My name is David Schlessinger, and I'm a senior investigator in the Laboratory of Genetics and Genomics at the National Institute on Aging. I have an auxiliary title now of distinguished -- NIH distinguished investigator.

I was born in September 20th, 1936 in Toronto, Canada. My family had immigrated from a small town in Eastern Poland in 1929, just after the crash. At that time, immigration to the states was already essentially closed, and so we went to Canada through Halifax. And when my family became citizens there, we moved across to Chicago in 1939, where we already had some family.

The -- there was a significant moment in October '42 when I was just becoming conscious. And the second World War had reached its low point. The Germans were at Stalingrad, the -- Europe had fallen out of North Africa, the campaign hadn't begun. And my oldest brother, who was a model for me, and 12 years older, had just entered the University of Chicago. He spent a quarter there intensely interested in science, and then resigned to enter the army, as many people did at the time. So, both the social significance of that, and the intense interest that he had shown in science, were part of my model for my later career.

My mother came from a moderately bourgeois family from a small town in Poland, Czechenov [spelled phonetically] and had been able to go to the gymnasium. She -- my father instead was already encountering the racial laws that limited the formal education of Jews in the schools to a few years. He had taught himself English, reading -- both reading and writing. He was a tailor in a women's coat and suit factory. My mother had had the model of Madame Curie, and she believed from the start that science was the root to liberty, and liberty from ignorance and want. And she had wanted to be a scientist, but that was thwarted by circumstance. So, she was also an influence on the children. Both my brothers and I, and our sister as well were -- started in Chemistry and were interested from the start in science. Both that may be genetic, but it was certainly environmental.

It was an interesting time for that. The Chicago school system that I was in felt that the best thing they could do was to get people through grade school as soon as possible, if they were serious students. And as a result, people tended to skip grades. This was socially difficult, but, of course, it made everything go much faster so, that I ended up with my own laboratory at age 25. The high school was quite another matter. Chicago had a strange self-selective system, so students could go to any public high school. They would come from all over the city. And the south side, they would go to South Shore, near the University of Chicago. And the north side, they would go to Roosevelt High School, which was where I attended. There were a lot of peers, fair number of nerds, and an extraordinary faculty. Because the people who were teaching, and especially women, had been through the Depression when it was extremely difficult to go on to advanced education, or to education at all, and very difficult for women to find jobs at universities. So, as examples, Ruth Bannister [spelled phonetically] our physics teacher, was the daughter of the chief associate at Rutherford in the neutron work; a brilliant woman teaching physics at our high school. Ellen Wheelock [spelled phonetically], who was the direct descendant of Eleazar [sic] Wheelock, founder of Dartmouth, taught us economics as science. We had remarkable teachers, and that was a great help in trying -- and so, the result was that I had a very good preparation when I later came to the University of Chicago. And that was notable for giving me many opportunities there.

The only biology course I ever had was a traditional botany and zoology course. And in fact, that's the only formal biology course I have ever had. I learned it as an adjunct to chemistry. Chemistry was a great love at the time. When I was in high school, biology was sort of messy preparations and observational work, natural history, which was interesting, but certainly wouldn't be described as analytical science at the time. Of course, that changed sharply at the time I was entering college. They -- I [laughs] could go on for -- The model, the DNA model appeared June 6th of 1953. The University of Chicago had a unique educational system at the time. Jim Watson went through there, so did Matt Methelson [spelled phonetically], my other mentor during my graduate career. They were among many scientists who were trained there. It was a kind of bridge system between the Oxbridge system of tutorials, and the usual American system of teaching. There were no textbooks, only original documents and papers. There were no lectures. Everything was done by discussions with high level of staff, professors who would lead small roundtables of students and get them to fight over all kinds of issues. So, the system was also one in which you took extensive exams when you arrived at the university. And if you placed out, if you were good enough at these exams, you were freed from taking those courses. In fact, theoretically, if you placed out of all the 13 required they simply handed you a degree. So, because my preparation had been so good, I placed out of a large faction of these courses. And so, I could double major in chemistry and in literature. I did my honors thesis on a comparison of Shakespeare's "Antony and Cleopatra," and Dryden's treatments of the same topic, all for love. But I could also finish really the advance courses in thermodynamics, and inorganic and organic chemistry. So, I essentially had finished the curriculum in science and math by the time I entered graduate school.

