160** Videotape interview for ASM. Barbara Hyde 3/22/96

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Oral History Interview

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Hyde: ?we can get it on tape this time.

Lederberg: No not at all.

Hyde: You seem to have developed had an early interest in science at a very, very young age. Is there anything in your early child that you could point to that directly you that way?

Lederberg: Well, that's something of a mystery to me. I seem to have been born a scientist as far as I can tell [laughter]- and who can say whether it was in my genes or not. My father was an orthodox Rabbi; my mother came from a Hassidic Rabbinical family. Certainly issues of learning and quest for truth were paramount in my family background, but there were no scientists, no physicians, no academic people anywhere in my family ambiance. It may have been a little bit of a generational revolt that I did strike out in that direction. And also being a second-generation immigrant --my father had come to America from Israel -but I was the melting pot American. Science was the pathway to mobility. Outside the family, figures like Chaim Weitzman, who became president of the state of Israel and was the leading proponent of Zionism before my birth and during my early childhood, but was also a renowned biochemist. And Albert Einstein. These were folk heroes in our community. So, they may have had-not may have-they certainly had significant influence in my own career aspirations.

Hyde: Tell me a little bit about your early scientific explorations-what you were interested in and how you went about finding out more about your interests and following up.

Lederberg: Well, I've kind of a curse. I'm interested in everything. And, I've taken on one project after another, which is okay, but it's very hard for me to remember when I've ever dropped anything. And I'm afraid that's dogged me ever since I was a very young child. There were no limits to appetite, and there are obviously limits to one's digestion, so I'm afraid that I'm still burdened with that at the present time. So, I really had the feeling that I wanted to learn everything that science had to offer. I wanted to learn everything outside of science that I could assimilate, but I knew there were some limits. I knew I'd never be a musician. I was unlikely to be a poet. But I still tried to find out what I could learn right across the board. As a youngster I was reading history and politics and philosophy and some literature, along with fairy tales on the one hand and science on the other-maybe they meet [laughter].

Hyde: Tell me some early things that you read that may have influenced you - that were important in developing your thinking, perhaps pushing you further into a scientific career?

Lederberg: Nothing pushed me further into a scientific career. It's very hard for me to convey this, but for as far back as I can remember, that was a very deep-seated drive. The only evidence I have on that score was my first composition, which and the mere fact that mother saved it will say something. But in second grade, "What do you want to be when you grow up?" "I want to be scientist like Einstein and discover theories in mathematics." I can document at least that part of it. [laughter] It's a mystery where that came from and exactly what drove it. What nurtured it were my teachers at school, the library system in particular - I learned far more from the books that I read than I did from in classes, and a somewhat ambiguous relationship with father, but in the end, one that was very encouraging. He was disappointed that I, in some sense, repudiated his Rabbinical approach to the meaning of life, but in the end it was not a repudiation. We came to a creative compromise that the Lord has many mansions and science was one of them. So his pride in me and my accomplishment-even though it was not in the immediate direction of his own calling-was a positive reinforcement. But I had no material content from that. The only books at home that would have had any bearing on this kind of learning and they were dictionary and encyclopedia. I read them from cover to cover When I said "encyclopedic interest," it had that manifestation.

Hyde: You've mentioned the Bodansky book on physiological chemistry that was an early interest.

Lederberg: Well, when I got to be a little older, that is when I was 12 or 13 [laughter], I started to differentiate my interests a little bit and I began to see that in biomedical science I could have a convergence of looking for scientific illumination and scientific truth and at the same time be working in areas that would be unambiguous in their humanitarian application. And the sense of having those two working in concert that I could indulge my own fancy about wanting to learn everything and yet would not be useless from the point of view of human needs appealed to me very much. And so I was thinking of myself as a medical research investigator from roughly the time I was 11 or 12. Before then I had somewhat broader interests.[laughter]

Hyde: So you started to follow up on that particular interest-particular direction when you were in Columbia University, correct-in your early studies there?

Lederberg: Yes, well, I don't want to leave out Stuyvesant High School. Stuyvesant is still a wonderful institution - it is the science high school in New York -sorry Bronx -- but I will hold to that even at this point. And it was available by examination to residents anywhere in New York City, so it was not a neighborhood school. It was one that collected students from all five boroughs. I had quite a commute from Washington Heights down to the downtown - was East 14th street. I would often take the 8th Avenue subway because that was the fastest way to go down and then and walk from 8th Avenue to 1st Avenue, which is a little bit of a hike-in order to get to school. That was a time and a place to get your homework done, and so forth. Stuyvesant was a science concentration high school and the most important thing that it brought to me was a peer group of youngsters who had similar interests, who could sharpen, in some competitive way, excitement about pursuing various things. I joined all the

science clubs from astronomy, to chemistry, to biology [laughter] and worked quite actively in them and did quite a bit of work after school. And I began to focus my interest first in biochemistry and then cytochemistry more particularly. I do recall as a Bar Mitzva present, I was very eager to get my very own copy - and here it is -- of Bodansky's Introduction to Physiological Chemistry. As you can see it is a worn-out volume. Read the print off the pages. I had had access to it through the public library before that time. And then Wilson's The Cell and Development of Heredity became my next major book and it's a whopper. And one, again, I tried to assimilate from beginning to end. My thought was that by learning how to examine the ultra chemistry of cells, or the chemistry of cells, at a microscopic and ultramicroscopic level, and this was a way to get at their secrets. I had always favored that somehow, against grinding them up and trying to extract their individual components, which of course is how biochemistry's made most of its advances. But you might say that at a time when many years later, that Arthur Kornberg and I were at opposite ends of a corridor in Stanford Medical School, we represented those poles of scientific approach. I think he won in that regard. [laughter]

Hyde: ..without the Waring Blender Inaudible response [laughter]

Lederberg: I've always has aversion to grinding cells up. I've always wanted to look at them more in their entirety. So, from and early time there's that difference in orientation. When I came to Columbia, I was not able to start right away because I had graduated from Stuyvesant when I was not yet 16 and Columbia would only admit students who had passed their 16th birthday, so I had a hiatus of about six month where I was able to work at the American Institute Science Laboratory, which was a precursor of the Westinghouse Talent Search. But instead of awarding prizes, they offered laboratory facilities for students who had a research bent. So I continued doing some cytochemical investigation, if you want to call it that-for that period of time, and I was slicing up onion root tips and other tissues and by manipulation both of the fixation media and of the stains, trying to get some insight about what the chemistry of the nucleolus was. I did not have adequate reagents for it. About the same time, Jean Brachet applied ribonuclease to that problem and demonstrated that RNA was the major basophilic staining component of the nucleolus, but that work was not available on account of the war until a couple of years later on. So, at the very beginning I was "scooped" by an excellent investigator.[laughter] When I came to Columbia, I tried to continue that direction of interest. I'm glad to say as an aside that I met Barbara McClintock very early as a freshman because I had heard that she had worked on the genetics of the nucleolus and the nucleolar organizer. She was very friendly to me- as was everyone that I met at Columbia. But it turned out that her interests were genetics and cytological, not chemical. Then I met Francis Ryan. He had been a post doc in Beadle and Tatum's laboratory during my first year at Columbia in 1941 - 1942. But I had heard about him and about the work that he was entering into, which was the very beginning of biochemical genetics of Neurospora. When he came back to Columbia in September of '42, I camped on his doorstep right away and I gave him no peace until he allowed me to try out to work in his laboratory. And I very soon learned the power of genetic analysis as an alternative to doing explicit cytochemistry in working out the fine structure of cells, details of metabolic pathways, and so on. It's from him that I learned the discipline of science plus an enormous amount about microbiology and the whole idea that one could use a genetic approach in microorganisms. So my apprenticeship was in Neurospora-the field that had been opened up, most particularly by Beadle and Tatum.

Hyde: You've spoken in other places quite fondly of Frank Ryan. He had a very, very profound influence on your life.

Lederberg: Oh, did he ever! Well, he has on many people. The one thing that I run into when people who have worked in his laboratories that they regard him in the same fashion that I do--a magnificent teacher; person of just wonderful personal empathy as well as the intellectual skills; put me through the Socratic method mercilessly-day in and day out. But also let me fly with my own wings and would always try to draw out from me rather than tell me the answer to a problem. Help me learn how to discover it for myself. I've never met a better teacher and I wish I were within ten percent of his capability in that sphere.

Hyde: Do you feel that you have similar types of relationships with your students that you had with him?

Lederberg: I would like to, but I don't think I can manage it with his degree self-effacement and skill. I don't have his teaching skills.

Hyde: Are there other people that you would cite as having significant influences on you during this time, people that you have worked with or in a mentorship capacity?

Lederberg: Well, none come close to Francis. I had any number of teachers who were encouraging and reinforcing. They did see me as little bit of prodigy - that's no secret, with the kind of reading that I was doing fairly early. They tried to help me along in various ways. Even the librarians at the local library would cooperate in getting books for me that were not locally available and so forth. I just had nothing but encouragement from any sphere, but the one person that stands out is Francis Ryan. Salome Waelsch was also at Columbia at this - a renowned mouse geneticist and she used to smuggle mice to me for my experiments in a laboratory where the lab head was not so keen about having mice there. I thought she was being very nice to me but lately she told me it's - she was happy to be playing tricks on that particular professor.[laughter]

Hyde: What was it like to be working in the field of genetics at this particular time, things seems to be just opening up-and almost this explosion of knowledge. Would you characterize this as really a revolutionary time?

Lederberg: Well, there was no doubt we were living through a revolution. I certainly experienced it as such and internalized it that way. When the paper by Avery, McCleod, and McCarty [1944] came along, I didn't use the phraseology, but my exclamations were equivalent to saying "This is the dawn of molecular genetics." For the first time we could have a biological assay for the genetic activity of an external molecule. So, that publication, next to Francis Ryan, was the molding effects on my career. Was talked about quite extensively around the department at Columbia. It turns out we had a couple of people who were important liaison. Alfred Mirsky, who has been remarked on as having been an inappropriate critic of Avery, McCleod, and McCarty. I don't think that it was inappropriate, but he was certainly a severe critic. But he was also the greatest herald of the story. So, we would hear about what was going on at the Rockefeller Institute on the other side of town as if we had been at the same institution. But also Harriett Taylor was a graduate student

working with L.C. Dunn-had become interested in it as well. She, in fact, went to do post doctoral work in Avery's laboratory shortly after that time. So we had very close information linkages to the research that was going on there. Perhaps that's why I have such a different perspective about the reception of the Avery school's work, compared to, say, what Gunther Stent has written. We were very well informed about it. We reacted to it. There was a lot of critical dialectic. But, it was not something that could be ignored. It was the most exciting thing that had happened in many many decades. And it was precisely because it was so important, that is, the identification of DNA as genetic material, that I empathized with the view that it should be subjected to the most critical examination. It was too important an issue to just accept casually. As long as the debate was alive, that was the way the scientific method operates.

Hyde: Did you know Avery himself?

Lcderberg: I met Avery a couple of years later on. He was a somewhat reclusive person, but he agreed to meet me-that was in '46 when I did pay him a visit at the Rockefeller Institute, shortly before he retired.

