NCI Laboratory of Molecular Biology
Oral History Project
Interview #2 with Dr. Susan Gottesman
Conducted on October 2, 2008, by Jason Gart

JG: My name is Jason Gart, and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is October 2, 2008, and we are at the offices of the National Institutes of Health in Bethesda, Maryland. Please state your full name and also spell it.

SG: Susan Gottesman. S-U-S-A-N—G-O-T-T-E-S-M-A-N.

JG: Terrific. Thank you. So today I want to first pick up on some things that we missed yesterday and then we will move forward to when you were elected to the National Academy of Sciences in 1998. Then we will switch from a chronological to a thematic approach and talk about what it is like to practice big science and conclude with some of your current research projects.

SG: Okay.

JG: Yesterday we spoke about several successes in research and I wonder if today you can start with a notable failure?

SG: A failure? [Laughs]

JG: Yes, one of the things that is interesting is that scientists may spend weeks of months on a hypothesis or an experiment and what happens if it does not . . .

SG: Well, it is not so much that it is a failed experiment because I do not set up my experiments with a hypothesis exactly. Usually it is "is it this or is it that." Hopefully, if we get an answer from the experiment at all we know something. We have disproved or proved and those can both be things that might be of value. I am not sure it fits quite with what you are asking. There are certainly lots of experiments that we did that still sit in the notebooks that never made it to papers for various reasons. In some cases just because we did not get to the papers, but in other cases, because we never understood what was going on. In a sense those were failures, those were things where we worked for a long time, usually not full force, but they were things that we were trying to understand and just never developed.

JG: Have there been examples of where you have continued down a line of research but you were never fully able to understood or figure out what was going on?

SG: Well, this thing that I was thinking of . . . I probably have a bunch of notebooks on a couple of different phenomena where we saw something that was tantalizing and it suggested that there was new biology going on and we did a lot of experiments to try to figure out what the possibilities were and in the end it just did not gel in a way. So they sit there. Now one of those, I had a conversation last week with someone who was coming at some of the same issues from another point of view and I am trying to

remember what we really learned and what we did not learn and maybe he will figure out what was going on or how how it relates to what he is doing.

JG: How do you know when the time is to—

SG: When to cut? [Laughs]

JG: Yes.

SG: That is really hard. That is probably in some ways . . . One thing is that a bunch of things are going on at once usually. Sometimes it is just a question of saying "Okay, let's push that to the back of the bench for the moment and go on to these that seem to be moving." I think that is in a sense one of the hardest things for postdocs, for anybody, to learn. You do not want to give up because the next experiment might tell you what is going on, but at some point you should. It is difficult to know when to stop.

JG: How have you tried to instill that in some of your postdocs?

SG: I think we just talk. I had a postdoc who started on a project which I thought would be interesting, and he got some results, but they were not really what we had expected. It was not that we did not understand anything but it just did not fit together and it was not very exciting. I think he was close to thinking about changing careers and we had, at the same time, something new coming into the lab, and I said, "Why don't you just quit that,

start this." He did really well on that and made a big splash very quickly and we were all very happy he had switched. Some of those original questions are still there unanswered. I would not put another postdoc on them because I do not want the same thing to happen. But I might find someone else who has less at stake and might be able to follow that and see whether there is something interesting going on in that project. It is a constant discussion to figure out whether it is worth pushing and how far to push. At some point you just say, "Well, we've got to write a paper on this or somebody else will or it will become obsolete," or something like that. Then you settle for what you have got.

JG: Let's go back to the Recombinant DNA Advisory Committee. I read that Senator Edward Kennedy had recommended research restrictions at that time. Did you face more problems being here at a publicly funded institution than if you would have been at a tenured position at an academic university where, at the end of the day, you were not spending public funds?

SG: In terms of the research we were doing, or having an opinion on it?

JG: Having an opinion on it or being active on the issue.

SG: No, I did not perceive a problem. Some of the time I was clearly representing myself and not the NIH. That was the idea. If I was a member of a committee and I was expressing an opinion it was quite explicit that I was representing myself and not the NCI or the NIH in any way. At other times, in what I did during that period, I was consulting with the

director of NIH on how to revise the guidelines and things like that. So then he was getting opinions from a lot of people and using it. It was not a problem. It might be more of a problem today than it was then. I think we were just getting into—biologists getting into public policy in many of those fields and that was the test case. I think the conflicts and the confusion was not quite as obvious as now where we have to have everything signed off on in a sense. If I were doing that now I do not know whether I would be allowed to participate on the RAC as an official activity or whether it would have to be an outside activity and it is conceivable it could be complicated. But at that point it was not a problem.

JG: Talk a minute about what differences in the lab between the early 1970s and when you returned after MIT. How did the pursuit of molecular biology changed?

SG: I probably should have brought pictures or some other crutch for my memory to remember who was where, when, and what we were doing because it all sort of flows together. In terms of the kinds of thing . . . This lab was probably at its largest when we came back in 1976 when Ira [Pastan] was expanding LMB. We got some space down on the second floor. Michael's group was there; others were there. It was a pretty large group doing a lot of different things.

JG: Did it decrease then over time?

SG: Gradually. What happened is to some extent people left and became heads of their own labs. I would have to look at those pictures and everything else out there but a whole bunch of people who were senior investigators in our lab who had their own lab groups became lab chiefs in other Institutes. Some of them are on your list of people to talk to: Bruce Howard, Ken Yamada, Michael [Gottesman] and then some other people left and went to other places. Benoit [de Crombrugghe] and others. Not all of those people got replaced by any means in terms of members of LMB. Eventually Max [Gottesman] left. When I came back to NIH I had a room which was enough for maybe three or four of us and that was my group. Space was always tight. I was partially doing the project that I had done as a postdoc, sort of continuing on that, and then began some other things. I started working on proteolysis which became the focus after a while. Then after Max left and went to Columbia I got a little bit more space and therefore a somewhat larger group. Then eventually we all moved from the fourth floor to the second floor. Ira was expanding some of his core interests and was starting to think about the immunotoxin switch although I do not know exactly when that started.