Well, the inclinations were in chemistry was in part because I had the examples of my oldest brother who ended up going through medical school, which was the requirement of the army. And did boards, and neurology, and psychiatry before becoming a psychoanalyst. And so, he was a constant example, where he would try and continuously introduce analytical principles. And was one of the founders of the chance to verify psychoanalysis, by re-interviewing former patients. My other brother got a PhD in physical chemistry. And I had among other jobs that I had to work my way through school, I typed his theses [laughs] in advance physical chemistry. So, I got a birth -- birthing there too, in terms of information. It's hard to know why you would like one thing rather than another. I mean, if a man likes a certain kind of dog, then that's the kind of dog he likes. And I was drawn to chemistry for those reasons. I entered the University of Chicago at 16, and again, socially rather unprepared but intellectually interested in everything going on.

I came in the fall of 1953, when the -- I mean, the Watson/Crick paper was already in the syllabus for the science courses.

It didn't make an impact at first. I should point out that at the time the first biochemistry textbooks were being written. And a typical statement in them about DNA would be, "A boring polymer of repeated units, four repeated units." So, it took some time for the model to have its full impact. The -- my introduction to science, to biochemistry and then later to molecular biology, the term for which was only coined during my graduate work. Was that I had -- it was possible at that time to work your way through college. I had a tuition scholarship, and then we

were allowed to work 20 hours a week. I took two jobs, I simply just didn't tell one about the other, so I could work fully. And that made it possible for me to live on campus and participate in all the activities. The -- among the jobs I had were mainly things like vacuuming all the books in the major library. But, a friend of mine who was much more savvy then I told me that you could actually work in a laboratory. And so, this was the laboratory of Eugene Goalhouser [spelled phonetically], and I entered that lab as a technician in my third year, that would be 1955, toward the end of the school year. And I did the first purification steps for erythropoietin. And within days I knew that this was it. I should point out that in chemistry I had been drawn most to physical chemistry, and I continued to be interested in that until now. But I didn't have enough capacity to use mathematics originally to tackle the projects I wanted to do. For example, there is in chemistry something called a, "Triple Point," where a compound can exist in three different states. And I was interested in what happened if you added two component system. Would that give you a line, rather than a point? And how could you predict it? There wasn't even a theory of water at the time, so that wasn't going to happen for me. And instead, the alternative was organic chemistry, which at that time predates physical organic chemistry considering molecular orbitals and things like that. It was simply memorization. There was a book with 560 name reactions. A mercury catalyst at 300 degrees for two and a half hours; it was agony. And instead, suddenly I was doing some of the first column chromatography. The "D.A. Cellulose" that had just been published, and we were getting purified fractions of erythropoietin. Of course, a purification factor was perhaps 10 to the fourth with the steps I used. No one knew you had 10 to the seventh, which Eugene Goalhouser finally achieved, and later cloned the gene for it. But at any rate, that was a revelation, that you could actually do work in what was a new field still, analytical biochemistry. And do something that might be of interest and useful for humanity. They -- and so that started me on my way. I was still a chemistry major. And so, when I finished, and I was going to graduate school, I looked around and applied to a few places, one of which was at Harvard. Jim Watson had just gotten there, in the fall of '56 after several years in the wilderness. At the -- actually, the dessert, literally in Pasadena at Caltech, and was starting his laboratory. He had a couple of fine research associates, Alfred Tessier [spelled phonetically] whom I worked with. Innerance Frieze [spelled phonetically], and his wife, Elizabeth [spelled phonetically], who were doing some of the first mutagenesis studies to analyze parts of the code by looking at phage mutations. And there were a couple of other graduate students, and me. Jim had the most interesting ideas of the people I talked to. And so, I entered his lab in the fall of 1957 when I got to Harvard.