Hyde: Do you think that if these types discoveries were happening today, would you have the same type of collegial relationship? We talked a little bit before you and I about the competitive spirit in scientific research these days.

Lederberg: Well, in terms of eagerness to exchange information, I think that's always there. The paradox about science that many lay people don't understand is that a scientist doesn't get anything until he gives it away. He has to give it away by publishing it in order to get the recognition of his or her peers standing in the field, and so forth. So there is that paradox that if you keep it to yourself, no one else will know about it and you'll get no recognition for it. Now this is somewhat complicated when there are discoveries that have practical applications and that's why we have the patent system so you can lock up the property rights at the same time that you also publish the outcome. But I think that there's very, very lively information exchange. The fact that we have so many hundreds of thousands of scientific papers that are published every year and the eagerness that their authors have to disseminate them to their colleagues is very strong testimony to that. I think there's so much larger scientific community now that issues get to be resolved more quickly - that there will be fewer delays before some laboratory picks up a controversial finding and attempts to replicate it or to use it-which is even more important - and build on it. So things move more briskly today even than they did then.

Hyde: Do you feel that the advent of electronic publishing and on-line journals may somewhat diminish peer review system in reporting results and how did this affect?'?

Lederberg: I've been very interested in the electronic journal; I've been pressing for it for a long time. You may not have known that my group was almost the earliest user of the arpanet to manage a laboratory program. This was in the early 70s out at Stanford and some of my colleagues were a little bit taken aback at my insistence that the handling of text and the communication of ideas was going to become the principal use of computers. And most of them felt computers were arcane instruments that should be used for very complex

mathematical calculations. Well, the explosion of the PC I think has validated that text handling is probably the major application of computers and their linkage with communications. We're just at the early stage of the transition and I think it is very important that we learn how to develop the same kind of discipline in what is a recognized publication over the Net as we have had in the print media. I attended a meeting in Paris about two weeks ago that was sponsored by UNESCO and ICSU, which I think was a major turning point in getting a consolidation of interest around those themes. It is the scientific societies that are going to have to lay the groundwork for it. Yes, we will need peer review - we will need to have on one the hand a full recognition that a peer-reviewed article that has appeared - even if it appears only in electronic form - it has the same authenticity and validity as if it is in print. But, the converse of that is that casual commentary that's just thrown up in the air and that is on an individual's own bulletins and so forth are just rumor and ought be given no more credit than that. So, I think we need to have every encouragement that would be characterized as having been submitted through some form of peer review process. Readers will insist on it because we'll very quickly run out of patience about having to look at everything that everybody had cared to dribble out on to the Net

Hyde: I think there's one journal in the physics field that's I believe is accepting all comers and just put something?

Lederberg: We'll there was some argument about this at Paris. Paul Ginsparg at Los Alamos has pioneered in the rapid dissemination of what he calls "preprints." And the idea there is that the ultimate publication will provide the validation. And I think there was a common agreement that high-energy physics community is structured so differently. It's quite small; everybody knows everybody else; the laboratories really carry their own imprimatur. You know that something has come out of a given lab has been reviewed very carefully, very extensively within the laboratory, so a somewhat different process has been applying there. The main issues that remain is how is all this is going to be paid for - it doesn't come for free and I've tried to press the concept that the most economic way to deal with this is through page charges. That authors have adequate motivation to want to see their work acknowledged, acknowledged as valid and authentic, and a page charge system could bear the freight in terms of the processing costs of handling the material. The authors could do almost all preparation from their own desktops. And if the funding agencies elsewhere, as is already in the case in the United States, will recognize that dissemination is a valid cost of research, I think we could have a very workable system. I don't know if I will I lament ten years from now that this [holds up journal] will still exist, but will exist because I have downloaded it from a computer file and printed it on my own high-resolution laser printer and it will be indistinguishable in appearance from this [printed version of journal]. There will be no need for you to have printed it at your central locale and if I want to bear the cost of the color print, I can do it, but otherwise it doesn't have to be a burden on the intrinsic cost of publication. I know that you are going through a terrible struggle about that at home [laughter].

Hyde: Exactly, the costs are skyrocketing. Okay, I think we have a take.

Lederberg: Want to have a good look at it? We'll come back to this - the substance of that paper. Okay, there you go. [ASM News close-up] We'll come back to this; the substance of

that theme is of some interest.

Technician: Okay, you can put it down now. [Break in tape]

Lederberg: [starting seemingly midsentence] ?seeing that things are kept in their proper order so that you can retrieve them - that's expensive!

Hyde: Uhuh. Absolutely, as libraries know.[laughter]

Hyde: Let's go back a little bit to the process of scientific discovery and I'd like to hear from you your thinking when you made your seminal discovery of genetic recombination in bacteria and some of the process that led up to that -- what your thoughts were and how you really came to this finding.

Lederberg: Well, my first important discovery came about through a rather unusual process. More than almost everything else I have done, it was theory-driven rather than being data-driven. It was theory-driven in a sense that a postulate had arisen out of the course of the examination of the contemporary scene. Namely, Avery, et al had shown transfer of inheritable characteristics in a bacterium. One was deeply motivated to want to know more about whether there were things like genes in bacteria. The approach that speculatively arose and how to respond to is, "could one would find out if there's a possibility of genetic recombination, of crossing between bacterial cells?" My work with Neurospora had given me the methodological tools to facilitate getting an answer to that question because I had been studying nutritional mutants in Neurospora and had been selecting for nutritionally wild type, where we coined the term "prototrophic" revertants as part of our study, their behavior. So, by that selective process, we knew we had a means by which a particular genotype could be fished out-a needle in the haystack - and the magnet would be their ability to grow on a minimal medium. So, on a theoretical basis one was able to put together a thought experiment that said, "If bacteria can be crossed, and if you start out with two different nutritional mutants, and if they exchange with one another, they will form prototrophic genotypes; you will be able to select for them, and define their occurrence even if they happened very, very rarely," by a rather simple procedure: plating the mixtures on minimal agar. So, there was a case where the experimental design was worked out as a theoretical postulate: "Does genetic recombination occur? Does it not occur?" and that was all worked out in advance of ever doing the experiment. Well, somewhat to my surprise, it worked very, very promptly. I was rather fearful when the first positive results came in. I was worried deeply that this was going to be an artifact; that my hopes would be dashed; I didn't want to get too excited about it. I was scared. I knew this was a very import finding, but I didn't want to be out on a limb until I could be absolutely certain. I didn't even want to commit myself emotionally to consequence until then. So, it was a matter of going back to grindstone and repeating the experiment many times, doing it different ways and being sure that it was a totally reliable and reproducible result. Put in every control I could think of to be sure I had controlled for possible artifacts. Happily, with bacteria, one can redo these experiments -- you can run one or two cycles a day on this kind of experimentation so within a few weeks it was possible to get a total validation of that. Well, all that happened almost precisely 50 years ago. I arrived in New Haven in March, 1946 and by early June had it completely taped down that crossing was taking place. So, that's a rather unusual circumstance. Since then, I guess most of my

findings have been data-driven, that is to say anomalies have arisen during the course of examination of a phenomenon and tried to explain the anomalies, would then be the basis of the research. So the discovery of Lambda, the discovery of the F Factor, the discovery of transduction in salmonella, specialized transduction with Lambda and E.Coli, these were all essentially data-driven. The serendipity of things happening that you had not expected and keeping an eye out for those anomalies and then starting with a phenomenon, trying to develop a theoretical interpretation. I don't want to develop two sharp of a contrast - you are always dealing in cycles. When I said that the original discovery of recombination was theory driven, it was because the data had all ready come in, had already been assimilated to then raise the question as to whether recombination could occur. In the course of further inquiry about that, new data would arise and then those would then drive discoveries that had not been anticipated.

Hyde: Was conjugation an observed phenomenon before you?

Lederberg: Oh, no.

Hyde: You were the first to recognize it?

Lederberg: Well, it was even hypothetical when you put your fingers together and use that as a simile for conjugation, even that is an inference that is still somewhat shaky. We don't have a good picture yet of the physical aspects of the transfer of DNA from a male to a female cell. One can see cells are paired up, come into some approximation of one another. The role of the pili, which are very tiny fibers that are a necessary ingredient in the process of recombination, is still quite obscure. I'm rather skeptical of the idea that the DNA is transferred through these as hollow tubes, which had some popularity at one time. I think they are more likely the attachment mechanism whereby the cells can get to some approximation to one another. But nobody has yet caught a DNA molecule in the act of traversing the membrane of one cell and getting into another one, although we have good inferential evidence about many of the further details. We know that only a single strand of DNA is what's transferred, so the DNA's unraveled in the process of being transmitted from one cell to the other. So, there are still a lot of uncertainties about mechanical details of the process. We understand this at the genetic level; we have the beginning state and the end state. There's a black box in between. I guess they make love in the dark is about the best way to put it.

Hyde: Conjugation, is it easily observed under light microscopy?

Lederberg: No, you can-- well proving it's conjugation is what's difficult. If you have, what were later discovered, particularly by my friend and colleague Luca Cavalli (Luca Cavalli-Sforza) HFR (High Frequency of Recombination) strains, you can accentuate the frequency of conjugal happenings to where a few percent of the population are actively involved at any given time. When you do that and you have appropriate cell markers so you can just look-you could not otherwise tell a male cell from female cell-but a few cells that already have morphological markers on them -- you can use one rather plump rather round strain and a long thin one and sort of tell them apart and sort of tell them apart even as you see them under the microscope. You do find not just pairs, but clumps of cell in which the two cell

types become aggregated to one another. And that's about as much as you can tell under the light microscope. You can't see any other process. You don't see cell fusion. You don't see any DNA transfer taking place and even under electron microscope, that is still quite obscure. Duerrenberger has published some papers, in [the Journal of Structural Biology] .. on his work with thin slices. His earlier papers were, on these aggregates and he was able to find some cases where the cell-to-cell approximation had some kind of interfacial structure. But really very difficult to prove its relevance to DNA transfer.

Hyde: You had the theory of the framework before you made this physical observation?

Lederberg: Yes, there was this black box. Well, in a way so much of genetics has been that. When Mendel did his experiments with peas, yes, he put pollen on the pistils of the plants, but he basically didn't see very much or know very much about what went on until the seeds came out. So, genetics has always had that characteristic of seeing input/output relationships. And yes, you do struggle with trying to see the chromosomes and see the other events, but they occur at such ultrafine structure, it's very hard to know the details. At this time, we know a lot more about the DNA/DNA interactions in recombination. And we have the role of the RecA-B-C-D system. ... little better than inferential evidence about the Holliday junctions and so on. We have a fairly good picture, even at the phenomenological level, of what's involved in strand exchange. But we don't have a good picture of how the DNA actually gets across from one cell to the other in order to enable that to happen.

Hyde: It's amazing that it's 50 years later and we still don't know all the ?.

