Adhya, Sankar 2008 A

Dr. Sankar Adhya Oral History 2008 A

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NCI Laboratory of Molecular Biology

Oral History Project

Interview #1 with Dr. Sankar L. Adhya

Conducted on October 1, 2008, by Jason Gart

JG: My name is Jason Gart and I am a senior historian and History Associates Incorporated in Rockville,Maryland. Today's date is October 1, 2008, and we are in the offices of the National Institutes of Health in Bethesda,Maryland. Please state your full name and also spell it.

SA: Sankar Adhya. S-A-N-K-A-R—A-D-H-Y-A.

JG: Terrific, thank you. The subject of this interview is the Laboratory of Molecular Biology. Established in 1970, the Laboratory of Molecular Biology (LMB), Center for Cancer Research, National Cancer Institute, National Institutes of Health, currently has among its ten groups four members of the National Academy of Sciences. LMB has trained many other prominent scientists and its researchers have contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history project to capture recollections of prominent scientists currently and formerly associated with the laboratory.

To begin please talk about where you were born and your interests as a child. Explain your family background and what your parents did for a living?

SA: I was born in Kolkata (Calcutta),India, in a large family where my father lived with many other members of his family, like his brothers and so on. My father was a lawyer, my mother was a housewife. I grew up in a family mostly involved in law or real estate business and no scientists. I was curious from childhood about, not so much about biology, but the engineering part of science, how things work. You see all these things around you, radio—not television at the time—and other mechanical things, and big machines and so on. I was curious about that and started learning math and science, mostly physics, chemistry, and mathematics. Chemistry was more appealing to me because I was fascinated with color and all these color combinations that changes with light and so on—all these things. Chemical compounds were very fascinating to me for different kinds of salts have different structure, different color, and when they dissolve, they give you another color and so on. So I became more interested in chemistry and I started doing that to understand science while I was in school.

JG: You went to the University of Calcutta?

SA: Yes. I did my undergraduate in the University of Calcutta as also my Master's in the University of Calcutta. I got a Ph.D. from the University of Calcutta in biochemistry, although more chemical biochemistry than any biological biochemistry. Then I became interested in studying genetics because I used to read *Scientific American* and all these fascinating articles about genes and DNA and regulation of gene expression and so on, mostly at the time written by phage biologists.

JG: Go back for a moment to your bachelor of science. You did chemistry?

SA: I had a major in chemistry.

JG: Was your father supportive of you going into the sciences rather than studying law?

SA: My father was very supportive, whatever I wanted to do, he was for it. My parents had four boys and two girls and did not have much time to pay particular attention to one of them, what he or she is doing. They were quite encouraging.

JG: When you first got to the University of Calcutta for your bachelors degree what were your aspirations? What did you see yourself doing with the degree?

SA: At the time I was seeing myself as a researcher doing experiments. I did not know at the time, my first year in college, exactly what kind of jobs were available to do research but I had seen research and that fascinated me. Mostly, again, chemical research, and all these large scientific apparatus converting one thing to another, and so on.

JG: What was it like at the University of Calcutta in the early 1950s?

SA: It is a large university. At the time many of the people who I was attracted to were professors with a name recognition, in the sense, they had been educated in another country, at the time mostly from Britain, very few from the U.S.A. This was in 1950s. It is a large university with renowned people including Nobel Prize winners. So it is a large, recognized, very old university.

JG: You decided to stay for your Master's degree and then your Ph.D. What was the decision there?

SA: Studying, doing research, mainly doing research, all along. I was not that much interested in going to medical school or engineering school or applied science. Doing some research. At the time I did not know where it was really leading to but I was interested in doing things.

JG: Talk about your advisors in your Ph.D. program? I was interested to read that your dissertation explored germinating seeds.

SA: Yes.

JG: Explain a little bit about that.

SA: Well, it was not so much of germinating seeds. I was not really a biologist—not formally trained as a biologist. I was attracted to a local professor who was a student of Paul Doty from Harvard [University] and he was interested in nucleic acid structure. At the time, double helix came around, of [James D.] Watson and [Francis] Crick, and that was fascinating to me, how it replicates, the mysteries of replication, and codons were coming out at the time, not quite known. We decided to study RNA. At the time RNA structure was unknown—nobody knew anything about that. RNA was supposed to be branched nucleic acid from the work of Alexander R. Todd from England. I started working on that. The only source of RNA we could think of to study as a material, as a model system, was ribosome. Ribosome was defined by Jim Watson and his colleagues, and we did not want to go into bacteria, because that is competing with other people. So we went to some plant source and germinating seeds were easily available. I wanted to see if there were any changes in the RNA structure. We did not know what was RNA structure. If we can find out this structure, what it was going to be, with germination. It was just a naive idea that we thought some changes might happen in RNA. At the time when I started, messenger RNA was just coming out, the concept of it. But I was not quite aware of all those details. It was hard to get books and the journals in India, because journals used to come three months later by surface mail, and there was, of course, no MEDLINE. I was not very updated on everything that was happening.

JG: You mentioned Watson and Crick and the discovery of the double helix. When did you first hear about the discovery and what was the impact on you as a biochemist? Did you subsequently in your career get to meet Watson and Crick?