Well, you've encapsulated some of it. Jim was not an experimentalist. His final experiments, I still remember he was doing an experiment labeling the ends of transfer RNA to see if they turn over in relation to protein synthesis. And he came to the point where he had to run samples in the ultracentrifuge. This was late at night, and he came to me, to have me show him how to put the tops on the tubes accurately, so that he could do a run. He was not adept, but he had enormous intuition. He's always seemed to know what would be the most important questions coming up, and which of those were mature. So, when I went around looking, at the time very few schools, incidentally, had departments of biochemistry. Harvard had just organized a committee on biochemistry, which had the number of luminaries as the faculty. And Jim was one of those. He suggested an experiment which followed up a famous experiment at the time of Meselson and Stahl, the experiment that showed that DNA replicates semi-conservatively. And it was possible to imagine a comparable experiment for RNA, to ask whether RNA and

ribosomes, which were just being discovered, would show comparable conservation. That was the origin of a good deal of my later work, and I really took on that experiment and -- as part of my thesis work. But Jim was always there. The setup at Harvard was quite amusing when thinking back to it. The biology labs, biological laboratories on the main campus at Harvard, not far from the yard are fronted by two large statues of rhinoceri, which I thought were symbolic of the university to a considerable extent, including the stuck-up noses. The environment was strange, because molecular biology was just beginning, and was named during the time that I was a student. It was not popular. Most of the faculty were traditional biologists, whom Jim referred to as, "Stamp collectors." And the laboratories themselves were just over the rhinoceri on the floor above. And we had a lot -- two large experimental rooms with a very large office between them, which was Jim's office. And the major goal was already stated. He had an old-fashioned ultra-violet desk lamp with the large bulbs, fluorescent for him. And taped across it was a small piece of paper saying, "DNA—arrow—RNA—arrow—protein." And that set up the lab for quite a number of years. But he's continued to, of course, to be intuitive in motivating Cold Spring Harbor to turn to viral genetics, and then to move into neurobiology, and so on.

My first work as an individual on my own was a paper that did the first attempt to see whether the structure of ribosomes was determined by the RNA or by some features of the proteins. And it used what was available at the time, a physical-chemical technique for looking at the degree of Hydrogen bonding across the RNA. I showed that it was the same in isolated RNA and then the ribosomes, and that suggested that the ribosomal RNA might be the basis of the structure. Ribosomes had been seen, and Alfred Tessier was beginning to work on them and show that the 70S large particle dissociated into two subunits of 30 and 50S. And I, coming from my physical chemistry background, wanted to apply some connotation. So, I did the first analysis using classical techniques of diffusion and intrinsic viscosity, and sedimentation to get several estimates of the molecular weights of ribosomes. I made the first large-scale preparations of 30S and 50S subunits by general centrifugation, at that time, and measured their molecular weights and the percentage of RNA in protein. Those turn out, fortunately, to coincide with what's done now, by adding up all of the molecular weights of the components. And so, that was another one of the projects. I started the Transfer Experiment. This experiment to look at whether ribosomes were conserved by a Cesium-Chloride method where you grew bacteria in a light medium and transferred them to a heavy medium. The same that had been done by Meselson and Stahl, except that you needed more of a difference in the densities for RNA, which is smaller than DNA. Part of that experiment had been done at Caltech by Rick Davern, a graduate student of Matt Methelson, part of the preparative controls. And I had done the other half. So, we flipped a coin and I went out to Caltech to do the experiment. It took another four years after I got my degree to finish that experiment. There were a lot of technical problems. So, during my time at Caltech, the experiment failed. But, it was a very interesting place led by Max Delbrück, a well-known physicist, well-known prize-winner. And a German guy [unintelligible] in his attitude in the lab. And -- but I also met my wife. She was one of the few women at Caltech, working in the -- working actually on a project on ribosomes in the plant -- in the plant facility. She had her background in plant physiology that time with a masters from Cornell. And she was both lovely and attractive and personable, and therefore very popular. I think she was intrigued by the fact that I thought I didn't have a chance. And so, I was rather distant at first. But we did have a couple of dates. When I went back to Boston we continued to write, and I was much better in letters than I was in person, I think. And so, later she came and did some more graduate work at

MIT. And we were married, and have been married since 1960, with two wonderful daughters and six terrific grandkids. The -- and Alice, my wife, interrupted her scientific work until the -- our daughters were both in school. And has done everything, freeing me to be the one who concentrated more on the lab.

Probably the most influential thing that I did as a graduate student was to develop the first invitro system that could actually make some little bits of protein. And the -- that turned out to be the system that was later used by Nuremberg and others, in the cracking of the code. And we just optimized lots of, again, physical chemistry. Turns out that things like optimization of the magnesium level was critical for -- to get anything done outside of cells.