Lederberg: Well, I'm a little concerned about it. I've wondered if I shouldn't jump back into that myself. But, I to some degree put E. coli behind me when I moved out to Stanford in 1959 and I've done relatively little work on E. coli since that time. The reason was that other systems seem to be more amenable to looking at the molecular biology of the gene and Bacillus Subtilis in particular, had an already well-crafted system of DNA transfer. Now, if I had waited another few years, I could have done it again in E. coli, but that's the way it went. So, my work on E. coli was at Yale and Wisconsin from '46 through '58 and only very lately have come back to using E. coli. E. coli had its run. It was probably the favored organism for molecular-biological research well into the late 70s or early 80s. Since then it's had plenty of competition from yeast on the one the hand, which bridges the world of the microscopic to the world of the eukaroyte. And, of course now that so many of the basic principles of molecular biology have been worked out with prokaryotes, there's a great eagerness to apply them to eukaroytic world, and in particular, to the human world. So, we have of course an explosion of activity using the same basic concepts, a very familiar set of methodology, but studying them directly on human cells, in culture and then extending those, of course, to the problems of live human beings. So, you have proportionately only a small handful of people are still working on basic issues of genetic mechanisms in E. coli today.

Hyde: You published your findings when, in 1946-47?

Lederberg: My first findings were in 1946. I mentioned that I became quite firmly convinced about the reality of crossing by early June. There was a Cold Spring Harbor symposium coming up in early July. I had been planning to attend as a very junior student-I

was a medical student on leave in Tatum's laboratory at the time. Ed Tatum had been scheduled to give a paper. But then when we saw how much interest there was in recombination and Hershey and Delbr|ck were publishing on recombination in bacteriophage, we thought this might be a good occasion in which to reveal those results, even at apparently a very, very early stage. And so, by special dispensation, I was given the opportunity to present them. On about the Fourth of July, 1946 and this is the eventual publication, which appeared in '47, although it's called the 1946 Cold Spring Harbor Symposium [showed paper].

Technician: Could you hold that up again for me?

Lederberg: Sure. This is the earliest statement. It has not much more than the raw data of the occurrence of crossing, but I had already had some unselected markers also segregating, showing that there was a wide variety of genotypes. And you can see we were quite cautious. It's entitled "Novel genotypes in mixed cultures of biochemical mutants of bacteria." While we were quite convinced there was a recombinational mechanism going on, we thought we would leave it pretty close to the phenomological level. It was a very brief communication. It had quite a reaction. I think, here was a 21-year-old shaking the icons. We had the whole world, as it then existed, not a huge world, but everybody who had any interest in microbial genetics was there at this symposium. And I would say to the last person, they would be very eager to shoot it down. And they tried very hard to do that. But, I had already done all the controls. I had an extended debate with Andre Lwoff, who kept asking me, "Had I made single-cell isolations?" to be sure the prototrophs were not just the two parent cells feeding one another through the medium. I said, "Dr. Lwoff, I really thought about that," and I tried to show how the segregation of other markers in pure form in these prototrophs was totally inconsistent with that possibility. But, he was quite stubborn. I kept saying, "You don't need to do it," and he said, "Well, until you do it, how do you know they're single cells? You're just using plating methods." Finally, Max Zelle stood up and said, "Well, let's defer this, Josh Lederberg and I will get together later on and we'll see about the single-cell isolations." He showed me the technique and a few months later we published that, and of course, it offered no change whatever in the conclusion. It was a wonderful opportunity to thrash it out. I'm not sure I recognized at the time what a blessing it was to have that occasion. I think all the criticism was exhausted. This was a pretty minor footnote that Lwoff had brought up. And that meant that it was impossible not to accept it because all the arguments had been out there. If this had been simply published in print, without that kind of personal interaction, there might have been rather grudging reaction and rumor and "well, who's recorded and what's the answer to this question or that one?" The fact is, all the questions were asked. I'm so sorry that I don't have the transcript of that occasion. It was really a wonderful debate.

Hyde: Tell me after the Cold Spring Harbor Symposium, what direction did your research take. You eventually found your way out to Wisconsin.

Lederberg: Yes, the immediate issue was whether I wanted to go back to medical school. I was on leave from Columbia Medical School. I was in the middle of my third year. Had just started to do my clinical work and as I mentioned earlier, I was going to be a medical research investigator. Until I had fallen into the hands of the geneticists, my general inclination was probably to go into neurology as an area that had sort of the most interesting

convergence of immediate medical issues with a kind of analytical and biological framework. And there's some merit to that. I think in retrospect, Neurobiology would have been twenty or thirty years ahead of the time to really accomplish the kinds of things that I was dreaming of at the time. So it was just as well that I was diverted through genetics. But genetics, Medical genetics was a nondiscipline. Jim Neel was only just getting started. He was the only person in sight doing anything significant about the genetics of disease afflictions in human beings at that time with his work on sickle cell anemia. I had gotten to know Jim when he visited Columbia, when he had decided to go to Medical School after his Ph. D. in order to embark on this. I remember the very quizzical reactions that people like Curt Stern and Theodosius Dobzansky, about someone who had abandoned drosophilae and was going to work on the genetics of humans. Well, he knew better, of course, and he's written a wonderful memoir, Physician to the Gene Pool, and of course, we've been very close throughout all these years. But it meant a little bit of a dilemma for me personally about exactly what I'd be getting into in returning to Medical School. So to begin with, I got a year's extension in order to follow up these initial findings -- otherwise would have had to return to in September'46 to continue my medical studies. In terms of scientific strategy, it looked as if there were two or three things that needed to be taped down. One was to verify the generality of the phenomenon, i.e., to introduce as many new markers as we could lay our hands on and show that they would all be reshuffled. Second, could we get evidence of chromosomal structure, that is, of linkage analysis? And this would be applying to E. coli what Alfred Sturtevant had done in 1911. In 1946, 1911 seemed like prehistory, I have to tell you. At this stage, I acknowledge some continuity that he discovered linkage-he discovered mapping, not linkage, but linear order of genes in chromosomes. The reason I bring him up is that there was a physical affinity. The first laboratory bench that I worked on at Columbia in Schermerhorn Hall was right at the very fly lab where Morgan and Sturtevant, then Muller and Bridges had done their work some 30 years before I had arrived there. So, while as I say, 30 years previous was before I was born, and so on, and that seemed like the very, very distant past. At this stage, it seems like a rather close proximity. [laughter] The linkage mapping became one issue, the generality of the phenomenon-I think I brought out a couple of those reprints. I did find that one could generate evidence for linearity - for constructing linkage maps. Ruled out some of the competing hypotheses as to what the mechanism of recombination was. If you threw deoxyribonuclease into the medium it had no effect whatsoever, and so this made it very unlike the pneumococcus transformation, where DNA was moving through the external medium. Tried, but didn't really think of any very good ways yet to get any further into the physical mechanisms of genetic exchange, so I went into formal genetic analysis. And I did that during the academic year '46-'47. And then, the question came up again, about going back to Medical School. At this point, Ed Tatum provided a possible alternative. He had learned that a job was opening up at his prior home institution, the University of Wisconsin, where he had done his Ph.D., his father had been a professor of pharmacology, where Ed had grown up as a youngster, so he knew Wisconsin very, very well. There was an opening in Department of Genetics--that they'd become interested in the genetics of microorganisms, either Neurospora or bacteria. That was the only job in sight-or the only job one had any prospects of expecting at that time in this field. So, there was a certain sense of "now or never" if you wanted to get into the academic world in this area. And he just put to me the possibility of my moving after I completed my work at Yale-to apply for the position at Wisconsin, which was opening up as of September was a small detail about my getting a doctoral degree, because I was not registered as graduate student; I was only a medical

student on leave and I was only halfway through my medical studies. But we found a way to cook that up. I was retroactively registered; I had attended all of the seminars. I'd had two and a half years of Medical School to begin with. All I needed to do was scrape up the money to pay the tuition to Yale University now that I was an acknowledged graduate student [laughter]. My research, this publication in fact, was my dissertation. I was also setting a precedent that I didn't want to bother to simply retype it all in the usual form and they huddled together and said, "Okay, if you want to bind together your existing reprints and a few pages of explanatory text, we'll accept that as your dissertation." [small chuckle] and that's what happened. So, now I had a Ph.D. and I competed for the position at Wisconsin and in the end decided to go there and continue my active experimental work instead of completing my MD training. At Wisconsin I had a wonderful environment. I made so many wonderful friends there. I want to mention Jim Crow in particular. Someone just a couple years older than myself and he remains that [friend] to this day. R.A. Brink and Bob Irwin were successively heads of the department there-people to whom I owe my position. It must have taken some courage for them to hire a 22-year-old as an assistant professor. Seeing that I had a Ph. D., but I had the experimental credentials, the findings and so on. And as young as I was, in fact, I had as much experience as any other graduate student. It's just that I had just started very, very much younger and I was as well read. I think that they discovered that it was a fair competition even if they had to blink a little bit and wonder about whether I'd lied about my age by ten years or something of that sort. [laughter] So, I was quite happily ensconced. I was missing just one thing and that's the medical connection because the Genetics Department at Wisconsin was in Ag school and really felt I'd given up something very important to me in the process and I wasn't going to stand still for it. So, a few years rolled by - it seemed long at the time - but by 1955, with a new Dean coming into the Medical School. I'd progressed through the ranks; I been appointed a full professor by the time I was 29; and could have a little more to say about how I wanted my life organized. Anyhow, I arranged with Dean Bowers to start a Department of Medical Genetics in the Medical School and the big difference there would be the teaching -- that Genetics would be introduced into the Medical curriculum; would put me in a little closer touch with other medical issues, especially the McArdle Cancer Research Institute. Wisconsin Medical School at that time was not a renowned research institution. Wisconsin was, but mostly through the College of Agriculture and the Biochemistry, and Nutrition, and Microbiological research that was being done at the Ag school. So I think we did an important thing for Medical School and importing more of those scientific traditions into the school.

Hyde: Tell me about the events leading up to your Nobel Prize. Were you aware of it (that your were a candidate) did you think you were a candidate?

Lederberg: I was totally oblivious to the Prize. I knew about Nobel Prizes, and I thought wonderful people had gotten this accomplishment. I thought of it then as being something that might grace the end of your career and had given it absolutely no thought and would have thought it preposterous that I was even being considered for it. This was not modesty. I felt my work was potentially as important as that of some other Prize winners, but I thought I was very young and I thought there was plenty of time to let that work out, so I was quite astonished when it came about. I had somewhat ambivalent feelings about the Prize altogether. I have a very deep sense of how science is so reticulated - and to pick out any one individual or any one contribution - you must be very, very careful that you're really doing

justice to the whole network of knowledge and science in which that's embedded. Now, I guess my own work was more singular than that of many others in that regard-I think there was no doubt that I wasn't being crowded with competition. On the contrary, I had a job selling the case about my findings and so forth. But the basic issue was that of timeliness and I was really quite astonished when the news ...

Hyde: The phone call came?