SA: Well, funny thing you ask because the double helix came in 1953 when I was an undergraduate in chemistry. I did not know anything about that. My major advisor came back from Paul Doty's lab and he is the one who first explained to the students, including me, the double helical structure in a class setting and the details. When I first heard I was in a classroom as a course material of a subject. From that point on I was curious about RNA structure and whether it was similar or not. We didn't get anywhere other than showing that RNA has also a melting temperature. There is some structure, there is hyperchromisity if you heat, and that is my Ph.D. thesis. I did not find any difference between ribosome isolated from the young seeds versus older seeds.

From that point on my interest became the coding aspects of DNA, how things are coded. And, again, I did not have much background to analyze the coding nature and appreciate genetic code which was going heavily at the time in this country. I did not have any access to that information. I read an article in *Scientific American* written by Seymour Benzer—he is a renowned phage biologist—about cistrons, how to define genes by *cis-trans* complementation test. That became my fascination. I decided to come to this country to understand genetics, which I did. Not so much about classical genetics, which I had a lot of, in my student days in Wisconsin. I had to take many courses in classical and molecular genetics. I became more fascinated in how genes are regulated.

JG: When you decide to leave were you also looking at opportunities in India or did you just focus on programs in the U.K. and the U.S.?

SA: No. I was looking to understand genetics. I decided to do a second Ph.D. because I did not have any genetics background in India during my student days. I applied to three or four people here in this country. One of them was Jim Watson. I wrote to him straight and very surprisingly he accepted me to do a Ph.D. in Harvard. I also applied to Wisconsin and the University of Pennsylvania because of the renowned phage people they have there, I found out from the literature. I got accepted to Wisconsin and Harvard but my father had a heart attack the time I was supposed to come and I was the eldest son, the most grown up, and I could not leave my father alone. I postponed my coming to this country for another year and at that time Harvard could not take me. Wisconsin allowed me to come the next year, if I wanted to, and I took that opportunity. I did not try again at Harvard.

JG: What was it like being at the University of Wisconsin?

SA: I was really excited to come there because so many people and so many subjects to learn in the area of genetics. I was quite familiar with biochemistry and chemistry, and physical chemistry already, but not genetics. I took many courses in genetics. The people used a completely different way of teaching. Not so much memorizing to understand things. There were lab courses, there were many lab courses. Particularly the one that fascinated me was a phage genetics course. Because of that laboratory course I remained in phage.

JG: Was it unique to do two Ph.D.'s at that time?

SA: No, I just wanted to learn genetics. I did not have any idea what genetics was. I thought the best way to learn, instead of reading, I needed a formal education. So that was the reason. And to me, time was not a problem. I did not want to grow up quickly and establish myself. I just was enjoying my education and life.

JG: What was it like to be a doctoral student at the University of Wisconsin in the United States after being a doctoral student at the University of Calcutta in India?

SA: The University of Calcutta did not have any course work. It is only research work following the system in the United Kingdom. Here I got a chance to learn, you had to take a lot of courses, and make grades, and so on. That was a better opportunity. That is the major difference between a Ph.D. in India and a Ph.D. here.

JG: Did you see yourself going back to India or did you want to stay in theU. S. and do research here?

SA: I decided to stay to do a postdoctoral. Actually my Ph.D. time was spent doing mostly bacterial genetics, not so much phage genetics as a research subject. I took courses, and I wanted to learn phage genetics, so I went to apply for a postdoctoral position. I applied to Allan Campbell. That was the only person I applied to and he accepted me to do phage research. That introduced me to phage lambda.

JG: Talk about some of the people that you got to work with at the University of Wisconsin. Who were some of your mentors? You worked with Dr. Harrison Echols?

SA: Yes, Hatch. Harrison "Hatch" Echols.

JG: What kind of scientist was he?

SA: It was funny because I was his first graduate student. He had just joined the faculty of biochemistry at the University of Wisconsin. He was hired to teach physical chemistry. He had a Ph.D. in physics, and he taught a course in light scattering, physical techniques, centrifugation, electrophoresis, and X-ray diffraction, all those things. But he got a job without having a postdoctoral because they needed a person and he was a local Ph.D. student in physics. He was hired, and right after he was hired, he took a sabbatical, a part-time sabbatical. He used to come and teach his course and then go back to MIT to learn bacterial genetics. He was looking for a graduate student and he saw my application among the admitted students at the biochemistry department and he wrote me a letter saying "If you are interested, we can learn bacterial genetics together." So I joined him. He learnt bacterial genetics in the laboratory of Cyrus Levinthal at MIT during his sabbatical. More or less he taught me whatever he was trying himself in his lab in Wisconsin. Then other students joined slowly. His group enlarged from one to about ten quickly because he was a good teacher. Although he was teaching physical biochemistry he was doing bacterial genetics and he attracted lot of students.

JG: What was it like working with someone who was also new to the field?

SA: It was fine because I think we discussed a lot. He read a paper and then asked me to read the paper. We discussed what the paper is all about. You know what I mean? Sometimes we differed in our interpretation. Of course, I give in because I did not have any previous experience in interpreting papers. He was far more experienced. Not much older than I was, but he had more experience than I did. So I yielded to him most of the time. He told me years later that I was sometimes too skeptical about scientific findings. [Laughs]

JG: Had you published anything at this time?

SA: Well, I had one article from my Ph.D. thesis on germinating seeds before I came here. After I joined his group I was developing, which he did not have any experience, how to assay enzymes; he used to bring protocols from here and there, and I was to develop those assays, biochemical assays for enzymes. We published a paper quickly. That stimulated me a lot because I got a paper published in the *Proceedings of the National Academy of Sciences*. I was very proud and it stimulated me to get more papers.