Alfred was a Swiss, and he had had a double life at Cambridge, England, working in the group of Kalen on mitochondria. With the sour experience of trying to isolate sub particles that were uniform from mitochondria. This has been suggested by several people, who can remain nameless, at the time. But they didn't exist, they were just fragments of membrane-bound material. And he was also one of the top climbing groups, mountain climbing groups, in the Hillary group. He was on all of the expeditions up to the Everest one, because there he was -- had come to Cambridge to work with Jim. He was a terrific experimentalist, and quite careful. Very good teacher, and very good at developing techniques. So, he was excellent for me, and we worked very well together. We worked closely together for years. He then went back to Switzerland and ran the molecular biology institute there for many years with a long and distinguished career. His mountain climbing essentially stopped at the time he got married, while we were -- while I was a graduate student. He thought it was too dangerous. He went on a final expedition to one of the big peaks in the Andes, and that was it. The -- so, he was a remarkable character, with a very dry sense of humor. He actually was in the labs in Paris when I was a post-doc there, for a while before he actually went back finally to Switzerland. I saw him again there.

There were different strands to molecular biology. During my graduate work, The Journal of Molecular Biology had started, and it's published sporadically. Jim would come through, again, late at night, and see whether anybody had finished something -- so, he could pull together some articles for another issue. Hard to believe now. The -- but there were schools. A biochemical school based primarily on purification and enzymology, which had been partially German, and transferred to the states with the flight of scientists at the beginning of the war, second World War. And then, there was a British tradition of structure with x-ray crystallography and so on, simplifying things a bit. And there was a French tradition, which was Claude Bernard, and Pasteur in physiology. And also, genetics. That was really the major source of genetics, I think, for the development of most molecular biology. And so, I was involved more in the French school at that point, then in the biochemistry school.

Well, the Pasteur was an extraordinary place. French science, like everything in France, operates by trying to develop a cadre of the highest quality at the special schools--The Polytechnique and so on in Paris--and then, not worrying about the rest of the country. But they draw on their very best for there. And so, it was not only Jacque Monod, and François Jacob, and Andre Lwoff, and Pierre Chefa [spelled phonetically], and Ellie Volnon [spelled phonetically]. It was a lineup of impressive people, all very original, very interesting. There would be a daily lunch that

everybody would attend in a kind of greenhouse as part of the Pasteur Institute. With a long table with the luminaries, the important people at the center, and then drifting out to the post-docs and students off at the edge. And the conversations were fascinating, the French are so highly intellectual in these circles. There could be long discussions of the use of the comma, as well as scientific issues. Jacque was a very impressive person. He was -- he had the fine Gallic features, and the personality and wit that you associate with French, stereotypically. And he led the way, he was often the major person. I could say that you -- there was a certain self-confidence which approached arrogance. He, for example, typically there'd be visitors giving seminars, and Monod would almost always say in the discussions afterwards, after the visitor was gone, [speaks French]. "He did all the work, but he understood nothing." And then, he would explain the significance of that person's work. In my own case, being in Paris was terrific. Alice and I had our honeymoon on the ship going over, and I still think that Paris is the best place in the world to be if you're young. And it's not so bad if you're old. But the laboratory experience was mixed, because essentially, I accomplished almost nothing while I was there. I had been -- come there supposedly to work on the physical chemistry of beta-galactosidase, which was a large molecule about which nothing was known. It had been studied genetically, and so I was supposed to do that. Instead, Monod knew that I had done this invitro system. And he wanted to use it to prove the messenger RNA hypothesis that was in the air at the time. He and Jacob were writing a review, which I proofread at the time. And -- on messenger RNA, and the idea that they would program the ribosomes. So, the notion -- the experiment that he wanted me to do was to take a population of messenger RNA, extract it from cells making huge levels of the enzyme, and supply it to a protein synthesis system from the cell that deleted the gene. And show that I could make beta-galactosidase. I didn't think the system was up to it. And unfortunately, I was right. It was very difficult to get messenger RNA as the size of beta-galactosidase intact. And they have a lot of structure, so that the ribosomes can't get past the beginning if you have a finished RNA. In vivo, of course, the ribosomes are adding as the message is being made, and so there's no problem. So, it took two years to show that the experiment had not worked. I told Monod that I preferred to work on what I'd come for, and he said, "It's my laboratory-- you'll do what I say when you're here." The -- and the -- it looked as if the experiment had worked, but I kept doing controls because I was suspicious of the fact that the counts were relatively low for incorporated radioactive amino acids. And it turned out to be adventitious binding to the enzyme. The enzyme was highly purified by a bunch of steps including columns. And then, immuno-precipitation, and washing the immuno-precipitates, adventitious binding still hung on. So, I did some other work on the side while I was there. But the actual work I -- my major work there produced nothing valuable at the time. Still, we had a great time, and I moved from there then to St. Louis with great anticipation.