Lederberg: ... the phone call came. I didn't believe it. I thought it was a practical joke. But it eventuated. It was so. And I was deeply honored by being able to be on the podium with my mentors - with Beadle and Tatum, who had sort of founded the field in which I had come up. And fifteen years later, well, it wasn't fifteen years later. They were fifteen or twenty years older than myself, but in fact, their work had been done 1941 and mine had been done in 1946. So, they weren't that far separate. I have to say that in retrospect, that wasn't the way it felt at the time. They seemed like so much more of an advanced generation than me.

Hyde: Uh huh.

Technician: We can change tapes now.

Hyde: Do you want to stand up? [Break]

Hyde: How do you feel that affected the subsequent course of your work? Obviously it brought you a lot of recognition in scientific community. Beyond that --

Lederberg: I don't think it altered very much my recognition in scientific community. I think I got the Prize because of my standing in the community. I don't think very many scientists needed to hear about me through the Nobel Prize. I'll be just very candid with you about that. I'll give you some particulars on this point. It came at a very awkward time in my academic life. I got notice of it in October of 1958 - and this was at the point where just a few weeks before I had agreed to move to Stanford University. These prizes are more important to the institutions than they are to the individuals and it was very awkward. The amount of hoopla that there was in the local press in Madison, "UW Lets Nobel Prize Winner Go," "What's Wrong With the Place?" and so forth. And the extra anguish it meant - there is a certain degree of turning your back on your friends and colleagues when you make a move of that kind. Wisconsin had been my first major academic job. It was difficult enough leaving and then this just aggravated it. Well many people? and then Stanford, well, I wasn't there yet. So they could say, "Nobel Prize Winner Joins Stanford Faculty," but it was not for work done at Stanford. So, there were all those ambiguities connected with it. The point I want to emphasize is that my offer to come to Stanford, to initiate a Genetics Department in the new Medical School was signed, sealed, and delivered long before there was any inkling about the Prize. Yet later on, many people would say, "Oh, Stanford went after you when you got your Nobel Prize." I'm trying to get that clarified. It didn't take the Prize for Stanford to make its bid for my establishing the department. As far as the public image is concerned, of course, that's how -[pause] the public can't make its own lay interpretation of the importance or validity of scientific work and I think the Nobel Prize committee has done its job well enough and you're in good enough company in that regard that statements from Nobel Prize

winners are taken fairly seriously. So, it's the public, not the scientific recognition-I'm sorry to have belabored that so long. But, I had very seriously considered not accepting it. It's very hard to validate that, especially when in the end I did. It seemed to me sort of against the grain of why one does scientific work, to be singled out quite that way. And especially, who cares about the public side of it. I had the respect of my colleagues; that was what really counted for me. But, I, what shall I say -- did I have tears on my face when I finally agreed to do it? Of course not! I was very joyful, very appreciative. Enjoyed some of the acclaim that went along with it, but not without some ambivalence. And I felt there were two reasons why one should take it. One was, yes, it did serve a-it was a public service; it served a socially important function. It highlighted the significance of science; it focused on authentic accomplishment; it was a way to keep the public aware of the excitement and importance of scientific advance. I think it still does that. I think that's the major reason why scientists would want to continue that kind of celebration. The other is, when it came right down to it, how could I even hint at not accepting it when Beadle and Tatum were there? It would have been a slap in their face. It would have seemed like here was a youngster trying to get still more notoriety by having been offered the Prize and then turning it down. So, I won't say I accepted it grudgingly; I accepted it joyfully, but I did have some-at least lingering-thoughts about the entire process.

Hyde: The fact that you won this prize at such a relatively young age and then carried that laurel, if you will, with you throughout your career. Has that created any particular issues -- either positive or negative - to deal with? Having "Nobel Prize Winner" connected to your name.

Lederberg: Well, I'm offended at the subjugation of my own individuality when I'm labeled as a "Nobel Prize Winner" rather than as "Josh Lederberg." That kind of automatic labeling -- I'd rather people know me for what I am as a person than through somebody else's distinction. That was something somebody else did, not that I did. That is the imprimatur, conferral of the Prize. I'd say that it's mostly positive. I had already been interested in impacts of science on policy, only in a fairly small way, but it was beginning to emerge. And I think I had a more effective voice for just the reason that you've mentioned, sort of easy name recognition. I'm sure I was asked onto a number of committees and task forces because of people who heard about me because of the Prize. There were also a lot of things I had to fight off - some people wanted to exploit me because of the notoriety that went along with it. So, that's the negative aspect of it - is having to be on guard. Do people love you for yourself alone or because of the Nobel Prize [laughter] that goes along with it? You learn to discriminate that pretty quickly.

Hyde: Around this time it seems you started to do some work in genetics of antigen recognition. Did you develop this at Wisconsin and further pursue this at Stanford?

Lederberg: Well, that's an interesting story. It was kind of a side episode. I had one excursion into immunology, which was consequential. I had been thinking about antibody formation as an analog to the process of enzyme induction. At Wisconsin, one of the major elements of my research program was to use the techniques of genetic analysis, which I had developed in my dissertation, to studying gene/enzyme relationships. That, after all, is what Beadle and Tatum were after in the first place in their work on Neurospora and I thought

bacteria would be even better tools-far easier to get the range of mutants to work with them biochemically, and so on, which indeed has proved to be the case and why bacteria are so popular for that purpose. And I decided to use lactase or beta-galactosidase as the target enzyme for this purpose. For a couple of reasons: one, some work had been done on it before. E. coli was notorious as being a lactose fermenter. Other Enterobacteriaceae are distinguished from E. coli by being lactose nonfermenters. Even if you new nothing else, you knew there was a genetic determination of that enzyme. There had been already in the literature reports of lac-minus of lactose-negative mutants of E. coli. In fact, some of the very earliest mutants described that way were on that particular phenotype. There was an indicator medium for it, Eosin Methylene Blue Lactose agar, which you have to do a little bit of witchcraft to make it work well, but when you pick out the right dye lots, it works very, very beautifully and you can distinguish lac-minus from lac-plus colonies very nicely on the plates-even down to fine sectors of colonies. So that was a great advantage to it. It's the equivalent of the red eye of the drosophilae and can see the white spots in it when you have somatic mutants. It needed some improvement and with the help of Karl Paul Link, the rat-killing biochemist, who was next door to me at Wisconsin. He used to send me postcards, "Karl Paul Link, Rattor," and that was for his discover of warfarin as, what is still the world's greatest rat poison. [laughter] So, he wants to be remembered for that, that's why I'm bringing it in in that way. Anyhow, I mentioned to Karl Paul that it would be very handy to have a chromogenic substrate for beta-galactosidase. I knew about nitrophenyl phosphate being used for phosphatase; Could he help me in the fabrication of a nitrophenyl galactoside. And he asked one of his graduate students and Saul Roseman took that on and made, what was then, a new compound and made a batch of it and it's worked out very well. And of course, it's been the prototype of all the indicators for the enzyme ever since. My first paper in J-Bacti was in 1947 on E. coli recombination. It was either my second or third one where there was a description of beta-galactosidase of E. coli using this substrate as a way to do its enzymology. We got a lot of mutants affecting lactase formation. I think we did make a significant contribution to that field. Tom Brock has summarized that better than I have in his book on the emergence of bacterial genetics. I don't totally go along with his overall characterization of the relationship of my work and the Paris school in that regard. They did an enormous line of work on the same subject and I think Monod, and Wollman and Jacob are very well and very appropriately recognized having developed the operon theory on the basis of their research on exactly the same system. But one of the progenitors of that was an observation that is often not recalled, that was from my laboratory, was the discovery of constitutive mutants of E. coli that would make the enzyme without its having to be induced with the external substrate. So, I had been interested for some time in looking at the gene enzyme
induction system and had reached the conclusion quite early in the game that the role of inducer was not to provide any specificity of the enzyme-was not an instructive role-as at that time Spiegelman and I think pretty much Monod felt during their early entrie into it, but rather that the capacity to make the enzyme was already inherent in the genetic machinery and the purpose of substrate was to alter the regulation of that gene. And the constitutive mutant was the key to that point. Here was a strain capable of making large amounts of the enzyme without any inducer whatsoever. You asked me about antibody formation and I was going on at some length about the background to it, but I wanted to bring it up to this point. I began to wonder about the analogies - as other people had - between inducing an enzyme by adding an inducing substrate and evoking an antibody by putting an antigen into the animal. There were certain superficial similarities between the two. At the Ford symposium in 1954, I

raised this question and said, "Yes, but? while I think the genetic information for the enzyme is already present in the cell, I didn't think that one could apply that analogy to antibody formation, because according to what the immunologists tell me, there's an infinity of antibodies, but we don't have an infinity of genes to deal with," so I was at that time only considering models where they would be a preformed gene for a particular antibody and I correctly concluded that there might not be an infinity, but there were too many of them. Just that time received a letter from Nils Jerne-let me get the timing right - approximately at the time of the conference 1955 . I had not carefully read the article until after the conference, Jerne published in the PNAS a theory in which he postulated that globulins are undergoing hypermutability in the serum and that the role of the antigen was to select one particular globulin by its reaction with it - and then through some magic that the globulin was self-replicating and that would be his mechanism of antibody formation. I wrote to him and I said that it was an attractive idea, but I just couldn't buy the idea of globulins being self-replicating. But discussed this analogy with enzyme induction. So I walked right to the edge of the clonal selection theory, but rejected it on the grounds of the premises that I had been given by the immunologists. So now we switch to a couple of years later. I'm on a Fulbright Fellowship to work with Mac Burnet in Melbourne. I'd gone there in order to learn influenza genetics. He had discovered a system of genetic recombination in the influenza virus and I sort of wanted to spread my wings a little bit into another system and went there to learn about it. When I arrived there I was dismayed. He said, "Oh, we stopped working on flu, we're interested in antibody formation. I have this notion about clonal selection." He started to recite it to me and I said, "Yeah, but it doesn't work, there are too many antibodies." He said "Well, how many antibodies are there?" and I said "I don't know, infinity - but there can't be an infinity - but maybe billions or hundreds of billions of them." I'm impressed by ... everyone else had been without a .... and so on, and he said, "How do you know that there are that many, how do you know that there are more than a few thousand of them?" I said, "Well, haven't you done panels of cross reactions, you know, a thousand antigens with a thousand sera?" I didn't know. He said, "Of course not, nobody's ever done that. How do you know how many there are?" And I'd have to say, "Well, I guess we don't know, maybe it's a somewhat more limited number." So, of course I instantly grasped what he was starting to tell me about -- the cell as the unit of selection. And that's what cells are - self-replicating - it didn't have to be the globulins that Jerne had invoked. And I became a very enthusiastic disciple on that score. The role that I played was that Mac had wonderful biological intuition, but he had very little patience for molecular genetics. I'm not sure he'd really gone in very great depth cognitively, but he also had an emotional reaction: he didn't like the idea that we had the material basis of the gene all laid out and he's expressed himself in no uncertain terms about that. So, I translated the concept of clonal selection. I wish that I'd had the wit to have taken that extra step, but I had not. There was no dispute about priorities. And I translated it into molecular genetic terms. I invoked the model that had been developed that Watson and Crick, in particular, had been annunciating. The pathways between DNA and RNA and just put his "scheme" into the language of molecular genetics and did it in a rather rigorous fashion with separability of the premises so that if something could be disproven, then maybe other elements of the theory could survive, and so on. I wrote that up as a paper, eventually it appeared in Science magazine. I gave it as the Mueller lecture at Harvard. Bernie Davis had invited me to come and talk and I decided to present this idea there and I have to tell you it was very critically received. The Felix Horowitz, Pauling ideas of the instructive role of the antigen in antibody formation were absolutely pervasive and [my paper]