JG: Why do you think—and I have been asking other members of the lab the same question—Ira made the switch? What caused him to make that switch?

SG: He is fairly explicit about it. He wanted to do something important for health. He wanted to cure patients. He wanted to see the kind of research that he did have an impact on patients. It was a long process getting it going to the stage where it got anywhere near a patient. I think most of us did not think he would get there. They have, they clearly

have. I think he just said, "I've gotten to a certain stage in my career, I've accomplished a lot, and this is what I want to do with the rest of my career."

JG: Is that typical of other scientists or of colleagues of yours?

SG: Well, no. Some of us work on the same thing forever. Some people do switch. Ira started out with an M.D., and began research from a medical background, then got into what turned out to be a lot of basic science. He has switched every so often. There are also just different personalities in terms of do they get bored, do they get restless. It is clear that he likes to switch fields after awhile and this is sort of a much more challenging undertaking because it has so many more parts than just trying to solve a lab problem or lab issue.

JG: You become chief of the Biochemical Genetics Section?

SG: That is when Max leaves. Yes, basically.

JG: Describe how that came about and how that changed your daily workload.

SG: Well it did not change . . . Sections in LMB, and in NCI in general, were in the past sort of small mini-departments. Originally this section probably had me and Max and Sankar [Adhya] and Don [Court]. There were a bunch of us in that section each with some people working with us and interacting a lot. The evolution over time has been that each,

and now just about every PI, every principal investigator, senior investigator, get their own section. We were sort of in transition there. When I came in I was in Max's section which meant that theoretically he was in charge of signing off on various things for me. He never interfered with what I was doing. We collaborated on some projects but it was not like he ever told me to "do this." Now we all sit around in seminars and say, "Why are you doing that?" or "Why don't you do something else?" That we do to everybody. When he left, my responsibilities were not a whole lot more because I did not have a lot of people under me in terms of other permanent scientists. I just had my group. I had a little bit more space to do what I did, but it did not change things radically, except that Max was gone. He has a strong personality and interacts, tends to foment ideas and bring people into the lab, he was always having visitors who came on sabbatical, who were also very interactive. Some of that went away and probably the group became a little less cohesive, the prokaryotic group, in a sense. We all went a little bit more our own ways than we had when Max was there, since he had put it together as a group in the first place. I think that changed a little bit.

JG: What are some of the research interests that you are now taking on in the late 1980s and 1990s?

SG: When I came back we were starting to work on energy-dependent proteolysis and how that worked in the cell. That was basically the focus of the lab through the 1980s and well into the 1990s.

JG: That is the ATP-dependent protease?

SG: Yes, so those are ATP-dependent proteases. We started with a protease called Lon—which was the only one we knew about when I started the work—trying to figure out what it did in the cell. When I started one of the people I was able to hire was a sort of senior postdoctoral fellow in the lab, was a scientist named Michael Maurizi, who is still at NIH. He was a very good biochemist and that was a good complement for my sort of genetic view of things. We started looking for other proteases and found this new family of proteases that we called the Clp proteases which turned out to have the ATPase subunits, which recognize substrates, and the chewing machinery in separate proteins and they come together and make a machine that does a very good job of recognizing and degrading specific proteins. That opened up a new field. We tried to do it genetically—but the biochemistry won in that case. We were figuring out what Lon did and we were moving into the Clp protease and then trying to figure out what Clp did. Again, I probably have to look at my CV to figure out what the dates were on some of those papers but we continued to work on Lon a bit and some things sort of fell out from that because of the way I was looking at a lot of that work.

For instance, for the Lon ATP-dependent protease, when you mutate that protease and take it away from the cell, the cell has some very striking phenotypes. It gets sensitive to ultraviolet light and piles up this yucky looking sort of mucus. It overproduces a polysaccharide so that the colonies look really pretty strange. We were basically dissecting out what is it in the cell that should have been degraded by this protease, is not

being degraded, and therefore is causing these phenotypes. We separated them out genetically; that is basically what we did in the early 1980s. Each of those then develops into a story by itself, in which a specific protein was degraded by the Lon protease. We had a few papers on the basis for the UV sensitivity. We did not do a lot. That was earlier in the 1980s. Then we worked on the capsular polysaccharide, this overproduction of this capsule. To find out why Lon mutants were mucoid, we had to analyze the whole pathway of how the capsule was made and how it was regulated. Defining those regulators is something that was going on in the lab sort of secondarily to the protease work. It was genetic regulation I was interested in. The transcription regulators we found for the capsule pathway have led us into other things and we re-encountered them again many years later. It turns out to be a really important regulatory system that is key to a lot of things. That was going on in the lab. I tried to keep a transcriptional regulation project going in parallel to the proteolysis project just because I was interested in both and one developed out of the other and sort of helped us understand the other. Then with the Clp proteases it was the same kind of thing, that is, what does it do for the cell and it was less obvious what the first Clp protease, ClpAP, did for the cell, since the mutants had very little phenotype. Then we found another Clp ATPase subunit, part of a different Clp protease, ClpXP, which did more for the cell and we got into further studies of that. Some of the protease work became much more biochemical and much more structural and moved out of my lab eventually.

JG: Do you recall specific "Aha!" moments in your research?

SG: A few of them. So one of them is associated with the protease work early on. We knew that cells were UV sensitive when they were missing this protease and we suspected that there was a protein that is usually degraded by the protease. The model was that there was too much of this protein and it was causing the cells to get sick because it was not being degraded properly. We were trying to find the gene for the protein because then we could actually look at the protein and prove that it was being degraded. Demonstrating degradation of a cellular protein and the role of degradation in protein function had not been done before. This is again very early in recombinant DNA and we do not have the sequence of the whole genome, and we are trying to figure it out and using lambda to pull out pieces of the genome. We finally get a piece and get a sequence of it that we think ought to be the thing and it has exactly the right characteristics. I mean it had regulatory signals in front of it that said it should be turned on when the cells are exposed to UV light. It would be made only after you UV'd the cells and we knew what those signals look like. It was very clear once we got that that we had the right thing and that everything else followed from that—that we could put the story together very quickly.