Well, the -- I took at it as a game. I had managed a few experiments on the side that gave me [laughs] some publications during the period. And I shouldn't underestimate the idealism and the impressive teachings of Monod. I think I've been too critical in describing him. For example, shortly before I left, he asked me to speak with him, and he asked me what I was thinking of doing. And at the time, I decided I've always been interested in starting something new. And that will be evidenced from looking at the course of what I've done. It's always more interesting to start out something, and the others are usually better at doing the continuations than I am, anyway. And so, I thought I would start on something that hadn't been done, and that would be the structure of membranes. Membranes had not been studied at all, it was considered that they

were, sort of, framework into which other proteins would sit in these lipid -- lipid-protein backbone membrane. But nothing was known really. And so, I thought I would attack that problem. And I told Monod that, and he said, "Well," he said, "That sounds interesting." He said, "I suggest that it's wise to take a problem on for your lifetime that you think may exceed your capacity to complete it. And then, if you finish it, you have tremendous satisfaction. But if you don't, you know that at least you've worked on what you wanted to, and you probably made significant progress." The -- and I valued that enormously, as an opinion. The -- so, when I came to St. Louis, to Washington University, I set out to work on membranes. And the experiments were quite difficult. They involved running columns in which -- in soap, or detergents of different types, and with very few markers for what might be in the membrane. And a little spectroscope for looking in cytochromes, and some other things that would be there. But I kept finding that my preparations were filled with RNA. And so, inevitably, I looked back at that, and it turned out what they -- what was bound to the membranes were polyribosomes. So, that was the first observation of actual polyribosomes from the bacteria. Normally the polyribosomes get cleaved and degraded to single ribosomes, which is all anyone had ever seen previously. So, there was the notion of polyribosomes, but these were the actual things. So, I thought, "Fate has told me that I should be working on ribosomes." [laughs] And so, I went back to that. Fortunately, the membrane problem was not ready for a solution at that point.

The Department of Microbiology in St. Louis -- Washington University had been a real center for many reasons, including the fact that they had no nepotism rule. So, that Colin [spelled phonetically] and Gerty Cori could both be on the faculty there and not in very many other places. So, they had a strong biochemistry department, excellent chemistry department. Dave Lipkin the -- who was the chemical discoverer of cyclic A and B. Many other -- Rita Levy Montalcini, Vector Hugger [spelled phonetically] in the biology department. And there was a network of colleges, which was very nurturing and terrific. The microbiology department, had been the start department run by Arthur Kornberg with all of his remarkable associates. And they had just moved en masse to a new building that was constructed for them at Stanford, so the department was empty. And Herman Eisen the immunologist of note, who later went to MIT took on the department as department head. And he went around looking for young people. He actually came to Paris to interview Clyde Wilson, who was another post-doc there at the time at the Pasteur. Clyde later went back to Berkeley and spent his career there. But we met, and later I went to look at a job at Berkeley to -- as a possible possibility. I must say that going to Paris was quite naïve in those days. The idea of going to work in a foreign country without any idea of how one might find work later in the states never occurred to us. We were simply interested in the science, and as it turned out, Berkeley had the virus laboratory, run by Wendell Stanley, a rather Eisenhower-like figure, very avuncular. And had some wonderful people, Gunther Stent, Arthur Perdie [spelled phonetically], Howard Jacqueman [spelled phonetically]. And so, they were looking for a young faculty member. And they invited me to come to visit.

So, the -- I see this in retrospect as watching the history of molecular biology unfold as a student and looking at all these higher ups and their achievements. So, it was an impressive lineup of faculty, but it was a strange setup. Where I would have been the only young assistant professor, and I knew what that meant. Lots of committee work, and the telephone problem, and the parking problem, lots of teaching, and so on.

And it was also an odd circumstance. I had grown up and been interested in quite intellectual circles, with a lot of discussion of science and art, and so on. There was a big party there, and the topics of discussion were brands of scotch, football, and cars, about none of which I knew anything. So, I was really sort of turned off by that; on the other hand, it was wonderful setup. But on the way back, Herman Eisen had heard that I was going to Berkeley and invited me to stop. And this was now in April, and --

What year?