was very skeptically received, I have to tell you. Well, it was just a hypothesis and there was no other contributory evidence, except that while I was down there, I also had a chance to start some laboratory work with Gus Nossal, who was a post doc, who was just beginning in his laboratory career with Mac Burnet. I had been doing some work on the serology of salmonella. I even had some reagents handy and so on, what we ended up doing on the basis of my own experience in manipulating salmonella motility under the microscope in the presence of antibody and so forth, was to use the flagella antigens of two different strains of salmonella as challenges in mice. Inject the paws of mice, extract spleen cells, some days later on and then ask of individual cells whether making antibody against one or other or both of the flagella antigens. And we could diagnose it in a microdroplet with one plasma cell and a small inoculant of the motile bacteria. And, depending which bacteria were immobilized, we could diagnose the antibody being made by that cell. So, I contributed the microassay for the antibody production of the single cells and we found to a very good approximation, that individual cells either made none, or one or the other of the antibody, but no one cell made both. At that was at least consistent with the clonal selection idea that it's at the level of the cell that you have differentiation of that capability. Well, we remarked that that doesn't settle it, we didn't have way at that time of cloning those cells. All we had was the phenotypes and we'd of course look forward to the day when we could do that. And, of course, that only happened with hybridomas a few years later on. What I did was to reformulate Burnet's marvelous intuition into a much more rigorous form where, with its roots in the genetic determination of protein sequences, were really quit clear - and it's stood up pretty well. It did also embrace how you would have to account for tolerance, for there being a different reactivity of cells during prenatal life and maybe later on, there's still a big debate going on about how much of that is cell pruning and how much of that is anergy of the responding cells and I don't take sides on that debate. I just presented them as options during the early definition of the theory. I will make one other remark, though, in retrospection on that story. I now have the feeling that Occam's razor is not applicable to cellular immunology; but then I had been very loathe to multiply any of these entities, so I only talked about one or two kinds of cells. And I guess nature has been much more profligate than that.

Hyde: At the time you were working in that ...

Lederberg: Just barely being distinguished at that point.

Hyde: Did you continue at Stanford on these experiments?

Lederberg: No I didn't do any more immunology after that, I felt it was in good hands with Gus Nossal and I made my shot at it with that one experiment, shortly before I went to Stanford. At Stanford I was eager to see this as part of the repertoire and it was one reason that one of the first people I recruited in the department was Len Herzenberg, because he in some ways has carried on that tradition, although it's flowered in many other directions.

Hyde: Tell me about Stanford, one of the interesting facets of that period is that you became quite interested in computers.

Lederberg: Yeah, let me first remark the main reason I went to Stanford is that I wanted a more biochemical cast to the research that I was doing. I had, after all, started working on E.

coli because of DNA transfer in the pneumococcus. And yet in E. coli, I felt quite frustrated with the tools and methods available. There wasn't very much you could do with DNA as such. It was only a little later on that we learned how to do transduction - how to induce competence in E. coli, but we didn't know how to do that then. Arthur Kornberg was organizing a Department of Biochemistry. It was really Arthur who recruited me to join the faculty there. So, I reorganized my laboratory toward much more chemically oriented activities. I would have been very happy to have joined Arthur's department, but it worked out as well - the mission of establishing genetics as part of the ideology and that the curriculum in a Medical School was best done by having a separate department. And that was the other attraction of going to Stanford.

While I was there, I had the chance to rekindle my interest in computers. This is something that had started quite a while before. I mentioned the American Institute Science Laboratory, when I was just 16. This was established in what was then one of the IBM sales buildings, on Fifth Avenue - just in the shadow of the Empire State Building. They had contributed the space and Westinghouse had contributed some of the funds and the equipment. Among the other accoutrements were what were then the computers of the day. And these were, I guess you would have to say, elegant card-sorting machines. I was very much impressed when somebody showed me how you could calculate the square root of a number by punching the number out on one punch card, putting it into this machine -- chew up probably hundreds of cards in the process because the only intermediate memory that these machines had were punch cards themselves-and end up with the square root. Just the whole notion that one could do sophisticated calculations on an electrical machine of that sort. It was a notch beyond the desk calculators - the Marchant calculators-- which were the nearest that we had to that. And I was interested in it as being a sort of a step toward intelligent behavior on the part of a machine. I looked for and failed to find any excuses to use that kind of hardware in my own research, except to keep catalogs of my strains or things of that sort. But the seeds to that were started right then and there. In the early '50s, I visited it again. Fred Gruenberger was on the Wisconsin campus and there was a new generation. This time of plug board program calculators. And so I learned how those operated. And this was a notch more sophisticated. There were some relays as intermediate memory and you could program it through plug board. I may be one of the last people extant who remembers how to do that. [laughter] Not remembers how, but can remember that he had done it. But it was still too clumsy and too limited to see how one would carry it further. That was the early '50s. Early '60s, I'm at Stanford, computers have come much further. There is now the Statistics department providing computer service for the entire campus. There is a single mainframe with batch processing so that anybody who wanted to could come in there. FORTRAN had recently been invented, okay, something like modern-day computing had arrived; I took the programming course to sort of familiarize myself with where they were today. First the 701 and then the 7090 machine came aboard. The 7090 was the magnificent electronic brain that served the entire Stanford campus. It was somewhat inferior to a 286 Intel-chip PC in its overall performance. But here it was, the machine serving everybody serially. You programmed it by punching cards, submitting your own deck of cards that would then be put into the pile and then when the machine got around to them, it would eat them up and execute your program. And then give you a printout - maybe a new set of cards. Usually an error flag saying "tilt" - you made a mistake, there was a compiling error and you'd better go back and fix it. And with about a 12-hour turnaround time between submitting something and

getting back some sort of answer. So you really tried to think very hard before you submitted your program. And I thought, oh well, if you really thought enough about it, you wouldn't have to worry about "bugs," and of course, it doesn't work that way. [laughter] The "bugs" predominate. You get a very humble sense about having machine instructions and doing what you say and not what you mean. You learn about precision of algorithms. You learn about the organization of programs, about segregation of tasks of the subroutines, calling procedures from various places, how data can be invoked at various times, and so on. It's a very valuable set of concepts in seeing how a system can be made to work - how it is put together and how the parts articulate and how mistakes propagate from one part to another. I think anyone who does biology ought to have that understanding of how this very primitive kind of device operates. [change tapes] These had the advantage that these were still relatively simple machines. I think the 7090 was as complex a machine as I could ever hope to have mastered from the point of view of its fundamental design. Today, there's so much on one chip that not many people would claim to go even that deeply - unless you were a professional specialist on that one function alone. So I did get a sense of how these operate as well at the operational level of how you program - machine-level, assembly-language-level programming as well as the compilers. We didn't have scripts, of course we didn't have the very high level mouse interfaces that we have today, but which also isolate the user from what's going on inside. To this day, I prefer Unix.- to Windows.-based systems because I can still program effectively with C language and so on in a Unix. base. If I have to put it into a Windows. environment, I'd have to spend another six months learning what you'd need to do for that purpose. I'd have to just use the packages that other people deliver and that always makes me uncomfortable if I can't do it myself. Anyhow, back to the early '60s. I began to get a healthy respect for what these machines could accomplish at this point. While they still have very limited memory (32,000 words store); they had no disk space; they had tapes if you had data input, but you couldn't use them very well for intermediate storage during a procedure. It was just enough that you could do some fairly complicated things with it and I began to fantasize how one might try to divert some of the growing field of what was called "Artificial Intelligence" away from playing chess and checkers, which was the predominant interest at the time, into solving real intellectual challenge in a scientific milieu. And just about that time, I had begun working on what later became the Viking Mars Lander project, working with NASA (National Aeronautics and Space Administration) on design of experiments for planetary investigation on the biological side. I had organized the instrumentation group to develop prototypes for that purpose in the Genetics Department. Got Elliott Levinthal to come in and help to run it and became very interested in mass spectrometry as the chemical device for that kind of analysis. And thought the only way that we could ever really get full utilization of that kind of information was to integrate the mass spectrometer on the one hand with the mass chromatograph, so that you have some separation of components from natural sources and so we can put it all under computer control. So, I think we were the first lab to actually build an integrated, computer-driven, GC MS complex and some of that was commercialized a little later on by Finnegan and then much more elaborate things developed a little later on. So we were doing very tangible, computational analysis for the particular purposes, but I began to dream about going beyond collecting the data to interpreting the data and that's where I felt the A.I. aspects of computation might come into play. In '64, I met Ed Feigenbaum. Came down to a seminar on the Stanford campus and I think it was '65 that he joined the faculty. Meantime, I began putting together the skeleton of what programs would look like for the interpretation of mass spectra. And that meant doing some modest amount of

mathematical, topological work on chemical graphs, i.e., the representation of the organic molecules as connection tables and this is trivial until you get to the symmetries and you can look at all the different ways that the same molecule can be presented to you and there is some entity, which is the minimum representation of that molecule. And that's what's the chemical graph is. We developed a scheme of algorithmic generation of chemical structures and the nomenclature that went along with it using very good, solid, mid-nineteenth-century mathematics, which - for reasons still mysterious to me - had never before then been applied to this arena and began to see how one could start putting together algorithms on the one hand for the generation of candidate molecular structures and the very beginning of how one would look at the interpretation of the spectra. But, I very quickly found that I was getting beyond my depth in the details of the kind of programming that would be involved. And I very luckily met Ed Feigenbaum, who had had a very good background in that regard, and was kind of looking for a good arena in which apply his skills. So we got together and started joint project called "DENDRAL" and have had a lot of fun with it over quite a few years and it ended up being first complex, expert system. I won't say we invented it as much as discovered it because we weren't sure exactly which direction we were going to go in exploring how to get effective ways to use the computer to solve these problems. I think it was a success; we had a lot of people working on it. There's a very comprehensive review that was published as a retrospection that I did a couple of years ago and maybe you want to take a look at that and anyone who wants more details can have them to read at their heart's content. There's a little book that came out of it as well. [Showed picture of report] I think the important message of that is that Expert Systems can work, but also they're very difficult to build and that the process of knowledge transfer from the brain into the machine really is the stumbling block at this stage. It took many person-years of effort to accumulate the few thousand rules, which are embraced about chemical behavior and if there's one principle that I'd like to have my name attached to, Lederberg's principle is that machines will become really smart only when 1) they can directly read the literature and 2) spend some time living in the real world where the survival of the fittest is what will determine who's out there. As long as we have to spoon-feed them datum by datum, they're going to be moving in a very cumbersome and costly way, indeed. I think this kind of arena of development - I won't say it has stalled, there are enormous applications being made of it - but there's not that much innovation in it. It looks today pretty much like it did 15 years ago. Sort of recycling the same basic notions. I think the stalling point is how to get the knowledge. I'm not sure that there are very good ideas about it, but I also don't thing there's enough effort being given to dealing with that interface - how to read the literature. If you look at bibliographic retrieval systems, I think you'd have to say, too, they're pretty much stuck where they were 15 to 20 years ago. There are beautiful implementations of them, but not much by way of exciting new ideas being laid on. We have so much enormous amplification of computer power that the point of stall is in how to develop this kind of smarter software to be able to exploit it.