Probably the other thing I can think of has ended up in some papers but it is in a sense an obscure side thing. We had some very funny phenomena in the cell in doing our genetics that we did not quite understand. And, again, it was a sequence that gave us the hint into what was going on. This was a medical student who was spending two years in the lab as part of a Howard Hughes program at NIH. We had a mutation on something. I mean, to try to explain all of the genetics would be complicated and I am not sure I would get it all

right at this point. [Laughs] But when he looked at the sequence it looked like a phage gene that is involved in bringing genes in and out of doing recombination—which is what I had worked on. It looked like the integrase that I had worked on in bacteriophage lambda. When we saw that we realized that in fact what we had thought was a mutation was actually a whole piece of the bacterial chromosome getting popped out under particular conditions. So changing the structure of the chromosome and then it got complicated. It took a lot of years before we understood it all. It was a lot of fun to all of a sudden look at it and understand a lot more than we had understood before. I am sure there are other little . . . Everything is like that a little bit but they have not left a real imprint on my mind in quite the same way.

JG: You publish on these areas. What are your feelings when you see other scientists pick up the science and move it further along? What is that like?

SG: Sometimes it is a lot of fun. Sometimes it is why didn't we do that? [Laughs] It is a little of each. Mostly it is great to see and I usually know them and I have interacted with them. It is exciting to see where some of this goes. When they are doing something that is very close to what we are doing then it can get a little competitive. But we deal with that. I would rather talk and tell everybody what we are doing than hide it and find out later that they were doing the same thing. That is in some ways a lot of the fun of doing it, you know, is to see where it can go and what it applies to that is not what you thought about in the first place. In terms of the proteases we talked about it and thought about it in terms of this is a model that should be true in many organisms and in many situations.

If the variations are entertaining, they are not totally shocking usually. I think that is true of the small RNAs too where we see what we are doing sort of expanding into other organisms. That part is pure joy because I do not want to work in any other organism. I am just happy to talk to people about it.

JG: During the 1990s there are changes in funding for basic research. Did that impact your work?

SG: I am not sure we felt it. That is the beauty of being at NIH, we are pretty well insulated. I do not think there has been a time here that I have felt seriously squeezed for funds. Money I guess got larger at that point but our group has sort of slowly grown over the years but not a whole lot. I think we saw a lot more sort of big science from other places. Which may change a little bit how things are done in sequencing genomes—that kind of approach-- sort of doing more global searches? We got into that a little bit eventually and certainly are doing some of that now. Probably my science was not infected drastically by too much that was going. It was just, you know, we had our Petri dishes and our toothpicks and our test tubes and I am not sure exactly what you're getting at—

JG: You are elected to the National Academy of Sciences in 1998.

SG: Yes, yes.

JG: Describe a little about how that came about and how you were informed and also what the recognition means?

SG: Okay. How it came about, in retrospect, I can speak to because I know what the process is. I suspect I have a lot to owe to Sankar who had been elected a couple of years earlier and I think put together the nomination maybe with a little bit of urging from David Botstein, who at that point was head of the Genetics Section, which is where my nomination came through and who I had worked with at MIT. So somehow the nomination gets submitted and there is a long complicated process. I had a few hints during the previous year that maybe something like this was going to happen because I had some strange conversations with a couple of people where they seemed to know about my work in a way that I would not have expected them to. They were a little bit outside my field. I knew what the schedule was for the meeting because we went down to the garden party, I think. There is a garden party every year on Sunday and then on Tuesday morning is when the election results are announced. I don't exactly remember why we were at the garden party but we were. Maybe because Michael got invited regularly because of his NIH position. People were a little strange there too, as if, you know, something was going to happen. So I can't say I was totally shocked on Tuesday morning. I actually walked in, stopped to talk to somebody outside, and then when I came in the phone was ringing and plus there were messages on the phone from people who had called already and missed telling me I had been elected. Then the phone kept ringing and e-mails kept showing up and so it was certainly a lot of fun. We had a party

too. [Laughs] I think there are a lot of pictures of it somewhere in our files. It was very nice. It was nice in many ways.

Locally, it was useful in a sense, because Michael had become by then Scientific Director, the DDIR. There were still people at NIH who did not quite understand that we were independent scientists doing independent work. I was a spouse of the DDIR and maybe I was getting special credit for that, you know. It was nice to have my own recognition which was independent of Michael's and sort of made it clear that I actually did some science of my own, that I wasn't just being given a position because I was attached to him. Most of the people I cared about understood that and it was not an issue. Probably the only perk I think of being a member of the NAS is that you can submit papers to the journal, *Proceedings of the National Academy of Sciences* (PNAS), yourself. You do not have to have them go through the same kind of review process that we standardly would. Now it has gotten a little more complicated and a little bit more stringent but at that point as a member if I wanted to publish, it was easy to do. I only had a certain number I could communicate a year and I have never used them up. If you wanted to submit a paper you had to have a couple of people look at it, handed it to them and said, "Give me your comments back." Then you would send it in. What I learned was two weeks later it would be in press, which was unheard of for the usual process. That turned out to come to our rescue because a colleague who had seen a presentation of our work at a meeting in the spring, and three months later in August, called me up and said, "By the way, we saw that and we have a paper in press on that same subject in *PNAS*." We had been writing our paper but we had been taking our time about it. At that

point, we just pushed it out so it ended up being back to back with this other paper, which was okay. If I had not been elected there is no way I could have done that. That was sort of a side bonus at that time. I have never had to do that again quite that way. So other than that I am not sure what else it helped with exactly. Probably a few more resources here. Eventually a salary increase here, things like that. Eventually more time spent doing things for the National Academy because right now they have got me on various committees.

