supportive of that, because a lot of it was public stuff and you could imagine they would have been very sensitive about various things I did, you know, talking to reporters, going on TV, going and teaching molecular biology in the Congress . . . but they were terrific about it. So that was good. And nobody ever worried about the time I was spending. I spent a lot of time with the NIH Director at that point, Don Frederickson, as he evolved policy on this. But nobody ever did anything but support that effort.

GC: That's great.

MS: It was a very difficult time for all of us, but I think we succeeded in what we were trying to do, which was to de-mystify things and have reasonable regulations but not legislation; we succeeded in stopping legislation and in getting reasonable regulations, which have mainly faded away as it's become clear that the work is not very dangerous at all. In fact, it's not dangerous, period.

But that took a great big effort, and there was an enormous public debate, and a lot of it was troublesome and difficult. And they were very supportive of that. Bob Goldberger was terrific, and everybody else was really wonderful.

GC: You said you spent a lot of time with Dr. Frederickson?

MS: Yes, in those days, from . . . oh, I would say from '75 to '78 or so. I spent a lot of time working with him on how to handle the recombinant DNA issues. I was very much involved in the writing of guidelines and the NIH's handling of the publication of the guidelines. There was eventually a challenge to the guidelines as having required an environmental impact statement. And actually, I and a man by the name of Bernie [Bernard] Talbot, after we'd all interviewed a couple of consultants whose business it was to write environmental impact statements and we figured out we'd have to spend an awful lot of time teaching them what this was all about, because this was science that nobody knew anything about except the people who were doing it, we figured out that it would

take just as much time if Bernie Talbot and I just wrote the environmental impact statement, which we did in a couple weekends' work in my dining room.

The consultants who were trying to get this contract for Lord knows how many hundreds of thousands of dollars were not very happy and were convinced and told a lot of people that it wouldn't stand up in court. Of course, it did stand up in court. It was also very short, and it didn't cost the NIH any money whatsoever.

[Laughter]

MS: So I have even written an environmental impact statement in the course of this. And, I mean, all of this was very time consuming. I wrote a lot of articles. But the NCI was extremely supportive of that, no question. It was good.

GC: Did you work with the NCI Directors as well as Dr. Frederickson?

MS: No. Frederickson really took the lead. This was a national issue, a public issue. It was one which the department, that is, HHS, was extremely nervous about politically and having it backfire. So Frederickson really handled that whole thing. It wasn't handled at NCI at all.

GC: Did you on other issues have cause to talk to the Directors, or did you have any daily interaction with the Director of NCI at all?

MS: No.

GC: Okay.

MS: Not at all.

GC: Which administrators would you interact with on a daily level while you were at the NCI?

MS: While I was the Lab Chief?

GC: Yes.

MS: Mainly I interacted with Alan Rabson who was the Scientific Director of our division, and that was a pleasure. Al is terrific, and he's terrific in every way. He's a great man. And he knew his way through the bureaucracy. At times I balked because his way of dealing with the bureaucracy was basically, "Do whatever they ask, and then they'll go away." But sometimes that required writing long memos which were redundant, writing the same memo six times. Al had the great patience for it which is why he was so great

for the rest of us, because he allowed everybody else to do things. But I didn't have a lot of patience for it.

And over the years, the bureaucracy became more and more difficult, more and more demanding, more and more time wasting. So finally I started telling Al that I didn't want to be Lab Chief anymore. I told him that over a couple of years. And he just ignored me.

I now understand why you ignore things like that. [Laughs]

But one day when I was particularly frustrated I guess it was in 1987 I got a call from the Chairman of the Board of the Carnegie Institution who said would I come and talk to them about the presidency. And I was particularly annoyed at the bureaucracy, so I said, "Sure, I'll come and find out what that's all about." And so that's how I got here.

And when I called Al and told him I was talking to these people, I don't think he took it seriously.

GC: Really?

MS: No. But when I began at Carnegie I was able to keep my lab, which I have now closed. For ten years, starting in '88, I had my lab out there, I had this job here, I didn't have this institution has *no* bureaucracy. It's not only that I'm sitting at the top; it's also we don't

have a bureaucracy. It's a very small institution, and it's terrific. And I had the best of all possible worlds for ten years, so it was great.

GC: So you kept your lab open at NCI.

MS: Yes, until this past September.

GC: Wow.

MS: Then I spent some months finishing up papers and things and then a couple weeks ago the last paper was accepted, it's in press, so now the lab is really closed. I still have a little office there, thanks to Dr. Klee. She gives me a little office, tiny office. Yes, it's tiny. It's three meters by four meters?