I guess it would have been '62. And the [laughs] contrast to the ideal climate, flourishing with flowers and beauty everywhere in Berkeley, it was a rainy, miserable, cold early spring day in St. Louis. But St. Louis was quite different. Especially with the departure of the Kornberg group, they were interested in having someone young in molecular biology. It was a new department, starting out, again. And so, I took that job, and derived there in August of 1962 with my wife and our little first daughter, who was a little baby at the time, and spent 35 years there.

Well, of course I've continued to be interested in it. At the time, I was writing bad plays. And the clencher for me was that I was fluid, and I could get people on and off the stage. But I wasn't good at character development. I just didn't feel I had anything really original to say. Furthermore, I thought, "Well, if I go on in science, anyone can contribute something in science. Whereas in literature, you have to be really quite special." And in any case, I can do it on the side. Okay. Of course, any real profession is consuming, but we -- my wife and I both had interests. Especially in theater over the many years. And my brothers and I, my sister, all shared that. That we were all editors on the high school newspaper, and I was the editor of The Chicago Marron, so we had a journalistic aspect that was appealing. My wife was in the first class at Performing Arts, the school with in New York, and was the only one in her class who turned to science as her preference. She doesn't want to spend her life in casting offices and lines. And so, it's been an advocation, rather than a -- rather than a serious interest. I can't say that I've done anything significant.

The -- I think, in retrospect, I was very dubious about my capacity to be an independent investigator. No one knows whether they can cut mustard. And I thought that -- I tried this membrane stuff, and then went back to ribosomes. And so, my interest was in trying to figure out what -- how ribosomes actually worked, and how that fitted into the paradigm of the intervention of DNA, into the cytoplasm of cells. So, I had a scientific goal that carried me through. And because I was in a medical school, I also turned towards the relationship between that and infectious diseases. I had a lot of contact with the infectious disease group, led by Gerald Medoff. Gerry Medoff [spelled phonetically], an old friend. And the -- so, my work on ribosomes turned first to the formulation of the ribosome cycle in protein synthesis. And the -- that was based on the hypothesis that once the 70S ribosome was formed, it was not permanently the same, but, would periodically dissociate into the subunits, which would go into a pool and be re-recruited into various 70S ribosomes on messenger RNA's. That was the model. We did a lot to establish that model. And at the same time, again in part because of the environment at a medical school, we worked a lot on antibiotics many of which were -- act on the level of ribosomes. We defined stages and protein synthesis on the ribosome initiation, and so on. And then, were able to classify antibiotics at the point at which they worked. For example, one of the

most interesting was streptomycin. That class of antibiotics blocks at a step-in initiation, which we specified exactly which points it would occur at. With one of my colleagues -- my post-docs at the time, and also a colleague Lucio Luzzatto. And it freezes the ribosomes into a dead form. And they can't continue, and gradually the ribosomes are depleted. That's why the cells die with that sidle antibiotic. So, there was a lot of work on why some antibiotics kill, and others just block growth. We extended that to anti-fungal antibiotics, which we did a great deal of work. So, there was a good deal going on that continued the ribosome work in St. Louis. Later, we extended it to mammalian ribosomes. Along the way we defined the steps in the synthesis of ribosomes. We found the first of the RNA processing enzymes, RNA's three in bacteria and E. coli. That's an enzyme which had been known to cut double-stranded RNA's, and we showed that it also cut double-stranded regions within otherwise single-stranded RNA's. And the base pairing principal has remained involved in nearly all processing steps they're analyzing. But, the -- that enabled it to start with the huge precursor of the ribosome RNA bacteria. Cut it up, and then there are further steps that are involved. We did the same thing in the mammalian ribosomes. And showed the large precursor and the steps in which it's progressively cut to form the final product. We did a lot of work on turnover, and what might be the mechanisms of breakdown of message, and of ribosomes. So, it's centered on that through a period of decades, up until about 1985. And that was the time when there was a big transition in the work.