JG: When you were elected how many women were in the National Academy?

SG: I don't know the numbers. So women were in the minority. They still are. There has always been a push to get women elected. There still is. My mother believes I was the youngest woman ever elected but she is not correct in that. [Laughs] Certainly there is a sense maybe I was elected sooner as a woman than I would have been if I were not. So if I had been doing exactly the same work and had a different sex it might have taken me a few more years to get elected and maybe I would not be in now. It is certainly a bit of an advantage at this point. Since I was not seeing it from the inside then, I don't know, but I certainly know since then that there is a push to be sure that women, appropriate women, are nominated and elected. There were particularly in genetics. I have a lot of colleagues in my field who do bacterial genetic research. There were a bunch of them that had been elected in the years before I was elected. So people that I knew well and that I respected, but that were basically my peers, had been elected. It was not that odd at all.

JG: You have approximately a 122 publications?

SG: Okay, yes.

JG: And Ira has eleven hundred?

SG: Many more, yes. [Laughs]

JG: Talk about the role of publications and citations in science today and how it has evolved since you attended graduate school? Is one number right?

SG: I think I said yesterday Ira is more entrepreneurial. He has always had a big group and a lot of collaborations and a lot of things going on and that ends up being a lot of papers of various kinds. While I have had significant collaborations they have not been ones where there are a lot of extra projects going on and things that we do. Publications are always what we present to the world. Different people publish at different points in a project. My feeling has always been I want a complete story to publish. I would not say that Ira hasn't also just in different fields there are different things that are publishable. It is very hard to compare a publication record in eukaryotic immunotoxin or multidrug resistance or some of the other projects he has been on. They are not always going to be one to one with the kinds of things that we may publish. I have always had a much smaller group than Ira has had. For me that is what I am comfortable with for the most part. If I have a good group of seven or eight people and they are all doing different things that is usually

enough. Also, I tend to have projects which the postdoc more or less owns and that means that there is going to be a fair amount of variety of what is going on in the lab and only a certain amount of stuff I can possibly follow. In many big labs that is not the situation. I mean everybody's sort of working together on different aspects. I am not sure the role of publications has changed. It has always been the evidence that we are producing. It is what the world looks at. How you find publications and where you publish them has changed with the Internet access and PubMed and things like that.

JG: How many publications do you think a scientist needs per year for funding and tenure? Is there a number? Has it moved towards that in a sense?

SG: Some places. It depends again on where they are and how big their group is. I just came off sitting on a study section which looks at grants. One of the things we look at is how productive people were over the last period. One thing that people do, and it is hard to say that they do not, is count publications. But you could have ten publications that do not amount to one or two from somebody else. That is very clear too. What the publications are, what impact they have, how groundbreaking they are, how complete the story is all matter. Just the quality of what is in there varies all over the place. A decent lab at NIH, some of us have a few people in the lab, some of us have seven or eight . . . I hope that most members of the lab may not publish every year, but every couple years the postdocs come up with a paper. So every two to three years they should have a paper or two papers. The rate at which those accrue varies. I have been looking at my 2008 publications and there is not a lot there although we have two papers we are just sending

back. A lot of people left the lab and a new project started and it takes a while for them to get going. There have been years when I have very few, and years when it seems like we have a fair number for us. In general we do not publish tons.

JG: Could a researcher or scientist today take years to come up with a terrific summation?

SG: You mean do we have the leisure to wait a long time before we publish something?

JG: In some cases it might be a leisure but some projects may require—

SG: Take a long time to mature? Again it depends on where you are and what the funding is. At NIH that is the hope, that we can do long-term research, that we can let things mature over a fairly long period of time. If that was all that was going on in the lab, it may be difficult to sell. If we get site visited, if we get reviewed in the middle of that period, and nothing has come out, whether you are going to convince somebody that we are on the right track and this is going to be spectacular when we get to the end is hard. So frequently we are doing more than one thing at once. So in theory, yes. Then the other reality is that most of our work is run by postdocs and the postdocs tend to have a shorter time period in which they can produce something. So again it takes either a very brave postdoc or somebody who has a very different viewpoint to take on a project where we know it is going to take a very long time. Sometimes it just does and we can't get there as fast as we want. For a postdoc who has theoretically no more than five years and frequently more like three to four years that is going to be the limit on when they should

get something accomplished that they can produce. Then it depends a lot on how you are looking at it, whether there is nothing along the way or whether there is, but at the end you have a much bigger story.

JG: Speak a little about the process of collaborating? I get the impression that it could go very well and it could also be very difficult.

SG: Yes. Collaborations always have complications. The advantages of a collaboration are immense. They can bring different expertise to a project, different points of view. I have had two major sets of collaborations in my career. The first one on the proteolysis, and the chaperone work with Michael Maurizi and Sue Wickner, who are both here. They bring a much more biochemical perspective and abilities to problems that I see from the more genetic and regulatory point of view. So it is a good match in terms of our expertise and our viewpoints. We can provide good advice to each other. At times it is "Who's going to get credit," or "Who's going to be the first author on the paper," or "Who's going to pursue this." Frequently credit is an issue and occasionally, because they both do biochemical things, there is some conflict there that has to be sort of ironed out so they are not conflicting with each other.

JG: How do you negotiate that?