GC: Oh, my gosh!

MS: Yes, it's really tiny. But it has a computer and a desk and bookshelves. That's all I really wanted.

So I try to be out there the days that the Laboratory of Biochemistry has its seminars. I don't always make it because I travel a fair amount, but Mondays and Thursdays I try to be there so I can participate in journal clubs and seminars and things like that.

GC: So you're still over there a couple days a week?

MS: I try. It doesn't work out that way, but that's my goal. Like I haven't been there in a couple weeks, because in the summer I always take two weeks and go away and hide and do some writing. So I did that. Then I came back here, where we have our summer teacher training program going, and I've got some things to do. Eventually I'll go on vacation, but next week and the week after I'll be there two days of each week.

GC: In the past nine years, I guess, since the lab was open, were you going over more than two days a week or were you still doing any research?

MS: Oh, in the beginning I tried to go over. I tried to split days. That was horrible.

GC: Like you'd come here for the morning and there for the afternoon?

MS: Every day I wasted time traveling, and that was really not efficient at all. So then I started two and a half days there, two and a half days here. And, again, I didn't always make that goal either place because the Carnegie Institution is very decentralized, so I have a lot of

traveling to do, and I travel to raise money and stuff. And scientists travel for their own scientific reasons. But that was what I was trying to do, right. Then slowly I just cut back on the number of post-docs. While I was here I had as many as four post-docs . . . and a technician, in the beginning. And then this great person, Ron Thayer, went off to be an administrator, and then I just stopped recruiting people and let it kind of . . .

GC: You just let people finish.

MS: Right. And the last person finished in September.

GC: How do you feel about that, about closing up the lab?

MS: I have mixed feelings. I miss it. And, on the other hand, I'm glad to have something less to do. It was like having two full-time jobs for ten years. And I'm not getting younger, and so . . . I have mixed feelings. But I don't think it was efficient for science for me to keep the space and resources, really. So now the lab recruited a wonderful young scientist, and that's the way it should be. And, actually, my office is in his lab, so I get to see him and so forth.

GC: Good. Who is that that is coming?

MS: He's there; he's been there for some months. His name is Yawen Bai. He's a protein chemist, which is good. Dr. Klee does a great job recruiting. She finds great young people.

GC: She kind of follows your lead?

MS: Well, Bob Goldberger's, Herb Sober's before. It's a real tradition in that lab, and it goes back, and it's very deep, that you recruit young people, and if they're good you keep them, if not you send them on their way, rather than recruiting more senior people. And it's really worked out well. The lab's had some great people in it and still does. But people with small groups, exciting colleagues, it's really good. Nice community. That lab is a nice community. There's not a lot of internal strife or competition. Everybody knows that the lab chief is always trying to do the best for everybody, and that's been a real tradition. And it's really worked. It's really quite nice.

GC: Were things pretty open in terms of people sharing research and resources?

MS: In the Lab of Biochemistry? Oh, yeah. Oh, yeah. Definitely. And it still is, I think. Everybody pretty much knows what people are doing, talk a lot. There's a lot of talk, which is the sign of a really interactive lab.

GC: It seems to be more productive, too, if everyone

MS: Oh, yeah, absolutely. It's great, and I wish more people would take it as a model for how to have a department. But it's not the style.

Actually, it's the style at Carnegie [Institution], which is one of the reasons I really like it here. It's definitely the Carnegie tradition. And, in fact, it's interesting because when I came here there were Carnegie scientists who were very skeptical about me because they saw me as coming from the government. And they were very much afraid, understandably, that I would bring government ways of administration and of thinking about science and so forth. Because they didn't know about this history from which I emerged. But in fact they're very, very similar in the whole outlook. So this is great for me. And by now, long since, everybody realizes that I'm not trying to duplicate the United States government at the Carnegie Institution.

GC: Would you ever go back full time to researching?

MS: No, I don't think so. I think it's extremely difficult in our fields to do that. I'm trying to keep a hand in by actually writing a biography of a scientist. I think it would be very hard. One problem in molecular biology is that the half-life of techniques is extremely short. There are new methods being introduced, and one of the real challenges is to keep

on switching methods because of the new ones, and they're much better than the old ones.

But every time you learn a new method, you have to re-educate yourself, and I think that would be very hard to catch up with. Finding a problem is not difficult. There are a million wonderful problems. But getting yourself to the point where you could investigate the problem with all of the state-of-the-art techniques that it would demand would be a problem. I think that would be a problem for me. So it's time in my life to do different things. I had a good run, so

GC: You mentioned you were doing something that involved historical research.