Hyde: Tell me a little bit about some of the other work that you were doing during the Stanford years. You were there for almost 20 years.

Lederberg: That's right. I've mentioned my research program. We did look at a number of aspects of DNA transfer in Bacillus subtilis. We were among the first to show - this seems like a very elementary point - that you can fractionate the DNA, and that DNA of different melting points, for example, had different biological activities. We ended up a little work later

on in using restriction fragments as means of that separation. But we made some strategic errors and I think my insistence on concentrating on an autonomous, free-living organism, namely the bacterium, was probably a strategic error. I had not wanted to look at viruses as the primary target - although I had done a lot of work with viruses - because I felt they were always living inside of a bacterium and you really, de facto, would be studying virus-bacterium complexes. That's proven to be a wrong judgment. I mean the statement is perfectly true, but the way viruses behave is sufficiently autonomous that you can forget about the cellular host most of the time. You mustn't forget it all of the time and I think there are some mistakes by thinking you're dealing with a free-living organism. But that meant I was always dealing with systems of unutterably greater complexity than our tools were good at. So, for example, quite early we were trying to splice DNA from Bacillus subtilis using various tricks to get DNA from different sources; chemically joined and put them back into the cells, and see if we could reconstruct the genome. That would have been the forerunner of today's gene technology. But we had very insensitive assay methods. The only method of any consequence that we were using was to show that you had artifactually generated linkages between markers that were otherwise unlinked. It's a very inefficient procedure. And so Stan Cohen really had it all over us when he was doing very similar kinds of experiments using a plasmid where the of activity is reconstituting its biological activity by repairing a circle - it's already enough, and so on and so forth. So, he just had much sharper insight into what the appropriate methodology was and I remember very vividly meeting him in the parking lot out in front of the Medical School and his telling me the experiments he had just concocted and my saying, "Well, there's five years' work down the drain, you did it so much better than we had." [laughter] [This was] largely out of choice of the experimental system that was involved. But I'll just give you some flavor of some of the things that we were into. So, I can't say that we made any really world-shaking contributions. We were part of the texture of the development of the field, but in terms of my own laboratory work, there were a few items of some significant interest. A. T. Ganesan found an association of replication of subtilis DNA with the bacterial cell membrane, which had not been recognized before. A few things of that sort. There were little bits and pieces; there were no major edifices that I can point to out of our molecular biology. I did become interested in the applications of these insights toward some broader issues of environmental evaluation. I thought we needed much more mechanistic approaches to the examination of environmental toxicity, of mutagenesis/carcinogenesis and so forth. Tried to develop a more explicit rationale. But in the meantime, Bruce Ames developed the set of assays for which he's become very well known and I guess those have taken center stage in that field. I had a small episode in which I was (and am) concerned that some rather banal materials, like chlorine can be demonstrated to be mutagenic and we did this in a B. subtilis system and began to be puzzled about why some things would generate very great excitement and others would be ignored in trying to get these kinds of assessments. So, I began to think more and more in policy terms, not just the scientific work per se. I also became very deeply involved in school affairs, much more than my title would have indicated. I was on the Executive Committee of the Medical School. I was very much concerned about medical education and about how to put an academic medical center together, so I was, informally, a very close advisor to all of our Deans. I remember Bob Glaser with a special affection. One thing I'm particularly proud of is: I am one of the founders of the Human Biology curriculum for undergraduates at Stanford. Together with a number of people, Don Kennedy, David Hamburg, Norman Kretchmer, Sandy Dornbush, we came to the conclusion that undergraduate education didn't give enough choices. Students

interested in science could become premature graduate students in one scientific area and they would be the darlings of the Chemistry Department or the Biology Department, the PreMeds were sort of barely tolerated and these were not the broader scientists we were concerned about. If you took a liberal arts degree, you'd be almost devoid of science. We wanted to have some concept of Liberal Education with a scientific bent. That's really what the Human Biology curriculum was intended to be and became eventually a resounding success. We put together an interdisciplinary program. The focus was the understanding of the human organism-biological, evolutionary, behavioral perspective and how that would also relate to what the disciplines of the social sciences would have offer. The really serious task was the faculty being able to get together - the geneticist talking to the economists and their conceptions about the nature of the human being and trying to find some synthesis from them. But our students enjoyed it very much. It's been very popular, I think one could say that it's been a resounding success and it's impossible to replicate it in any other campus-the way the disciplines are organized. Craig Heller, who was later on one of the directors of program, has now been extending this curricula concept to the middle schools, where it might become the dominant way of teaching science at an even more influential age in human development. Human sexuality was a not unimportant aspect of the teaching that was involved here and, needless to say, that was probably the most popular course on the campus.

Hyde: Your academic background at Stanford and some of those interests laid a good foundation for your tenure at Rockefeller. Can you talk about making the transition from Stanford to being the President of Rockefeller and perhaps some of the challenges and accomplishments?

Lederberg: Any number of people were kind of surprised that I had jumped from what seemed like a junior administrative role as the head of a department to being the President of the university. People who thought that don't know how much goes on informally in the councils of an institution. I had no ambitions about being an academic administrator. I thought of myself as a scientist and an educator. But the Rockefeller is a place that is just really quite special. And I felt, and quite authentically, that this would be the one job in the country where one could have a position of leadership at a significant academic research institution and still stay close to the scientific content. The domain of interest of the University does not exceed my own. There was nothing going on on the campus that I couldn't get quite excited and quite interested in and be willing to extend myself to learn in some depth. I'll put high energy physics aside. That was something I don't have comparable pretensions to - one of my failings - I never got that deeply into it. Didn't have the intellectual apparatus for it. But the organization of the Rockefeller University also meant there were no layers of authority. The President deals directly with professors, who are heads of laboratories. We don't have departments and schools in between. So, when I dealt with this , even on purely administrative matters, I would be talking to the professor about his or her own sphere of concern. And, it was both interesting and important to me that I have a pretty good idea about what work they were doing as well as the other administrative nitty gritty. I also felt very fortunate that I came here knowing that I would have the support of Rod Nichols, who had been here a few years before with Fred Seitz and who was my executive vice president and dealt with a great many of the more purely administrative affairs, although I would say he and I were alter egos in many in many respects. I always felt that any decision he made was always with my full blessing and understanding and vice versa. I made a

cardinal rule that I was not going to pass the buck to somebody else - especially not for difficult problems. The responsibility did finally have to rest in my own hands. My major aspiration for university was, in fact, a very conservative one. I had been deeply imbued with the concepts behind the Rockefeller Institute for Medical Research. I didn't need to be told more about the glorious traditions that there were behind it. I had already read the histories of the University. There's a fictional history called Arrowsmith [Sinclair Lewis] that I also knew about (deKruif's accounts of it), but also the sheer weight of scientific accomplishment that comes from this place was something I was very much impressed with. And, of course, Avery was outstanding in that regard, Wendell Stanley and many, many others. So, I felt my mission was to be sure that there was a strategy, a sense of focus - that it would be consistent with those traditions; that there be a reason that there is a Rockefeller University - maybe change that, a Rockefeller Institute. That one could see the logical rationale for why such an institution was necessary. And I thought there had been a few experiments - just the second law of thermodynamics - that there had been a certain amount of diffusion; that things simply had happened, not always under such clear direction and sense of purpose, and I was going to be sure there was that consistency. So, tightening up the ship from that point of view, that we had a clear cut ideology - that we were a biomedical research institution; that our appointments would be just those and only the ones that would further those objectives, that would sustain the collegiality of the place - that we made appointments for a functional purpose and not just because someone happened to be at a certain stage of their career. It is, in a very serious way, put the institution first, make it a place that would be very happy for those few individuals who had really earned the right to be here by their accomplishment, their effort, their diligence, their integrity. That they would never dream of going any place else. And it's not just a collection of individuals to find ways in which once could be sure that they were mutually supportive of one another, maintained a high degree of mutual intellectual stimulation. I wanted it to be a fun place for me to be-and it's intellectual leadership. So, those were my aspirations. I went a certain distance - not everything worked perfectly. You run into all the usual problems. Most things could have been fixed if we had more money. You have to make due with what you have -- the other historical legacies. But, I'm proud of the tenure that I had. It didn't make a huge splash because it is so conservative. I felt that the underlying traditions of the University were so important that they were very much worth that. Embarking from that platform, the institution can continue to go forward and remain a rather unique place.

Hyde: Had you not been forced to relinquish that presidency because of mandatory retirement age, would you have liked to continue?

Lederberg: Well, I'm not sure I had the utmost wisdom on planning that. I guess, when I first came here [1978] in my mid-fifties-I was 53 at the time. I thought 65 was a pretty advanced age and I wouldn't be thinking much about that at that stage [laughter]. As I got there, I found there's plenty of life after that point. And in retrospect, it might have been even better if I had relinquished the job one or two years earlier. I think twelve years in a very considerable period of time. The job becomes rather routine after a certain stage. You can't give it the same life and vitality year after year and you accomplish a certain set of things -- maybe that becomes a good time to think of stepping down. So, quite the contrary, I think eight or ten years is a very ample and appropriate term in that kind of a role and just be sure that there is provision to really go on further from that. I've been very happy to have been the

President, I'm very happy to have the role of President Emeritus, and, more importantly, having been able to continue to be a professor here.