SG: I think eventually everybody goes off in different directions a little bit. There have been points where we had to sit down and talk about things. Maybe times when not everyone

has been entirely happy with everything. Overall, I think we all realize that we all benefit from it. Now the minimum requirement for a good collaboration is that we believe that the other groups' scientific judgment is good and that when they do science, the science will be good and believable, and that you are not going to be in a collaboration where the other guy is making things up or doing poor science. Both trust and quality are the basics for doing collaboration. For a while I chaired an ethics committee for ASM [The American Society for Microbiology] and got involved in this and we had a meeting, and we put together a couple days of meetings to discuss the issue of how you do collaborations and what you really should do to make sure that they work and that you don't end up in trouble because of your collaborator. One conclusion was that the more you talk out ahead of time how publication will be done, the better it is supposed to be. Nobody does that quite as much. It is very hard to do that. The second set of collaborations I'm in now are with Gisela Storz who is in Child Health and works on small RNAs and our views are somewhat different, but they are not as different. It is just that we both sort of hit this new field at the same time and so having our combined forces and groups that do things a little differently and can talk to each other and share approaches and share projects back and forth has just been very useful. In both cases it is very nice for me in a group meeting to not be the only senior person in the room. This means we get a lot of different opinions of the work that is presented, what to do next, and what it may mean. Now, whether the postdocs always want to hear opinions from all of us is another matter, but I think it is useful. They have to learn to take all that in and then filter it and take what is good and not just follow my advice but go beyond that.

JG: You have served on several editorial boards. Speak about that and what that entails?

SG: Yes. I am still on many and I have got a pile of papers on my desk. The first major editorial board I was on was *Journal of Bacteriology* and I did that for almost the full ten-year term. The job was as papers were submitted to that journal they got sent out to the various editors. I was an associate editor. Let's talk about that job, which is a little different from being on an editorial board. Then I would send them out to reviewers. I would get back the reviews. I would make a decision, write a decision letter, look at the revised manuscript when it came back in, either send it back to the reviewers, tell them to do additional experiments, reject it, accept it, whatever. I was asked to do that after I had been on the editorial board. So editorial boards, for the most part, what you do is somebody sends you a manuscript and asks you to review it, and reviewing it means looking at the science, looking at the organization, looking at the data. Is it significant? Is it believable? Is it well presented? All of those things. I do a lot of that and doing the *Journal of Bacteriology* for ten years and getting on the order of twenty to twenty-five manuscripts a month to deal with, each of which came back once or twice, a least a couple of times, it was an enormous job. But it made me good at looking at manuscripts quickly. I mean, one, it exposed me to a much broader field of microbiology because I got papers and things that I did not know anything about and had to learn at least some about it although I was not the expert reviewer. Then two, after the first while of doubting your judgment about this you get used to making those decisions and so it becomes easier after a time. I was very happy to see that end.

Then the editorial boards I am on now are much less of a burden in terms of time and even number of papers, but I do a lot of reviewing. For an editor getting a reviewer to review it and do it on time is the most important thing and it is frequently very hard. You send papers to some people and they would be black holes—you would never hear from them again about the paper. Or they would say, "Yeah, I'll send it next week," and next week would come and nothing. The author is not happy, you are not happy, it is not good. Therefore I think I am a good reviewer now. I feel sympathy for all those editors. When somebody asks me, if I possibly can review, I try to do it at least close to time although the last few weeks it seems like it has been falling behind. The editorial boards I am on now for the most part I get interesting papers that I like to read and I don't get to read all the literature that I would like. It is a way to keep up with things too. I can easily handle a number of them a week so it gets to be substantial portion of my time in some ways.

JG: Talk about the changes in technology in regards to microbiology and how it has impacted your research? How do you remain active with these changes?

SG: Well, sometimes we remain active because the postdocs know what they are doing, even if I don't. [Laughs] So that is part of it. You get in people who bring new technology with them. Obviously recombinant DNA and things associated with that mean that we can engineer pieces of DNA and look at things in much more detail much more quickly. Sequencing, and ease of sequencing, is the other enormous change. So those combinations, that we have the sequence of the whole organism that we are looking at

and that we can modify now at will basically means that for somebody who does the kinds of things I do, which is *in vivo*, try to understand what genes are doing and how they are related, that the limitation is thinking about the right things to do now, and then we can do it pretty quickly. In the past, we were limited by what we could possibly do. There are not any limits anymore in how I can manipulate the organism. The art when I started was to figure out how to make that mutation in that gene. I was interested in how to move it into a context with another mutation that I was interested in. Now that is trivial. *E. coli* was always a good place to do that but there were still limits. Now, there are basically none. That means, in a sense, some of the day-to-day how to do it is gone and now you have to spend your time thinking about what it is you want you do with all that information and how to make use of it.

The other thing is that having the *E. coli* genome means that—and having the sequence of other bacteria—means that we can do a lot of comparisons and that helps us define things. One of the things that we have done in our groups collaboratively with Gigi Storz is make use of that kind of information to find these small RNAs that we are interested in now. That is something that we could not have done without those sequences. Without the computer programs and approaches that allow you to manipulate them easily and look for things. The computer access to the literature is enormously useful. It used to be that if you were interested in a gene you knew which journals to look in and maybe you would remember reading an article or go at the end of the year and look at the index for the past year to find all the papers on such and such that you might have missed along the way. Now you put it in the computer and everything comes up, including papers in

journals that I would never think to pick up. That is very useful for the kinds of research we are doing now in which we run into genes we did not know anything about last week. I have to find out everything about them to see if anything that has been published helps to explain our results.

I have become relatively adept at that computer stuff. We use global ways to look at gene expression, microarrays and things like that now that we obviously did not have before, that depend on having the genome sequence but go to the next step of asking how it is being expressed. The people in my lab, I do not know how to do that with my own hands, I know it exists, and I know what we can use it for. I know something about how we want to analyze it because I figured it out as we go along. To do it day-to-day, no, I am not the one doing that. The other people in the lab have figured it out. Probably for a long time there are many things that the people in my lab know how to do that I do not do. I still do the bacterial genetics and some other stuff that I knew how to do before and I count on them to know the rest. I try to keep my eye out in talks and in meetings and in papers for things that they will find useful and then say, "look at this," and figure out whether this is something we can use, but it is not like I can do it myself.

JG: Talk a minute about when you learned about polymerase chain reaction (PCR) and how that impacted your lab?