JG: You decide to do a postdoc at Stanford University?

SA: I wrote straight to Allan Campbell at the time lambda was coming to be the biological system to study and he accepted me. He was at the time at the University of Rochester in New York. He said you can come, but I will be moving to Stanford in a few months. If it is okay, you can come now and move with me, or you can join me at Stanford six months later—or a few months later—I do not remember the time scale. I decided to come right away and move with him to Stanford and I was at Stanford for about two more years.

JG: What was the University of Rochester like during the brief time you were there?

SA: Yes. At the University of Rochester I was at a classical biology department. People were doing all types of biology from flower, amoeba, and nematode; and I used to go and listen to them. Those are more complicated genetic system and I was much more molecular oriented. I did not connect with these guys very well. I mean, I used to talk to them, but at that time molecular genetics of lambda was proceeding at an astronomical speed and I was in so much in that and did not bother to learn other things.

JG: What is the significance of the phage lambda? Why is it so interesting?

SA: Well, at the time it was a model system to understand developmental genetics in the sense that lambda is a temperate bacteriophage which unlike many other bacterial viruses has a dual life cycle. It makes a decision after infecting its host either to be part of the host as a parasite and stay with the host as a prophage, or has a lytic cycle that replicates, it kills the host, lot more particles come out. That is the way virus normally works. This guy can go and become a kind of latent pro-virus, or prophage, but when the virus sees that the host is in danger of dying it decides to come out and replicate. That developmental decision, which fascinates me even today. We are still studying that. Many people have many models and it is still not clear. The reason lambda is so important, besides other aspects of phage biology in general, is that we understand lambda in a molecular detail more than any other living creature.

JG: You go to Stanford University in 1966?

SA: No. I went to Stanford, I think, it was 1968. Maybe, 1967, I don't remember.

JG: What was California like in the late 1960s?

SA: [Laughs] Going from Wisconsin, which has minus 20 degrees, minus 30 degrees temperatures normal, and Rochester, which is not that cold, but very snowy, California was heaven, I drove all the way. I bought a new car with all the money I had.

JG: What kind of car?

SA: It was a two-door Mercury Cougar. It came out at the time as a flashy model. I bought that and drove all the way to California alone. It was a fascinating experience to see the country, and second, arriving in California was a wonderful place. Stanford had a different architecture, different structure, different kind of—even people, I should say. It was very relaxed, laid back. Stanford University at the time, I am sure still it is, was a place where Nobel Laureates walk around the corridors and so on. I had many role models: Dale Kaiser, Arthur Kornberg, Paul Berg, Charles Yanofsky, they were there. I used to talk to them. Life was very exciting at Stanford. My two years in Stanford was, I think, in terms of learning experience and interacting with people, was the best time of my life, in my young life.

JG: Go back a moment, going across the country, what were your impressions of America?

SA: Well, there is another short history, which might not be relevant here, is that I did not have much as material possessions. I had a few clothes, and I had a bunch of books and some notebooks, and I had a radio clock to wake me up in the morning, and a camera. That is all I had. I was traveling with that car. I stopped to see a friend in Cleveland,Ohio, the first night of my travel. I stopped there to say hello. We were talking late, drinking a little bit, and so he said, "Why don't you stay here and leave tomorrow morning?" I decided to stay and the next morning I found out—I parked my car in this parking lot—the car was empty; it was robbed. The car was broken in and they took everything from my car. Everything. I felt cold that I lost everything, including the bacterial strains, the research materials and notebooks I was carrying. I was most sorry for the strains and notebooks more than anything else. I did not have much money, maybe a hundred dollars with me. I did not know what to do and my friend did not know what to do.

We called the police. Police came. He took a report and said, "We'll call you." I did not realize what they meant by "We'll call you" means whenever we find something. It was Friday morning that this happened. The day almost passed and I was kind of worried that nothing would happen. I was stranded—I didn't live there. I called the police again. He said, "Well, these things happen every thirty seconds in Cleveland, so we cannot attend to every case." They told me, "Your time will come." I came back, and thinking and thinking, I called the FBI. Somebody told me that my research materials I was carrying with me, belongs to federal government, because my supervisor who paid me from his research grant—it was a federal research grant—and I called the FBI. They asked me what these materials are. I said they were bacterial strains, and so on. Immediately they said to come over to the local FBI office. I went there, I told all the details. They said, "We'll get back to you. Don't go anywhere." I was very hopeful something will happen and I came back. About fifteen minutes later I got a call from a local news reporter. They said, "You have some federal materials which could be dangerous and you lost them?" "Where are they?" and so on. I did not expect that, and I somehow avoided them saying things I don't remember. The FBI called me back by saying "No," we found out when a federal grant is given to any university, they belong to the university, not the federal government anymore. So they withdrew their hands. That was the end of that story.

I borrowed a few dollars to survive because my money was also lost. I kept travelers checks in the glove compartment. They were all gone. I had to borrow some money to survive the rest of the way. It was an interesting experience.

JG: Talk about Allan Campbell and your work with him at Stanford? What were you thinking of doing after the postdoc?

SA: First of all Allan Campbell was a decent, nice, very smart man; kind of quiet type, not flamboyant.

JG: Where did he do his Ph.D.?

SA: If I remember he was a math undergraduate but did a Ph.D. with Saul Spiegelman at Urbana, I think it is Urbana,Illinois. I can't remember where he did his postdoc, but he was in the group among . . . The leader of the group was Salvador E. Luria, a Nobel Laureate, phage biologist. They were very close.