MS: Yes, right. He's a very important geneticist in the twentieth century. His name is George Beadle.

GC: I really want to back up to one thing. When you came into the NCI, it was right in the middle of the big War on Cancer. I just wondered how aware you were of the 1971 Cancer Act that passed under President [Richard M.] Nixon and this whole feeling that cancer was going to be cured by the Bicentennial, that that was the bigC

MS: I knew about it. I thought it was ridiculous, and I largely ignored it.

GC: Really. So it didn't impact your . . . ?

MS: No. I mean, the deal in the Laboratory of Biochemistry was, and is, that you are free to do whatever you want, because Dr. Rabson certainly recognized that without fundamental research nobody would make any progress on anything. So this was very specifically a lab where there was not a requirement to tie everything you did to cancer, except to find a way in the report every year to say, "This is important for cancer research because" But if it's fundamental biology, you can say that. And for me it was actually easy because I was dealing with a tumor virus, you know. So you had to say that once in a while, but that was all. Once a year you have to write down a sentence. But people, happily, were much more focused on the quality of the science than on anything else.

Dr. Rabson was an extraordinary leader. He really understood.

And yet, he is a clinician himself, so he understands the different needs for science and for making progress, and that different people need to do different things. But he also understands the fundamental issue that the best things get done because you put well-trained, intelligent people to do what they think is important and feasible to do. You don't get it done by telling them what to do. And Al understands that in his bones, and that's the way he encouraged us to operate.

And actually, he isn't the one who hired me. We had a different Scientific Director who hired me, a man by the name of Nathaniel Berlin.

GC: Yes. I've met him.

MS: Another super guy, just like Rabson; very, very tuned in to the importance of independence and excellence and originality in science. If you make a program, you're going to do this and that and the other thing and you hire people to do it, you don't get good science that way, and you don't ever solve the problem you set out to solve, because the answer always comes from left field where you don't expect it. It's just the nature of the thing. It's the nature of ignorance.

You know, when you set yourself to try and learn about something, you're basically saying, "I'm ignorant." And if you admit to the nature of ignorance, you admit that not only are you ignorant about the thing you'd like to learn about, you don't even know where to go and look for it. That's the nature of real ignorance. And that's why planning to do things by saying, "Well, I want to solve the cancer problem so I'm going to do all the studies on tumors," overlooks the fact that you [should be] confronting your ignorance. It's papering over your ignorance. It's saying, "Well, I know enough to look at a tumor," but you don't.

GC: Right.

MS: So it's a strange thing. Now, the tumor virus program, of course, really turned out to be great but for the wrong reasons. And that's a perfect example. It put science way ahead. Eventually it discovered oncogenes, but not for any of the reasons anybody thought.

GC: And that was a program that was really criticized at first.

MS: That's right. That's right, because it wasn't getting anywhere. "There are no human tumor viruses, so why should we do this?" You know, Bob Gallo doggedly looking for a human tumor virus. And it was the right thing to do because they could have been there and not been found. But other people were saying, "Why are we spending this money, because there are no human tumor viruses. Most human cancers are caused by other things. Why are we looking at these tumor viruses?" And yet, in the end, for all the wrong reasons the tumor viruses held the clue. So that's a very good example.

GC: Were you involved with the people I guess that you weren't really involved with the virologists at all.

MS: No, although of course CSV-40 is a tumor virus; it causes tumors in fetal mice and newborns and stuff like that. It doesn't actually cause tumors in primates, as far as we know. And actually, we know a fair amount because a lot of us got a lot of SV-40 because it was contaminating the first polio vaccines.

GC: Oh. I didn't realize that.

MS: Oh, yes. I mean, basically a huge experiment was carried out. Nobody knew it at the time. But the polio virus was grown in African green monkey kidney cells, which turned out to harbor this virus. And all the polio vaccines were contaminated with it early on. So people who got the early polio vaccines, particularly so I think in Australia, a very large population of people, they got vaccines that were contaminated.

So now, it's, what? almost fifty years? And there's been no indication of any kind of rise in tumor formation that can be related to that. But it was a big risk.

Anyway, people were interested in SV-40 for that reason and because it was a good model of a DNA virus. But it didn't turn out to be anything particularly important for human cancer.

But the RNA viruses, the RNA tumor viruses, which got most of the attention and which were the ones that led to the discovery of oncogenes, really, those were a completely different kind of virus, which I didn't work on, although in the last years when I was working on human transposable element, I was actually working on something that was more akin to an RNA tumor virus than most things are.