Hyde: [Can't understand question]

Lederberg: No, I ? others will have different views of the matter? but I knew I could not do justice to my lab work if I was really spending most of my time and energy to my primary responsibility as President, and I put it in that order. It's difficult enough, even without incumbency, for me to provide the time and energy that my lab deserves by way of direction. There were a lot of other things that I've gotten involved in. So, for my own personal decision, I felt that it was not fair to any lab that I would have had to run. I also didn't want to be in competition for resources with other people on the faculty. I wanted to be certain that there would never be any question about my fair-handedness. It's necessary, it's built in, there's no way to avoid some ambiguity about. If the "boss" is also running a lab, are the people in that lab really on par with whatever else is going on in the institution. It can be done, people have handled that very effectively and I would recommend it for people who go into it for a shorter term. I think if it's going to be three-four-five years, then, of course you have to maintain that continuity. It takes heroic effort to rebuild it afterwards. So, there are plenty of personal motives to want to be able to continue, but it's a very stressful situation, especially from the point of view of the lab. Like a Chief Executive also trying to stay "hands on." I also felt "hands-on" could refer to the science; I could stay in touch with the scientific activity of the whole institution without having had my own lab. And I'll make another, somewhat confessional point. I remarked about coming to Stanford in order to take a more biochemical approach to my genetic research. I've also remarked that, it was okay, but in some respects, my own outcome there did not meet my own expectations during that period of time. There are a lot of exceptions to it, but by and large, I might have hoped for more. And I realize that a part of it was that during that epoch and through the late sixties and early seventies, to do molecular biology required a convergence of methods, of apparatus, of tools, and of reagents. You could really only do it well if you had a fairly large staff. You couldn't buy most of the things you wanted off the shelf. And I think the big turning point on that that dramatizes it, is PCR [polymerase chain reaction]. Without that and what it represents and the commercial availability of any number of reagents, it was very difficult to break into it on the kind of scale of activity, which is my own mitier. I don't like large groups. I want them small enough that I can stay in close, personal contact with the work - with no more that six or eight or nine people all-together. It's just not feasible to do the kinds of things that I would have wanted to do in the early seventies. I'd have to go around begging on my hands and knees to Arthur [Kornberg] and his colleagues for the scraps of material that would be needed. And that works in a special case, but it's very difficult to do that on a day-to-day basis. So, I was kind of ready to put my lab work aside. I was not in sync with the capabilities. When I retired in 1990, that picture had been transformed. I can't say where I could have anticipated that or not, I certainly would have hoped for it. And it again became possible for a small laboratory to really dip in. You could buy the reagents-the polynucleotide synthesizers were there on a commercial basis. You could buy most of the enzymes that you need. That's totally transformed it. So now, with a quite modest and quite small group, you could still operate until we are in sync with the times-that we're not hopelessly behind every other laboratory in the things we try to do.

Hyde: Is this the reputation ???

Lederberg: Well, it's a matter of taste. I really think brains are the most important ingredients to scientific work. I don't think brains and big science mix that well. So, I tended to think of its most creative aspects of being [???] [Missing something? Jumps right into discussion about copies of tape]

Hyde: ?tried to follow the tape, but you can't play it in a VCR [laughter]. Right?

Lederberg: If you could give me two things, which would be another master at that level, a VHS format, maybe three or four copies of the latter. I'll put the master into our archives and I'll use VHS. Who's ever going to see this as far as you're concerned? I have no problem with it, but I'm just curious.

Hyde: We're going to use this for immediate purposes for our general meeting in May. We'd like to make up the tape, I believe that I told you with Ira Baldwin, Larry ??, and you [unintelligle]

Lederberg: So, there will be a couple of occasions where it will be projected.

Hyde: It will be shown at the exhibit of the ASM Archive at the general meeting

Lederberg: To whom are you going to send copies of the tape, if anyone?

Hyde: Let's not plan to send copies to anyone in particular at the moment until ???? we don't want to [break again?rolling?believe that this discussion about use of tape was meant to be fill during change of tape. However, it was a rough entry into this next question.]

Hyde: The atmosphere that you'd like to see in your laboratory, which you personally feel is most conducive to scientific exploration and discovery. Could we talk a little bit about the work that you are doing now in the laboratory, which you laid aside for the administrative mantle and got back into the scientific exploration..?

Lederberg: Let me first pick up a little bit about your first question about the context of doing science. Scientists have to be "schizoid" in some way. They have to be able to sustain some contradictions in their personality and in the way they do things. I've already mentioned one of them. In order to get you have to give away - in a very clear sense. You want to be competitive and generous at the same time. You have to put yourself out as an individual-not only satisfy your own ego, but in order to have the resources and capability of doing the scientific work-and you recognize that you're part of the community. At an even deeper level and a little closer to the cognitive realm, the effective scientist - the really creative one - is the person who one minute can be fantasizing with no restraints, imagining all kinds of things-blue sky-and the next can be his or her own harshest self-critic in saying "Look, this is what reality is really like: A,B,C,D, and G are not going to work. Well maybe F survived and that's what worth considering." But, to be able to have a lot of fluency in scanning a wide range of fantastic notions-things that had never been done before - which probably aren't going to work and give them a little bit of attention and then have a critical

regard for how to discard them. If there's any essential ingredient to scientific creativity, I think that's where it would be. So, this is random mutation and natural selection, if you like. [laughter] I would like to help in teaching that concept, that it's this disinhibition with respect to the enunciation of our ideas and relentless and unabashed criticism a little bit later on. And I hope I can take it as well as I can give it on both sides. Now, to come more particularly to work I've finally focused on in my own laboratory. So much has been said about the structure of DNA as a primary sequence of nucleotides and almost all of molecular genetics is predicated on that. The whole concept of the genome project - let's get out the sequence and that's the whole secret. In fact, DNA and the cell has a shape. It has a secondary and tertiary structure. A lot of people have been recognizing that. It's been understood this played a very significant role in modulation for transcription. As you get chromosomes in Eukaroytes, you have higher order structures where you have quite some complexity. We don't know very much about that in prokaryote cell, but even there, there are hints that they are maybe 50 or 60 domains because if you look at how many x-ray breaks it takes in order to totally relax the DNA, you get that kind of a number. So, there is some degree of intranuclear organization of the DNA with respect to supercoiling domains at least. And, I've been wondering about the intersection of that degree of order in chromosome structure with problems of mutagenesis and of evolution. Because issues like transcriptional induction and environmental signals do feed into the secondary structure of DNA, it can be a way in which the environment and evolution become entangled in ways that don't fit the narrower neoDarwinian paradigm. Now, that's easier stated than demonstrated and we have had great difficulty in getting a clear outcome of - a phenomenological outcome - in our experiments with E. coli. We've attempted to introduce them to a peak -- some time ??? experiments on effect of preinduction of lac operon [lactose operon] on mutagenesis in the lac operon. I have to say after a lot of work with quite ambiguous results, we still don't understand exactly what's going on. So, we're continuing to pursue that line. So, anyhow, it the implications of secondary structure for mutagenesis and how, in turn, that feeds into physiological state and external signaling to genetic change, which is our primary focus. [aside]Oh, why not?? I'm just speculating about how much to go with this stage of our work. We're particularly intrigued with the idea that there's an intermediate activated state, which is universal in mutagenesis. Whenever you introduce a chemical change in DNA, it virtually has to be on just one strand. It's almost impossible to have appropriate complementary changes simultaneously on both DNA strands at the same time. How would you do it? So, if you're creating thymine-dimer with ultraviolet light or if you nicked the DNA or deaminate it with cytosine or you alkylate a base, whenever that happens, it's going to be on one strand. I call that an unstable intermediate because the cell has evolved dozens, if not hundreds - I guess dozens for sure - of enzymatic mechanisms for the prowling around, looking for those mismatched/mispaired constructs and trying to do something about them. Usually it finds them and repairs them or have some other kind of repair mechanism. So, it's unstable in that regard-in the context of the cell. That intermediate state has two possible fates: It can either revert back to the original ground state or it can be converted into a stabilized DNA with an altered double-helix. The latter would be the mutational result, the former we call DNA repair. What needs to be emphasized is that - and by working it you note this very well -- repair is what happens 90 to 99 percent of the time. So, it's only the rare exceptions from the intermediate state to go on to give you a new product? All this is familiar. A rather new notion -- though a couple of people have articulated some form of it - is that even that intermediate state may have a phenotype. The fact that it's unstable, the fact that it may be short lived doesn't prevent it, for example, from

being transcribed. And so, even before mutation is fixated, and before it may with 90 to 99 percent probability be reverted, it has a chance of being tested by the environment. And that, again, under certain conditions, could be predicted to influenced, thus, does it become fixed or does it revert. So, we're more actively investigating whether that's really for sure whether this actually happens in a less-than-contrived situation. So, it may have some bearing of the role of different environmental states on exactly which repertoire of mutations are the final outcome of mutagenic treatment. My colleague David Thaleris an assistant professor here and has been doing most of the work that I've just been describing. He has also been interested in different chemistries of DNA-like backbones and he's just published a couple of papers in which either RNA patches on the one hand or ??? analogs on the other -can be introduced into DNA in vivo and showing that you can get information transferred from those constructs but often with high mutability. Have some interest in the implications of the latter let's say for questions of toxicity of antisense, constructs which I think need to be looked at very, very carefully or the natural occurrence of RNA patches, which we do see as, for example, residual ???? fragment thing DNA replication, which are particularly prominent in mitochondrial DNA and in fragment DNA under certain circumstances. So, there's a common thread here of what might be called nonstandard structures and/or nonstandard confirmations of the DNA and how they intersect with mutagenesis. That's our current pattern of research activity.

Hyde: Could be Cairns's type of mutation????.

Lederberg: It could be one interpretation of Cairns's notion. Now, the idea that the cell has the wit to know which mutations to undergo in the first place, I think is unacceptable. But, there might be intermediate states that are then tested to see whether they're going to become mutant or not-could be, in fact, a very direct interpretation of some of those results. We're looking very particularly at that.

Hyde: Do you often or have you thought about the using the amount of knowledge that we've gained ?life form?has really taught us so much ?microorganisms have come into their own?vehicles for understanding basic life processes.

Lederberg: I've always looked on bacteria being wonderful experimental prototypes for processes that are universal in their application. One has to be a little bit careful. [change battery here] [believe the following was a side conversation thinking that the tape was not rolling]?TVs and all the rest. We'll be back to the libraries, we'll be back to consumer choice on what you can get hold of. And so all the wonderful visual media are just now becoming available?] We were talking about the world of the microbe, the microcosm and how it is a prototype of biology at large. Now, Jacques Monod used to say that what's true of the E. coli is true of the elephant and it's not precisely right, but so what? Everything you learn about E. coli is helpful in understanding the elephant. Eventually you'll have to look at elephants as well. But considering the experiments you can do with billions of E. coli and I don't think you want to have billions of elephants running around as part of the laboratory activity [laughter]. So, I think the advantages are obvious. I spent most of my scientific life working on that premise that the study of bacteria is experimentally so convenient, so focused, simpler objects, smaller genomes, made many mistakes ??to not get even smaller ones most of the time. As the objects of inquiry and then you end up with experimental possibilities that become enormously more costly and more difficult. They eventually do have

to be applied to human tissues and human beings. When you get to the human being, of course, there are a very limited range of actual experiments that you can do and when you actually do have one that involves a live human, there has to be enormous background of prior work to give you the assurances of safety and of utility. As you're going to have to have introduced first. I'd like reinculcate the sense of wonders of the microbial world and, besides its own intrinsic interest about what it has to offer about the rest of life. When people talk about biodiversity, they have to look at this at the level of the microbe as well as well as that of the forest tree????

Hyde: Another aspect of your career stemming out of your scientific expertise -- when you've been asked to be a consultant for social and governmental activities. Can you tell me a little bit about your forays into the arena of the interface of science and public policy and what you've been involved in and what you've found most interesting and challenging about that and perhaps the role of the scientist in setting public policy.