JG: Who were some of the people you got to meet? Talk about the phage group because it goes back to the beginning of molecular biology.

SA: Yes. When I joined the phage group I started to going to Cold Spring Harbor phage meetings regularly. I think Luria and [Max] Delbrück and Alfred Hershey were almost retired, used to come and sit around, ask a few questions, and so on, but they were not very active.

JG: Describe Delbrück?

SA: Oh, he was . . . [Laughs] I did not have much close contact but he was very—I don't know what is the right word—dogmatic because he had certain views about everything. If somebody says something he would immediately make an opinion, "Yes, you are right," or "Oh, it can't be right," and immediately turn around and leave. That kind of person. He was never offensive or anything; it was just scientific opinion. If you were telling him a story he would ask, "Have you done that experiment?" And he would leave by saying, "Do that experiment and come back." Luria's much more friendly He would sit down, and if you tell him some story he would again tell you back some other story from his life on the same subject. He was very nice to me. I found while I was in Allan's lab—he used to visit Campbell's lab once in a while—I discovered an *E. coli* gene called nitrate reductase, and I found a way to use that as a selective marker in doing bacterial genetics. I told Luria this story and he immediately said there is a guy named Puig, P-U-I-G, in France. He works on the same subject. I had no clue. He put us together. He said, "You should talk to him. I'll tell him." So that kind of thing to enhance science. He did not have any other interest than connecting two people for expansion of science.

JG: Speak about Cold Spring Harbor and what that was like.

SA: Cold Spring Harbor at the time was a fascinating place. Going to the phage meeting and participating in that meeting, in the discussions, the presentation of the talks was really a life changer for me. You learn how to think about science, how to do science, and although competition was always there, these are all friendly people, friendly collaboration, and they will stimulate each other, and argue with each other, and come up with an idea that is better than you had before you came to the meeting. It happened year after year. You used to look forward to go to that meeting. Even after I came to NIH, until recently when the phage meeting changed its structure. Now it is more bacteria, more compact, more crowded. It used to be very relaxed and you could talk to anybody. Talk to people about science all day and all night—have a beer, etc. I met lots of good friends at Cold Spring Harbor in the sense of collaborators and I still have those connections today. I know them, I exchange telephone calls, and discuss science even today. Many of these people became very successful scientists.

JG: In the phage group there were a lot of physicists?

SA: The original phage group there were a lot of physicists.

JG: Why was that and how did that impact the field?

SA: Like I said Delbrück was a physicist. So was Francis Crick, although he was not part of the phage group, but he used to come once in a while. Jim Watson was a chemist and biologist. I think it all started with Delbrück, he wanted to know what is the gene structure, the minimal, like atoms in chemistry. He thought gene is a minimal thing in biology. He thought phage would be a fine example to study what gene is all about because it is small and it can be handled easily and he thought genes are unit of life. It turns out to be much more complicated than that but that is the way he thought. I think physicists want to know what is the minimal—they are reductionist—they want to know what was biology's basic unit. Biology at the time was going toward more biochemistry, to open up the cell, analyze what the constituents are—the chemicals and the enzymes, catalysts and so on. But Delbrück had a holistic view. He wanted to know how an organism functions; what are the unit component functionally. In his mind, to my knowledge, gene was a unit of function in biology.

JG: You are at Stanford University and then you go to the Bose Institute in Kolkata,India?

SA: Bose Institute. At that time I was thinking about where to go for a job. I needed a job and I was thinking of university job to do research and teaching—I did not mind teaching. I applied for two, three jobs while I was still at Stanford.

JG: Where were they?

SA: One was at the University of Michigan,Ann Arbor,Michigan. Another was University of Rochester. I can't remember the third one.

JG: You did not want to stay in California?

SA: No, I had to move on in my life and I do not think there was an opportunity there. I was not thinking about California. Whatever the jobs openings were I applied. While they were making a decision I decided to go back to India because I had been away from my home and parents for I believe seven years by then. I went back and decided to stay for a few months and wait for a job offer. At the time India had a system of so-called, I forget the name, some visiting pool of scientists that you can join, look around, do some research in a host Institute. I do not know what Bose Institute was like but it gave opportunity to people to find their own way. I joined Bose Institute simply because it was in my home town, Kolkata, so I can see my parents and second, somebody I knew asked me to join Bose Institute. I went there and stayed there for about ten months. I think less than a year.

JG: Was it difficult to be away from India for all those years?

SA: Initially it was hard for me to stay away for that long because I lived with my parents before I left the country. Being away from the family and at the time telephone was not very cheap. It was very expensive. The communication system was very bad, so writing letters back and forth is the only communication I had, and exchanging pictures once in a while, that was all. I missed them and I went back. I was happy to be with them. I traveled within India a little bit about other job opportunities; first two months while I was waiting to hear from this country. I did not like much because there was no molecular genetics in India at the time. Genetics was chromosome dissection and so on; not much molecular genetics. Something funny happened while I was waiting for a job. The Michigan job, I got a letter from them that the job had been given to somebody else, not me. Which is fine, and the person who got the job, David Friedman, who was at NIH; he got a job there, who I knew very well, and he was one of my closest friends in terms of science and friendship-wise. He got that job. The second job I applied to was at the University of Rochester. They sent me a cable. In those days . . . you know what a cable is?

JG: Yes, absolutely.