GC: I have a couple more general questions.

MS: Yes.

GC: How do you conceive of cancer? When did you kind of come to conceive of cancer? Did you consider yourself a cancer researcher or just associated with cancer research?

MS: No. I never, ever considered myself a cancer researcher. I consider myself a biochemist. For a while I played at being a virologist. And then the word "molecular biologist" became popular for people who were doing the kinds of things I was doing. So sometimes I call myself a molecular biologist, sometimes I call myself a biochemist. I have never in my life called myself a cancer researcher.

GC: So it was just incidental that you were working on Cwell, not incidental, I guess, but it wasn't a main focus?

MS: It was completely incidental that I worked at the National Cancer Institute . . . or that I worked on a tumor virus for awhile. It was a convenient way to study things I was interested in studying . . . which had to do with the structure of the genome.

GC: We're coming right up on 11:30.

MS: Right.

GC: Is there anything that I haven't asked you about that you would like to add about working at the NCI or about the NIH?

MS: Yes. I would just make the one more comment about how the early days at NIH were different from the later days at NIH and NCI. One of the things that has happened is that the NIH has grown larger and larger. And contrary to what a lot of people think, I think there's a huge price to be paid in a scientific enterprise for being too big. And I think the NIH is currently paying that price and has been paying it for a while.

I would very much like to see it be smaller. I certainly wouldn't want to see it grow any larger. I'm one of the few people who actually, for example, thinks that it ought to be decentralized.

GC: As in not have one campus at Bethesda?

MS: Well, they might have to do that because you have a big investment in that campus, more and more every day. Have you been out there recently? You can barely walk from one side of the campus to the other because of all the construction.

But I think if each Institute was independent, that would allow some decentralization. I just think that centralization is not appropriate and hugeness is not an appropriate community for doing science. It gets in the way too much. It's too time consuming, too overbearing, important decisions are left in the hands of people who don't appreciate what the actual mission is, and I think it's largely due to size.

GC: In terms of you're saying they're paying a price right now. Do you think the quality of the research is slipping?

MS: Absolutely. I think it has been for a while, and I think there have been several big, important committees, one of which I was part of, which have concluded that; you know, the huge groups, the overbearing administration Example: One good way to look at this is, when the labs were established in Frederick [Maryland], a lot of people on the main campus at NCI thought this was a terrible thing, it was way out in the boondocks and it wouldn't be any good and everything like that. A couple years later everybody woke up to the fact that there was this great place out in Frederick; terrific scientists doing great things, they recruited great people. And it was very much, I think, because it was small. And it didn't come with all the baggage which, by that time, the NCI had.

Science thrives under conditions where individuals of talent and skill, have real independence, that's the way science thrives. And when there are too many people making too many rules, it doesn't work.

For example: Young people. The spirit in big labs used to mean that people were there weekends, nights, people were working all the time. Nowadays, you go in Building 37, there's hardly anybody there at night or on weekends. Where are they all? What are they doing?

They're obviously not driven for their research. Well, why not? Partly because they're doing somebody else's research, partly because it's not as inventive, it's too institutionalized. And I think also there's been too much tolerance of large groups. When you build big groups, a person who's a leader of a big group wants to have some permanent people around who will do the leader's work instead of their own. So part of the way they get it is by keeping post-docs for years, part of the way they get it is by giving permanent jobs to people who wouldn't get tenure in most universities, but they toe the line. So you get some mediocre people in.

Then what happens when the leader of that group leaves? These mediocre people have permanent jobs, they demand independence, they use the resources in less than optimal ways. They don't do great science. We have too many people like that floating around.

So partly it's the whole system of doing science that has changed and partly it's the NIH that has changed to form a dramatic example. If you go outside and talk to people about the NIH now and the NCI, you will receive a lot of criticism.

So if you look, for example, at the reports that were done by the committee that Mike Bishop chaired a couple years ago on intramural science, or the committee I was on that was chaired by Gail Cassel and Paul Marks. It was an external committee, and they counted me external. I guess maybe somebody thought I'd be a partisan for the NIH. But you'll see. You should read those reports because they summarize some of the history and they all conclude that the NIH is not what it used to be.

Now, [Harold] Varmus has made a difference, there's no question. He's done things that are important and improved things.

But some of the things that were changed in response to these reports look great on paper, but in practice it's the same old stuff.

I ought to stop now before I really get in trouble.

GC: [Laughter] Okay. This ends the interview. Thank you.

MS: You're welcome.

[End of Interview]

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