SG: I am not sure I know. [Laughs] I think it would be hard for me to reconstruct where it became obvious that it was . . . That we could do it and that we could pull out pieces of

DNA that way. The point about PCR is . . . So let's say I want to go in and I want to get a particular piece of the genome in *E. coli* and clone it into a plasma. There were ways to do it before PCR. It just got a whole lot easier with PCR. In a sense, because we were in *E. coli*, and because we had so many other tools at our disposal that we could use, the change probably was not as dramatic as it was for people working in eukaryotic cells or mammalian cells where getting at some of those pieces of DNA or the RNA or anything else was just about impossible or very, very difficult and became a lot easier with that. I have no idea how it—

JG: What about the role of the seminars at this lab and how that has changed over the last three decades?

SG: People do not smoke anymore in the seminar rooms. When I first came there was a smoke filled room. It was always a very interactive group. That was the expectation that Max and some of the other people had.

JG: And this is every week. These are meetings every week?

SG: Yes, they are . . . There are multiple meetings a week. At the very beginning of LMB it was everybody together because they were doing prokaryotic transcription, etc. That did not go on for terribly long. Then it split into animal data club and vegetable data club and an animal journal club and vegetable journal club. So we were the vegetables.

JG: As an aside, this is a kind of joke, a running joke, the animals and the vegetables?

SG: Yes. It was some way to distinguish the people working on mammalian cells and the people working on bacteria. So they were the animals and the vegetables. The expectation always has been for seminars—let's talk about the vegetables since those are the ones I was involved in—that you could be asked anything and you are likely to be asked anything, and Sankar always has another way of looking at something that he will challenge you to defend to your view of how things go. There are other people too that you would be asked everything. Once you had presented a talk to this group and to the Lambda Lunch group, which is sort of a NIH-wide parallel to that, you would not be afraid to present your work anyplace. You could go to any meeting or any university and it is unlikely that someone would come up with something that you had not already been asked and had to think about. That is what made this a wonderful place to do science was that interaction and that sort of expectation of quality and that everything would be examined and that you would be able to defend it. That has been a constant, I think, all along. Maybe it is a little less so or a little more polite now than we were.

JG: Where did that come from?

SG: Well, I think it was a legacy of the phage group. I do not know whether Sankar talked about that at all. There was . . . Molecular biology began with physicists as well as biologists in the phage group. That group was not quiet and so we went to Cold Spring

Harbor to the phage meetings every year and there was a lot of discussion, very active discussion and argument, and that was what we expected. That was our reference point.

JG: Talk about Cold Spring Harbor and your impressions of the physicists?

SG: Well, so I did not interact much. I met [Max] Delbrück maybe once when they were dedicating some building to him or something. I was a little bit behind the peak of that because when that was going on I was probably still in elementary school for the most part. I was the next generation. I knew [Salvador] Luria pretty well because he was at MIT and had the lab next to Boris Magasanik's. His science was beautiful but I can't imagine that he was the one that was asking people nasty questions or walking out if he did not think they were doing decent work. I did not really have that aspect of it. I was just sort of aware of it as the background and partially it was because the science had at that point not expanded infinitely. That is, a lot of people were working on things that were related to each other and so they all had a lot to say about what the other person was talking about or had a slightly different take on things. They were talking the same language so it was a little bit like an expanded group meeting. It was people that talk to each other all the time scientifically.

JG: You mentioned that it is a little bit more polite now?

SG: Yes. Well, right.

JG: Do you think that something has been lost in that?

SG: Well, it is more fun when there is a lot going on and a lot of questions asked. It depends a little on how we are and . . . We wake up some of the time. It varies. It is okay. The science we listen to now in seminars is usually a little bit broader. So there is not the same intensity of involvement by everybody in the audience with what they hear. That affects them too, I think.

JG: What about your insights on mentoring and teaching? How do you train the next generation?

SG: Yes, I do not know yet whether I am doing it well is the first thing. [Laughs] From my own perspective it is important to give kids in high school and college the chance to work in a lab to find out whether that is something that they want to do. I think science as it is taught in courses is frequently not so exciting. It depends on who is teaching it obviously. Doing organic chemistry may not be too exciting. When somebody goes off to college thinking they are interested in science and then it is two or three years of the basic coursework before they ever find out what doing science is like it is very hard for that to compete with courses which may be much more interesting in English or government or something else. On a regular basis I have had summer students at various levels of their careers, but high school and college frequently. We have two high schools interns that are working this year in the lab. At that stage, the point is, one, to find out what it is like to play in the lab and get a result out and the excitement of it—or discover

they hate it. Some of my first summer students were students that worked in the lab who ended up being lawyers. That is fine too. But they should know and at that stage that is the most important thing. We do not see a lot of graduate students here so I do not see a lot of scientists at that stage of their career which is really obviously a critical one for developing your sort of lab habits and how you go about doing science. We see them as postdocs. Postdocs, hopefully when they come in they are on the edge of being ready to be independent and so we come up with projects that allow them to do that. My problem is that I, at this point, I sort of know how I think it should go and sometimes I tend to start presenting my ideas. I need to remember to ask them "What should we do next?" So I'm still training myself to let them get a little bit further out on a limb themselves because I think that is really critical for them to find out what works and what doesn't. You also want to get things done. Sometimes letting people follow their own ideas does not work.

JG: How do you help postdocs and other young researchers understand the importance of scrutinizing errors and of being creative. It is quite a creative field?

SG: I am not sure that I do these things super well. First of all the postdocs come in different flavors and different personalities. Some of them are pessimists where they doubt every piece of data that they produce and there are others that are optimists that think everything is going to change the world. I see my job as taking the opposite tack, whatever it is, you know. [Laughs] If they are optimistic, I am pessimistic. If they are pessimistic, I am optimistic, to some extent. It is back and forth to encourage them when things are bad, or at least figure out which part of it is actually okay. That is part of it.