SA: Yes. They sent me a cable that the department has offered me the job and the detailed letter will follow. I was very excited. I was planning to wind up and leave. About two weeks later, a letter came, which was a bombshell. It said that because of some administrative problems—I don't exactly know what the administrative problems in the Department of Biology—an advisory committee suspended all future appointments until the investigations were completed. I think this was an old department. I have no clue what the problems were and so on. I immediately wrote to Allan Campbell what to do, and told him about this situation. He said, "Well, you know, there'll be other opportunities," and so on. "Don't worry." I remember I came from India to that year's phage meeting and met Robert Weisberg who had already joined the NIH in the National Institutes of Child Health and Human Development, who incidentally retired yesterday, just two days ago. He said there was a possibility at NIH, and he said, "Send me your CV." And I did. And he said he will look into that. Next thing I knew Max Gottesman, who had already joined the Laboratory of Molecular Biology, he said, Ira Pastan and him are going to create a new lab at the Cancer Institute. He was at a different Institute, the Arthritis Institute, at the time. He said, "We would like to have you there." And so I said, "Yes, of course."

JG: What did you know about the NIH before you arrived?

SA: I accepted the job without knowing what NIH was all about. I had been, you know, familiar with the university settings and research at the university settings. I knew many people, by reading papers and so on, who were very well-known scientists at NIH. I just realized I do not need to know anything other than people are very successful there. It must be good place. That's all. I even did not know Bethesda. I was in Washington,D.C. once in my life but I did not visit Bethesda. I accepted and Max said, "Come over and visit us." I did and I met Ira Pastan and the lab was still not in this building at the time. They were scattered all over. I think I came here and talked to Ira and Max and other people and they were doing fascinating work.

JG: How did Max and Ira explain the new lab at that time? How did they describe the aspirations of the lab and their research? Also, what were your impressions of Max and Ira at that time? They were both very young.

SA: At the time Max explained to me, "It is a great opportunity, it is a new lab at the Cancer Institute." He told me that Ira's lab has a lot of money. That is important. He got a lot of money to form the lab and had a lot of positions. Second, talking to Ira, it was clear to me, I think he had a great insight to hire people with different expertise—not just cancer and eukaryotic cell cultures he was working at the time. He was also interested in hormones—came from a endocrine background. He wanted to integrate the department with various expertise and try to find common interest and to exchange ideas. That was Ira's idea. I think that was very attractive and I thought it would be wonderful. Ira was doing at the time bacterial gene expression. Cyclic AMP was just discovered. It happened just at that time, and I was fascinated, and Ira wanted to combine biochemistry and genetics together to what became known as molecular biology. It was a most exciting lab because in this lab cyclic AMP and cyclic AMP receptor protein were discovered. That became the protein to work with. The other fascinating protein in molecular biology was being worked on at Harvard was *lac* repressor, a negative control protein that causes gene repression. Ira's protein, cyclic AMP receptor, is a positive control which turns on genes. It was an ideal system to study gene expression in molecular details. He hired a bunch of people: Benoit de Crombrugghe, of course Max was there, Peter Nissley, Wayne Anderson, Shigetada Nakanishi. At the time, I was doing mostly genetics; I did not do any biochemistry.

JG: Explain the worldview of a biochemist versus the worldview of a geneticist. How are they different and how are they complementary to each other?

SA: A biochemist is more or less like a physicist—reductionist. They want to purify every system, go to the minimal system, and try to duplicate what they expect to be *in vivo* properties. The problem is that doing pure biochemistry, classically, they do not know what is *in vivo* system. How those enzymes and proteins behave *in vivo*. They had to go back to genetics to understand, to make the correlation. In genetics, we study the behavior of the cell and the contribution of those genes or proteins towards a phenomenon, how genes are turned on and off, and then you try to duplicate that system *in vitro*. Ira's lab has contributed tremendously to duplicating, in a purified system, what happens *in vivo*. Landmark papers came out of his lab at that time. I was fortunate to be a little part of that.

JG: Describe your impressions of Bethesda? You mentioned that you had only been in Washington once before.

SA: Well,Bethesda was very small at the time I came. We used to live in an apartment in Bethesda, which was full of trees out of nowhere. Two years later,Don Court became a member of this laboratory and I knew him from Allan Campbell's lab. He was a country boy from upstate New York. He said he cannot live in this town Bethesda. He said let's move to the countryside which is Gaithersburg, Maryland. I said that it is too far; it is about fifteen miles. He said, "No, no. We'll carpool." So he drafted two other people. We used to discuss science all the time; all of us were working on phage lambda, different aspects. We had a great time. Bethesda developed slowly, but I remained in Gaithersburg, and didn't move back.

JG: Let's talk specifically about some of the important projects during that period? What was it like to do the research in the 1970s?