Lederberg: I have for a long time been very much concerned about trying to introduce the best of scientific thinking into public policy concerns and public policy debates. I guess I'm at the very tail end of the generation of -while I was not involved - I was very much influenced by the physicists, the development of nuclear weapons, and their concern that they were not given enough input in the management of these terrible artifacts. People like Leo Szilard and Aaron Novick were folks who had an important influence on me quite early in my career. So, I guess arms control one of the first areas I did become actively involved in. This reached a climax in 1970 when I was asked to be an advisor to the United States Government in the Arms Control Disarmament Agency and I was consultant to our delegation in Geneva during the negotiation of the Biological Weapons convention. I also found that when I could offer a very cogent, scientific arguments about how some of the language of the treaty that the diplomats had put together didn't make too much sense and were going to cause difficulties in implementation, that we'd better leave well enough alone - that to revise anything would have required ten more years of negotiation and just be thankful that you've got what you've got - so I can't say I'm always eternally happy about the final draftsmanship of things that had been largely left in the hands of people not very skilled in the science, but the basic thrust, of course, was one to rejoice in - that there was by international recognition a repudiation of these kinds of weapons and a rejection of one of the most terrible things that could happen, which would be the habit of using germs as ways of expressing you anger and of trying to settle a conflict. I can't think of a greater catastrophe for the human race and loss of civility- the possibility of civil order if this ever got out of hand because, unfortunately, as every microbiologist knows, all too easy to do. So I continued to put a very large part of my policy-directed efforts in this general sphere. They have broadened a little bit-other aspects of arms control and national security policy. One of the activities that I was involved in at Stanford together with Sid Drell and Pete Panofsky and then later on Bill Perry was the Center for International Security and Arms Control, which was both a graduate research center and an undergraduate curriculum. Originally I taught the BW-arms control aspect of it, but I became a totally integrated member of the group and after twenty-five years of study I guess I can argue about other issues in that sphere as well. I've always felt that scientists had a very deep obligation to really make a study of the problem, not just go off half-cocked and I've tried to understand clinical science and social science and economic perspectives and I think that I dabbled in it evenly from the scientific perspective. I've made a very strong effort

to do that over a long period of time. I've served on the Defense Science Board for quite a while and again mostly from point of view of trying to see about rational policy in our armed forces, but the place that I had the major impact I think is in defense against biological weaponry and most recently have been most gratified because there's eventually been a response to the questions of organizing a robust civil defense against such attacks, particularly on the part of terrorists. This didn't have very high credibility until the AUM Shinrikyo incident in Tokyo, but had really taught a lesson about what we might be up against and the kinds of things we have to be prepared for. So, it may seem a far cry, but I spend a day or so a month down at Quantico, Virginia with the US Marine Corps and helping them out in organizing their training for a special cadre of troops who will be trained, equipped, disciplined, exercised, have the right mobility and logistics and communications to be ready to go on short notice in the event of an emergency. The shame is we haven't had such courses until now, so I feel there is a growing recognition that we need emergency response capabilities. I work very closely with Dr. Frank Young, an old-time member of the [AMS] society and former Commissioner of FDA, now an Admiral in the US Public Health Service. And, he is the leading civilian officer in charge of emergency preparedness for the Public Health Service. I've helped to cross-wire the liaison between civilian and military in other policy authorities in trying to deal with those kinds of problems. The other aspects of science policy I've been most concerned about have to do with a certain number of environmental issues. The last four or five years I've been trying to alert the world to what every microbiologist knows very well and that is: We not conquered microbial disease. There are a lot of old familiars and a lot of new faces coming along in emerging infections and trying to get some degree of awareness and preparedness. For example, for a recurrence of the 1918-1919 flu, which is the greatest plague of modern times and one which will certainly recur and one which we're very poorly equipped to respond to on a kind of time scale that will be necessary if we're to deal appropriately with it. So that's been a multifaceted activity. Gail Cassell is the President of the Society and someone I've worked very closely with on those matters and I'd say between that and the BW problems, about two-thirds of the time I spend in Washington and the like is on those kinds of policy matters. There are other aspects of science policy. I was Chairman of the Technology Assessment Advisory Council for some time. This was outside civilian group advising the OTA [Office of Technology Assessment]. Lamentable that it was taken down. I've been as much concerned about process, about substance - I don't insist on my own views as being paramount. I do insist that good authentic contact with range of opinion throughout the scientific community is absolutely essential if there is to be wise policy. And that doesn't always go with the political grain to operate in that fashion. Political leaders look to counting votes, and then do they attempt to try to get the best ideas and the best political judgments about the kinds of policies and legislation they want to get after. I co-chaired the Carnegie Commission on Science, Technology, and Government, which was a very broad consideration of process -- of the relationship of scientific expertise to every branch of government. We got quite a long ways in reforms within the executive branch. We were able to collaborate with some very important progressive forces within the judiciary. If I mention names, Steve Breyer, who is now on the Supreme Court, he was a very active coalition member from the Judiciary in some of those efforts - about trying to find better ways in which scientific knowledge could be part of judicial analysis. I've mentioned the OTA and I guess you have to say the very unfortunate record of final dissolution of that - very much against any of our recommendations -- and I know we're going to try and regroup and try to figure if there's some way to reconstitute that

kind of advisory activity for congress. That gives you some sort of outline of the things I've been involved in. I hop around Washington like a bumblebee moving pollen from one flower to another. The problems of turf, of different agencies - I find the bureaucracies organized so ridly -- are immense and it takes a few people who have been around for a little while and can communicate information and inspiration and exasperation from one place to another. I've been very glad to have been able to make some contribution in that direction -- mostly in the service of a process of openness and insight and access to and from scientific information and policy formation.

Hyde: Can you tell me what percentage of your research has been publicly funded?

Lederberg: Almost all of my research has been publicly funded, except for the most recent period. When I was at Wisconsin and at Stanford, the NIH and then on the instrumental side NASA provided almost all of it. Getting started again as a novice, which is how I was viewed in 1990, I was very lucky to have a couple of Foundations who have known my record over a period of time providing that support. The younger people in my lab have been trying very hard to get NIH grants and they've fared just about as well as most in that predicament and that's not very well under current funding circumstances.

Hyde: ???And it looks like it's going to get worse.

Lederberg: I'm afraid so, there's a real imbalance between kind of talent that we have-very worthy of getting that kind of funding and the level recognition about what the social gain would be of meeting it. I don't think we're overproducing scholars, I think we're under funding our activity and I think the country will lose a great deal by discouraging these youngsters and others won't even try as a result. It's terrible! So we have to do a better job of making a case and I do spend whatever time I can on that as well.

Hyde: On the scientific front, is there one issue that you could pick out as perhaps the most challenging, the most significant, the one with the most potential impact for the future that you would identify as something that we should be all concerned about?

Lederberg: Well, there's a lot of activity going on for almost all of the programs that one sees some concern about. We know that heart disease is the major cause of death in the United States, but I'd be had put to say that there's proportionately an under emphasis on cardiovascular research-it's making very great progress. It would profit by more investment, but no differently than almost any other field. Cancer is in some sense proportionality over invested, but in absolute terms we can use every bit we've got. There are ways in which it can be done better. When we confront something like AIDS, I would go along with everything that the Presidential committee said about how, again, the texture of it. And that very often the basic message is: "Don't be so impatient, you have to lay the groundwork, you have to get the scientific foundations first. There aren't going to be any easy solutions unless they're wrong ones." That's something that's very hard to get mission-oriented agencies to do. So, I have more concern about process than I do about choice of areas. I've already mentioned the quantitative aspects and the worst element of process-there are youngsters who can't get funded. When they do get funded, they are hounded too much. They're put under too much pressure to perform. They've signed a contract to make a discovery and that's an

oxymoron to begin with. You ought to identify the best people, look at their projects, but not because the projects are worthy, but to the extent that they tell you something about the individual and leave them alone. Give them the encouragement that they want and need and don't hound them with having to come back for renewals every two or three years. I'm really more concerned about those (issues) than particular subjects in research. That having been said, I think it's perfectly obvious that infectious disease research is relatively grossly under funded. A lot of what there is goes to one disease - it's worthy, certainly - it's AIDS. But it is out of proportion. We're paying the price for this in what we don't know about how to deal with tuberculosis. We have disease of the Third World, which we've shamefully turned our backs on to a very large degree. That there's still malaria in the world is a scandal, and yet it's the world's most common disease at this time. So, in terms of applied activities, I think the grossest discrepancies really are in this very end. And that's the most important contribution of basic science. The derivatives of that are really filling the edifice of knowledge and then eventually the technological application. If you don't have that critical culture to being with, none of this is possible and you just go off in tangents in several directions.

Hyde: Uh huh. Exactly. One of the things that we're working with at ASM is the study at the University of Chicago Academy of Science - a couple of years ago???? [sounded like a break in the tape-seems like a jump]

Lederberg: I'm trying to get away from the word and against the concept that ?we'll it's hard to and write examination papers as you know [laughter].

I'm quite happy with these tapes. We could go on for a lot more detail and where would ever be the end of it - and you have very good sample.

Hyde: There's so much to talk about and it's very hard to hone down, but I feel we're got a good ?I can't thank you enough for.

Lederberg: I thank you. [Break in action - switch to DNA]

Lederberg: DNA, this is the prop that I used for that.

Hyde: No, sure, that's good.

Lederberg: We'll if you could splice this in. When I'm talking about confirmation, secondary structure, and just have some of this writhing and supercoiling.

Technician: You've got your microphone off. Okay, I'm ready now.

Lederberg: Okay, I want to say something about the secondary structure and confirmation of DNA. All of us are quire familiar with the primary structure and the double-helix, which is the first element of secondary structure. Here we have the molecular model of that. I was delighted to have Alex Rich show me in some detail exactly what the right bond angles are and to put it together in a coherent way-it has some resemblance to reality. It's an exercise that I recommend to everybody. Don't just let the computer do it for you on the screen - actually build this yourself if you want to have the hands-on feel for just what's involved

with in getting this structure as Watson and Crick did in 1953. But DNA can go into much more contortions than is hinted by this crystalline kind of structure from which you can get x-ray diffraction patterns and so forth. And that's what I mean by confirmation. Here is a much grosser model out of a couple copper wires and it does have the flexibility that DNA can be bent, twisted, and uncoiled and overcoiled and there are many other dimensions of structure that can be imposed on DNA when we get to the very large complexes that you find in chromosomes of bioorganisms. It's the relationship between changes in conformation - open vs. closed structures and so on -- and mutagenesis, which is what we're concentrating our laboratory work on at the present time.

Technician: I want you to take that up again. I just want you to bend it like you were doing before.

Lederberg: Well, I'm putting DNA through some contortions that will give you some idea of what it can do by entering into different conformation. These are some of the levels of coiling and one can go through two or three orders of coiling beyond this one before one gets to the complexity of what we have in the chromatin of the organized chromosome in a higher organism. When we are down to the DNA level itself, some of the most important conformational changes have to do with supercoiling, either negative - the opening up the structure, or positive - of tightening it up in that fashion. It is the relationships between changes in conformation within the cell in different physiological states and accessibility of DNA to mutagenesis, which is the primary focus of laboratory at this time. I was quite surprised?[Sound turned off-just show DNA.] end of tap