Ethics, boy, we hope we do not push them to the point where there is something bad. We are required to have discussions once a year about scientific ethics. We hope it is by example. I am not sure that we sit down and specifically talk about things. I have not had issues that I know of. I think sometimes there are issues of writing papers where people, particularly foreign postdocs, who do not speak the language that well are likely to pick up paragraph from the introduction to another paper and want to use it. There have been a couple of times when we have had to talk about what is acceptable and what is not in terms of doing that. They are not really ethic issues they are really just how to go about putting things together in a way that is appropriate. Creativity, that is letting them figure out what to do next and then asking the right questions at the right time, that is, how would you go further. I have had some people in the lab who I felt were a little too cautious. Just talking about seeing how you can go to the next step, or taking some chances, is worthwhile. It again depends a little on the person and the personality and where they are going to end up because not everybody who walks in the door is going to end up doing independent science. If they do not have any of those qualities they are better off being someplace where someone else has the creative ideas.

JG: What about working with the colleagues that are further along in their career? How do you manage a bunch of very bright people? How do you negotiate that?

SG: In terms of what? I'm not sure—do you mean postdocs or other people?

JG: I mean other people beyond that.

SG: Well, I am not managing them really to tell you the truth. Most of my career it has been me and my lab and collaborations and not much else. I have not been heading a department the way Ira has. Ira basically has let us do what we want. So now I am co-lab chief with him of LMB and I am just getting into that stage and we are doing a little bit more of sitting down and chatting with other people and asking them what they are doing and why they are doing it and trying to give feedback. It is not something that I had to do as a real part of my career other than going out to meetings and talking to people. It is a lot of fun to see colleagues maturing—hear their first talk at a meeting and then see them develop beautiful stories. That is something that I really enjoy. But it is not that I am really having to manage them. I just have to be a sort of a cheerleader and interact and review their papers.

JG: Yesterday you mentioned that there were only a few women in the lab. How has that changed?

SG: There are more. Clearly in this lab there are three women PI's among the nine of us. Around NIH there are a fair number more. They are still a minority. In my field again there are a fair number of women. Probably most of my closest colleagues are women. It is still true that women do not as automatically assume that they will go on. So I see it in my postdocs, that not all of the women see themselves as going on to an independent career, for various reasons. Some of them family reasons, some of them self confidence reasons. And depending on what it is we push them along. I think it is still a lot easier to

be a woman scientist with a family here than it is in some universities. When I travel around and give seminars there are some places where everybody seems pretty happy. There are others where the graduate students see very unhappy and overcommitted women faculty and say "I don't want to do that." Women either feel that they are not properly appreciated or they just do not have the time to do everything they feel like they have to do. It depends very much on the local environment in many ways. This has always been a good environment. Presumably I would not have stayed here if I didn't think it is a good local environment.

JG: How have you worked to bring more women into the profession?

SG: In terms of the students we take and the postdocs we take I certainly have had a lot of women. There were times when my lab was almost all women postdocs. It is more mixed at the moment. Hopefully, I help by encouraging them and pushing them a little bit harder to think that they can do it and that they should do it, that they really are good, and then supporting them when they are out. Although I do that for anybody who has come through my lab. I will do whatever they want me to do to help support them and we try not to compete with them either. So the projects go and they take them with them. In the wider world, I am not sure I have been super active. I do a lot of traveling, giving advice, but I am not sure that I have actively done a lot.

JG: You wrote a chapter on your career for ASM. Speak about that because it is a very interesting book—

SG: Yes, it was an interesting idea and he pushed me to write it, so I wrote something. Then he pushed me to make it more interesting. I'm not sure I did. I can't even remember exactly the process. What was interesting to me, looking through those chapters, is I mentioned yesterday that it was *Microbe Hunters* that brought me to science. They had just a whole section on people that came into microbiology through *Microbe Hunters*. I found out a few of my colleagues who had been brought in through the same route. Well, this is hard too, sort of trying to capture how it is you think about science and why you do what you do is not easy to describe—you just do it for the most part. What I liked to do is logic puzzles and that is what I organized a little bit of that chapter around the idea of what I'd like to dissect out and logic puzzles. That is what the cell is. That is what the regulatory networks are and that is what I enjoy doing. I tried to put a little bit of that in as well as. He asked me partially because of my role in the recombinant DNA committee.

JG: Michel Morange, writing in *A History of Molecular Biology,* has argued that there are research questions that scientists avoid. They avoid them because they do not want to risk their reputations or their careers on the topics. Is this true and, if so, how does this affect the profession as a whole?

SG: We all to some extent do what is possible and either you have to create tools or you have to work with the tools that are there to answer questions. There is a perception that people are a little bit too cautious because of the way they are funded and because they

have to report the grants and get those grants funded every "X" number of years. There is no way to take on a problem that is not going to go any place or has a reasonable probability of not going anyplace in that kind of context. That is presumably part of what NIH is about. We see it as a problem when we are advertising and when we are recruiting new people to NIH. I have been on search committees. I have chaired search committees. Finding people who are willing to say, "I want to take a chance and do something that is high risk but really interesting," is sometimes difficult because they are applying also at the same time to a lot of places who want to be sure they are going to get their grant and get funded. There probably are things, topics, and issues that do not get attended to quite as much. It is a difficult problem. You have to have protection from the funding and the evaluation for a long time. Then if it really is high risk maybe nine out of ten people are not going to succeed at that. Are those people that you will then throw away and you will take the one that did succeed? Maybe they would have succeeded if they had been doing something else. It is not clear that there is a simple solution to how to pick the right people and let them do things. We are evaluated probably more here at NIH than we were thirty years ago—certainly for getting tenure. I have certainly heard people complain that, or say that, they never would have gotten tenure. They did something wonderful but it took a while and if they had been in today's atmosphere maybe they would not have gotten much of anything. They are probably wrong. They probably would have done just fine. [Laughs] It is clear that there are people at NIH who have a different style that has been possible because they are at NIH.

JG: You have a cartoon that was published in *The NIH Catalyst*.