SA: Like I said this was a place to combine genetics and biochemistry, as you mentioned before. I still have these vivid memories. I had a great time, really great time, doing science in this lab because of Ira, Max Gottesman, Benoit de Crombrugghe, and Don Court. Susan Gottesman came and joined the lab later, and several other people—we used to discuss doing science all the time. At lunch time, in the corridors, and on the chalkboard, and all those things. We used to propose hypotheses, and by discussion an hour later, let's say there were ten hypotheses, eight of them are discarded in our discussions. We needed to test the two others experimentally. So science going on with more than one brain. It was a very good learning experience—exchange ideas. For example, if I go and talk to Max and say something, Max will say typically, "Well," he would ask some questions with skepticism. Then five minutes later he would come back and say, "You have to do this experiment." "Let's do this experiment." That involves genetics. I would say, "You have to test that idea by doing this biochemical experiment, so go to Benoit's lab and talk to him if this is feasible," and so on. Two things are going on at the same time. One is the duplication of gene regulation from *in vivo* to *in vitro* system. At the time Max and I were mostly contributing genetically and Shigetada Nakanishi and Benoit de Crombrugghe were experimenting biochemically in a purified system. Also at the same time we were working on phage lambda gene regulation. Initially the concept of gene regulation was really that genes are turned on and off at the level of initiation of gene expression, like transcription initiation, or translation initiation. We came to the idea that gene can be regulated at the level of transcription elongation and termination. Gene transcription terminated at the end of the gene, or continued to express downstream gene. That was one of the things that we discovered in this lab and demonstrated genetically. Benoit helped us to show that, at the level of RNA, there are truncated or elongated RNA. That was very exciting and I used to work late nights. It was very exciting being with those people. Max, Don, and Benoit; they have all gone different ways now but I am very proud of those days. Good memories.

JG: You mentioned Ira, Max, and Benoit. Well, Ira and Max, they were trained as medical doctors. How does that also diversify the research?

SA: The projects I was involved with were mostly microbiology projects, nothing to do with medical problems. At the time Ira had other research on eukaryotic cell cultures and hormones and effect of cyclic AMP on fibroblasts. I was not involved with that. Ira, in my impression, had a wide knowledge about human physiology, which I had zero idea. He used to explain things, put the basic findings in terms of human physiology in discussion time. We did not do anything . . . Max had a M.D., Ph.D., both. Max never said anything that would impress me that he had a M.D. degree. I don't know why. He almost never discussed in his scientific discussion—never mentioned anything that would say that he had a medical degree because he was so much into doing basic research. Ira, I think, all along, the way I understand him, is that although he had an M.D. degree and wanted to solve some clinical problems, he realized that he has to do basic research. He did a lot of basic research. Later he engaged himself to solve cancer. He had great foresight. He studied everything at the basic level to go step by step to come to a point where he was able to deal with cancer.

JG: You mentioned the intellectual community in this lab. What was it like to be in the broader NIH community?

SA: I have never been to another place. This is my first job and most likely this will be my last job. [Laughs] NIH is a great place because it is unique in the sense . . . If I were doing research, sometimes you have to develop new things, new techniques, new ideas or sometimes old ideas, but new techniques that I do not know anything about. I had to use them, I realized that. You can always find somebody, a world expert in that field, in that area, with that kind of expertise in some building, sometimes in your own building in a different floor, sometimes in the same floor. You can always walk into them, and discuss it with them, and get the help, and get things done. That helped. The speed of research was enhanced tremendously because we did not have to learn from the beginning, or go somewhere out of town, or go on a sabbatical and learn something and bring back the technology. That epitomizes the uniqueness of NIH. There is always some expertise in the campus that can help you. And they did. I got tremendous help from other people. Everybody does. The interaction is great. That is the key thing at NIH; interaction, physical interaction and intellectual interaction. You see them in person and talk with them for hours and whatever needs to be done gets done. From genetics to biochemistry to physical biochemistry.

JG: During the mid-1970s you have the recombinant DNA controversy. Talk about how this impacts this lab. What is this debate all about?

SA: Before recombinant DNA technology came around, we had ways, Max is good in that, to create methods by which you can do so-called recombinant DNA without the modern technology, not available at the time, by doing manipulative genetic techniques. I did a lot and Max helped me a lot. When recombinant DNA came around, people were skeptical, as you know, that we are tinkering with God-given genes. The other concern was that you open the DNA, and transfer the DNA from one organism to another. But it is happening in nature all the time. So I was not scared. I do not think Max was scared by recombinant DNA technique. Some in the community became scared and they formed the Recombinant DNA Advisory Committee. The first meeting at NIH, I was there, I was invited to go. That was my last one, because I saw the futility of those things. I was more interested in not bureaucracy, but in doing research. Whatever I was doing I did not think it was creating any danger, or any such thing. I welcomed the technology.

JG: In 1975 you become a senior research geneticist, and then in 1980, you become chief of a section. Talk about how your career progressed at NIH.

SA: I came as a non-tenured . . . I do not know what I was called at the time. Things have changed now. I think three years later I got tenured at some level of government job. I was in Max's section at the time the laboratory—each laboratory has separate sections—and at some point in time a new section was established for me. I became chief of that section. Max was Chief of Biochemical Genetics and mine was Development of Genetics Section. But we were doing the same thing. Maybe there was a $2,000 dollar pay raise or something like that. In terms of the research and job, and interaction, nothing changed. We used to do the same thing. Chief-ship does not mean anything in terms of research.

JG: What about funding for your work?

SA: The way I understand funding was given to the laboratory and it was managed by the chief—Ira in this case—who would spend the money. There was a common budget to buy things and spend money. If there was any shortage Ira would always go and bring some more money back. There was never a problem. Later, not just in this lab, the whole NIH changed slowly. This concept of section chiefs and so on are no longer that important. All became Principal Investigators—PI's. Non-tenured PI's and the tenured PI's. That is the way it operates now. Each one has an individual budget. The laboratory budgets are distributed into individual PI's and the PI gets his or her own money, which I do. We are accountable how to spend the money and have to report back. In the past, Ira would report back how the money was spent. Now we have to do our own. There is a site visit committee that comes every four years or so, and interviews everybody, and we present what we have done, and what we plan to do in future. It is more individual responsibility, money-wise than before. But research-wise, I think it is the same thing—every scientist has to report.

JG: During the 1970s and the 1980s who is LMB competing against?

SA: In the 1970s I think NIH was doing cutting edge research in duplicating or understanding at the molecular level gene regulation using purified proteins. There were other competitors, from Harvard, John Beckwith and Wally Gilbert. Because of integrated approach, in my mind—I am sure I am biased—NIH LMB won the game. We continue to characterize them; we are still working on cyclic AMP in great detail. Most other labs are out of business on that subject. They gave up after certain level of understanding, or failed to compete, whatever you call it. I think in that way NIH, Ira's lab, was at the leading edge, which I had a small part. I am very proud of that. Slowly during some time, I think in the late 1980s, Ira was losing his interest in basic science, but he never, never discarded his support for basic science, which we're doing. He was always very supportive. He turned his interest slowly to finding a cure for cancer and he had these new ideas about what he calls now immunotoxin. Initially, he was doing chemical conjugation to a bacterial toxin, proteins like EGF receptors which are recognizable more by cancer cells than ordinary cells. David FitzGerald, who was a young postdoc at the time, recruited by Ira, a very smart guy; he gave the concept of using bacterial toxin, because his Ph.D. was on pseudomonas toxin before coming to NIH. Then I started participating in the research and suggested to make a protein fusion which was not a technology available routinely. This is before PCR and so forth. I found a way to make protein fusions in a cumbersome way, but a successful way. Ira got the gene for immunotoxin from somebody, I don't remember who. We manipulated that and showed, by genetic deletions, domain aspects of that which Ira confirmed biochemically. The concept of gene fusion came along, and Ira progressed much more from that early stage to fuse the toxin domain to cancer specific single chain monoclonal antibodies which is the hallmark of his laboratory now.

JG: What do you think—knowing Ira in the 1980s—what do you think caused him to switch or change his area of interest?

SA: I am glad you asked me. Once in a while I think about that. Ira was an M.D. He started his research . . . I am pretty much sure that his goal in his own mind, maybe he did not speak of it, was to solve cancer. He was hired by Cancer Institute to do something about cancer and he was very serious about that. But initially he seems like he is all over, but he is collecting data, enhancing knowledge, basic knowledge, doing basic research, to do cancer research. I think solving cancer, treating cancer, find a cure for cancer was always in his mind from the beginning. It is not obvious in the hoopla of molecular biology and genetics, but he had this idea. I do not think he decided overnight, I had enough of bacteriology and I'll move to cancer. He was an endocrine expert. He was an endocrinologist. He had these connections all the time, back and forth. Half of his research program, even in the 1970s, was eukaryotic cell culture, cancer cells, and so on.

JG: Describe some of your successes and some of your papers in the 1980s. You mentioned that your first paper emerged from your first doctorate at the University of Calcutta?

SA: Well, when I came in the 1970s we quickly got involved . . . I was interested in what Max Gottesman was doing about site-specific recombination; that concept originally came from Allan Campbell who proposed a site-specific integration of a piece of DNA into the chromosome and Max was working on that. He made a major contribution to the field, along with Bob Weisberg, who was at another Institute and collaborated with Max. I was working on gene regulation, which was more my passion, I realized that there is a lot of gene regulatory proteins in bacteriophage lambda. One of them is a protein called N which is coded by lambda which turns on genes in the rest of the phage. Initially people thought that like cyclic AMP-CRP turns on transcription, it is a positive control system. In the community at the time, another concept was around, but there was no molecular picture that N acts and helps the expression of distant genes not by regulating transcription initiation but by manipulating transcription elongation. Because at the end of each gene there is . . . Benoit de Crombrugghe, Max, and I discovered that at the end of genes, more or less around those areas, there are transcription termination signals. The distant genes, genes located distant to the frontal genes, are not expressed unless you have the protein N. We showed genetically that N acts as an antitermination factor. It helps RNA polymerase override termination signals. That was fascinating. We did an enormous amount of genetics on that to prove that concept. Other people confirmed the biochemistry. One of them, Asis K. Das, who was in my lab as a postdoc earlier worked on biochemistry of N *in vitro*. He got a faculty job at University of Connecticut where he still is. I switched my interest from there again, came back to how cyclic AMP-CRP repressor work.

I think in my own mind, my best contribution to science was that we discovered how distal elements in DNA communicate with each other, and we do not know how. DNA segments located hundreds of bases apart have some kind of communication to control gene expression. I brought the concept that proteins bound to distal sites interact and form a DNA loop to communicate with each other. That was my original genetic concept, from genetic experiments, and then we proved biochemically and then physically. It is a very popular model now, people explain many things by saying that the two distal sites on DNA chromosome get together and communicate with each other by looping and the DNA of the intervening region. That is a very standard concept now.

JG: You mentioned Benoit de Crombrugghe and Don Court. What type of scientists are they?

SA: Benoit de Crombrugghe was from Belgium. He had a medical degree. Like Max he never impressed you that he knew anything about medicine. They would talk about basic research. I am sure they had sometime, Benoit and Max, great exposures to genetics and biochemistry. Both were very smart. They made a biochemical attack on a biological project. They would not hesitate. Benoit taught me how to purify proteins. I had some knowledge before but not expertise. He said "Let's open up the cell." We would go to the cold room, and I was helping him to learn how to purify proteins, staying in the cold room. I think he is a great teacher. Both Max and Benoit have a great sense of humor. We discuss everything, not just science, but other things, things that I cannot mention.