SG: Yes, okay. You know about that?

JG: You know where I'm going with this?

SG: Probably.

JG: It was a guide of why people become scientists.

SG: Right, yes.

JG: I was struck by it—

SG: You should see the rest of those cartoons. We have a folder with a whole bunch. He is a very talented cartoonist and he was here as a postdoc for a number of years, churning out these cartoons on a regular basis, and sent some after he went off to his own faculty position. I tend to keep a file of them because they are entertaining and relevant. There is that one and then there is another one which is the nine types of principle investigators at NIH and the advantages and disadvantages of each. They are very funny and on the mark.

JG: There is the humanitarian, the academic, the mentor, the regretter, the empire building, the geek—it is fascinating.

SG: Yes, the artist is the geek. If you know what he looks like. I am somewhere between . . . I do science because I enjoy the problem solving, I enjoy thinking about it. I find it interesting always and I want to know what the next answer is. I am not sure where that puts me. I am not the empire builder for sure. I do it because I enjoy it and I can't imagine not doing it. That has been true from the beginning. But there is not one flavor, you know. You need some mix of approaches.

JG: A few more questions. One of them, I hope you forgive me for asking this, because the interview is about you, but your husband Michael also works at NIH?

SG: Yes. Right.

JG: Talk about what the relationship is like and what it means to be married to a colleague. Do you get to see each other during the day and what do you talk about on weekends?

SG: Yes, right. I would say we rarely see each other during the day. I mean, we probably had lunch together, maybe a dozen times in the time we have been here. It is just we are both busy and we are doing things and we sometimes pass in the hall or something or once in a while we arrange something but we don't do that a lot. For me there are various levels. Having a spouse who is a scientist who is in the field has lots of advantages. I think people who are married to non-scientists, the non-scientists have difficulty understanding how involved you are in what you do. You know, depending on what they are doing.

This is a job in which we are involved. It is what I am thinking about in the shower or what I am thinking about at odd moments. Having somebody else who is doing those same kinds of things means that he understands when I really want to get back to the lab. I don't do so many experiments and come in so much at night anymore but in the earlier days that we could understand each other's need to work. We might not always like it but we could understand each other's commitments to what we had to do in the lab. So that is great. Obviously we both think we have both been pretty successful. There is not a competition in terms of success, I don't think, I'm sure there is a little bit but NIH has been a good place for both of us. We have not been in the situation when one of us was miserable and wanted to move and the other one didn't. We have really had it pretty easy. At home on weekends, well, right now it is grandchildren all the time. I would say we do not talk science a lot at home. If we're excited about something then we will go on about it, right? We have two children who are now grown and out of the house. When they were home they were the focus and that was where our time and energy went at home. Michael coached soccer and we did the usual things. We were co-PTA presidents in the elementary school and in the junior high then did some other things in the high school. So we were very involved in their school, in their education and everything else. Now we are going to get in a car tomorrow and drive up to our summer house to close it up for the season. Some of the time the conversation might be science, what is going on and what somebody's doing and what we are thinking about. Michael had a big paper last year and they were very excited about it. I heard a lot about that. We talked about it because the interpretation was challenging. It was difficult and complicated and if we are doing something like that then we are excited about it. Other times it tends to be the sort

of standard family things and, as I said, right now we have two little granddaughters and they live next-door to us.

JG: How very nice—

SG: That is what we do on the weekends. We got home last night fairly late because we had a late meeting and I was trying to finish up some stuff and then we stopped at the store. By the time we got home it was 7:30 pm but we went over for fifteen minutes to visit them because it makes the day to see them for a few minutes before they go to bed. My daughter thought there was too much science at the family dinner table when she was growing up. Although she got more interested after she left home.

JG: You touched on it before, but how do you help your postdocs balance their professional and family obligations?

SG: I think the main thing is to help them talk through what they are thinking and what they want to do and the alternatives. They know that I have a family and that I am involved in my family and that when my granddaughter was born I was going to be out for a couple of weeks helping take care of her. That's the given. A lot of them seem to have children while they are in the lab because they know I like the babies and that I am sympathetic and that if they want to take time off or they need to take off to do things that I will be supportive. That is the first part. The other part is talking about where they want to go and how they can get there and helping them figure out what their priorities are. I think

for anybody, man or woman, the question is where are the priorities, what are the really important things that we must have, and then how do you fit the rest into that. The hardest part is finding positions and good places. Obviously I try to help them do that by keeping my eye out for openings, by giving them good recommendations, by trying to steer them to the right place. I have had a lot of foreign postdocs where how they move on is different than for Americans, so it is a little different, depending on where they are going and how they are going to do that.

JG: The field today, is it a healthy field?

SG: I think we are. So the field being prokaryotics, sort of working in *E. coli*, which has been this model organism for many, many years, is a tough field, in the sense that it has been worked on for a long time. It is not just that you can go and find a gene and do something with it. You sort of have to be doing something that is cutting edge if you're going to get funded out there. To some extent I think it is healthy and we are still finding new things in the broader field but it is harder and harder for young people to make their career entirely in this organism. They frequently move into other organisms or combine them in some fashion just because it is difficult. Twenty years ago some people thought *E. coli* was all over with, that everybody was moving into yeast or other organisms, as the methods to do that became available because all the questions had been answered in *E. coli*, and yet we still manage to find things that we knew nothing about, fifteen years ago.

JG: Last question, if you had one piece of advice, one lesson learned that you would like to pass on to a future scientist or researcher operating ten, twenty, thirty years in the future, what would that be?

SG: Don't do it unless you really love it. It is a hard job. If it is something that you just totally can't stand not doing then do it and stop worrying about the details of whether you will get funded or anything else. It will work out one way or the other. But if you are just doing it as a job, go find another job. It is not something to do if you do not love it entirely. I am not sure that is the advice you are looking for.

JG: I think that was some of the best. Thank you very much.

SG: Sure, okay.