JG: Yes. [Laughs]

SA: Don came along and Don is really a geneticist. He had good training in genetics. He thinks very clearly and always comes up with a very unorthodox explanation of some findings. People have one interpretation and Don would come up and give a different interpretation. Many times he is right. I learned a lot from them, Max, Benoit, and Don. Too bad for us that Benoit decided to move on. He started collagen research here in this lab and is continuing that in Texas. Don, after some time, got an opportunity to move from this lab to another lab at NCI. I forget the laboratory's name. That lab moved to Frederick which NCI has a branch and he remained there since then. Max moved to head the Cancer Institute in Columbia University in New York. I do not have much of a research communication nowadays with Benoit de Crombrugghe, because his subject is totally different, but we see each other. But Don—the telephone that rang—that was Don Court. We talk every day, two, three times every day, about the lambda research that we do together. I also talk to Max routinely.

JG: In the 1970s you started to teach. You became an adjunct professor at George Washington University. What brought that about?

SA: NIH has a night school called FAES [Foundation for Advanced Education in the Sciences]. I do not remember what the acronym stands for. Ira asked me—I can't remember when, about mid-1970s—let's teach a course for students. I did not know before that that there was such a thing. Ira and I taught a seminar course at NIH with some students. At the time, there were many medical students working at NIH who wanted to learn biology, basic research, and particularly microbial biology and gene regulation. They did not have such exposure so they took a course. Ira and I taught a seminar course with about fifteen students—for one year. The next year Max Gottesman suggested we give a formal course. He recruited me,Don Court, and Susan Gottesman to start a new course on bacterial genetics, gene regulation in bacteria, and bacteriophage lambda. That was very successful. We had many students, not only that, many senior people, members of NIH community, took that course.

JG: And this is for postdocs, visiting scholars, and PI's?

SA: Yes, right. They used to take the course. It is not restricted to students only. Anybody can take the course. Night school; used to teach after hours. That course became popular and then Don and Max left the campus and Susan and I continued till last year. We taught that course at NIH. It changed a little bit, it was less phage, and more bacterial gene regulation till last year, and then Susan walked into my office last year, said she is too much preoccupied with the other aspects at NIH, so she does not want to teach any more. It left to me to teach. I recruited somebody else—Debbie Hinton from another Institute to continue to teach that course. Now there are more students than used to be that would like to take the course.

JG: Tell me about your work with phage therapy.

SA: Somewhere around 1980s, Carl Merril, who was a PI at National Institutes of Mental Health, now retired, and I got involved in discussing application of phage to solve human diseases. It is called phage therapy.

JG: Phage therapy was developed by the Russians, right?

SA: Yes. We will come back to that. Carl was an adjunct professor at George Washington University and he used to teach—I do not know exactly what was the total contents of the course. He asked me to give some lectures there. It turns out that the students there were more interested over time to learn molecular genetics in bacteria than eukaryotic genetics. Eukaryotic genetics was not much developed at the molecular level. So they were more interested . . . The Department of Genetics found that out and asked me to join as an adjunct professor and teach a course. I started teaching a course with Carl. He revitalized the course. I still teach that course, but only a few lectures. I am not fully responsible for the course now.

JG: How does teaching improve you as a researcher?

SA: One of the assets of being at NIH is that you do not have the teaching responsibility. You can devote full-time in science. I must admit that that helped me a lot. But teaching is also very educational for me because I get to read the current papers on the subject. We update the course every year. We do not teach the same thing every year. To think about how to explain things to students and first to think about how to explain things to myself. "Do I understand those things?" It helps a lot. A lot of thinking. It improves my thinking ability, that is for sure. The second thing, while I am teaching I come across something that has not been explained properly. So I plan, once in a while, some experiments that I should do to find a clear answer, which I have done. Textbooks are kind of wishy-washy. They describe science, they are not critical. We decided that, which I continue to do now, we should not deal with textbooks much. We should give original papers for them to read and answer critical questions. Asking questions and having an answer with an experimental system. That is the way we teach. Much of the time we do not use any textbook.

JG: You were elected to the National Academy of Sciences in 1994. Talk about what this recognition means and how it has impacted your career.

SA: I do not know how much it has impacted my career but to me it was a surprise. I was very happy that somebody working on bacterial genetics . . . Fashions nowadays are to do more applied research, not basic research. I was very happy for two reasons. One, of course, is that I got recognition, and second is that basic research got also the recognition. I got lots of phone calls congratulating me after the election news became public; they were happy, not just for me, but that basic research, what I do, is appreciated. That I think was the one of the central theme at the time in my mind.

JG: How did you hear the news?

SA: I think Ira who went to the meeting . . . At the time I did not know how those things happen. I didn't know. Now I know a little bit. Ira called me from downtown where the election happened. He said "Sit down." [Laughs] I did not know why he asked me to sit down, then he told me the news and I profusely thanked him. I did not know how it happened. I did not know the mechanics. I was so happy; was kind of elated. Then I got a call from Boris Magasanik, one of the pioneering MIT professors in bacterial genetics. His call was a surprise to me. I did not know if he even knows me. He called me, congratulated me, and asked me to join the Genetics Section of the National Academy. I said, "Of course." And I did that. Then other people started calling and wrote letters. I have a bunch of letters I filed from people I admire very, very much.

JG: Let's stop there for today. We can continue next week?

SA: Sure, okay.

JG: Thank you very much.

SA: Very good.

[End of Interview]