At that time, and perhaps still, there were two kinds of graduate departments. Some, usually at state schools, or larger schools would have enormous numbers of students. And then, there were schools like Columbia or Washington University, which had small graduate programs of highly talented students, but in small numbers. So, over the years I had relatively few graduate students, but they were all terrific. And so, the lab ran mainly on my own hands [laughs] and post-docs. And science has always been international. There were people who were appealed to by the work, and came from many places, and I benefited enormously as any scientist does from these colleagues. Over the years, I've certainly had well over 300 fellows, and a very large fraction of them are -- have had real careers of -- and some of them of real note. The -- and that's part of the satisfaction of the work, of course. The science is always so international -- actually, it's a step back for the Transfer Experiment, where we needed heavy media for ribosomes. We needed to have pure cert C13 for the experiment at Caltech, in order to make C13CO2, which we fed to yeast. We broke open the yeast, and that gave us amino -- radioactive amino acids to feed bacteria, and also to make them heavy. Linus Pauling was a connection. Went to the academy in Russia, where they had a production of pure C13. And we got C13, which we could use for the experiment. This is in the depths of the Cold War. There were always the scientists I'd contact.

Well, the -- my own work had continued, and one of the frustrating parts of it, which was a minor element overall in the -- in the real world, but major for me, was that we wanted to look at the units of ribosomal DNA from mammalian cells, from human cells. It was too big to be cloned. And so, we couldn't get the material we wanted to start from, to look at how it would function, and whether all of it was necessary to make a ribosome, and so on. At the time, one of my colleagues, a critical college in genetics was Maynard Olson. And Maynard does not suffer fools gladly. But I had given a seminar that he'd liked, "The End Termini of Proteins in the genetics department." And what was known about them, and how difficult it was to study them, because most of them were just imagined from sequencing. We didn't really know what was

there. So, it was very difficult to discriminate between theories about how degradation or synthesis would work. So, Maynard called me one day in the hall and asked me whether I'd come to see him, and I did. And at the time, the yeast community had already established the rules for how to make an artificial chromosome in yeast. They had isolated telomeres, and centromeres, had selectable markers so you could make an artificial chromosome. In Maynard's lab, his graduate student, David Burke, and another graduate student -- with another graduate student Dan Garza [spelled phonetically]. David wanted to try to see if he could use artificial chromosomes as a cloning vector. Maynard had been uncertain about that, because David had -- Burke had another project that he should finish for his graduate work. But graduate students being what they are, they went ahead anyway. And they had made some clones, and Maynard called me to his office and said, "You know, we have this potential to make clones with yeast artificial chromosomes. We were thinking of trying to apply it to human case. We don't know anything about human DNA or human genetics. Would you be interested in working with us?" And I can still remember the words because it was something like the road to Damascus. I had this instantaneous flash where there had been some initial discussions by Renato Dulbecco and others, about whether genome could be investigated and analyzed. And I realized at the moment that this could be it. Here, I'd been struggling with clones just to get out of ribosomal DNA unit. If you could actually make large clones, it would make all the difference for trying to recreate human chromosomes outside of the cell. The analogy that I used for church groups and middle schools was that the cloning that had been available was something like dealing with an advanced jigsaw puzzle, with tens of thousands of pieces. All of which were about the same shape, and had similar color, and trying to fit it together. Whereas with big clones, it would be like a child's jigsaw puzzle. A small number would fit together to form a chromosome. So, the technology, and much of the ideas were really Maynard's. And a subsequent conversation, we came to the possibility that we could develop a center, because it would require very large-scale effort, much larger than an individual laboratory, could not muster, to try to see whether we could actually capitalize on yeast artificial chromosomes; to do maps, that is, to recreate physically chromosomes in overlapping clones outside of the cell. I should point out that the initial ideas of the Human Genome Project were not popular. There was a very large fraction of scientists who thought that this was a technical exercise, it had no hypothesis to drive it. And so, peers were appropriately skeptical. I wrote an initial grant, where we had already made some clones with the groups jointly between Maynard's and mine. And we -- I said we wanted to try to capitalize on this. It would give the two requirements of mapping, which are continuity and totality. You have to have all of it, and you don't want to have holes, gaps. And I got the worst reviews of my career. One of them was essentially one line, "This is only mapping." So, when we started out, we planned a center. And I can go into that, it had some unique features for things done in biology up to that time. But we had to do everything, we had to get resources. I told Maynard that if he would continue to do his wonderful technological advances and contribute those, I would take on the implementation of the center. This was quite a dare for me. I don't -- have never considered myself, and I just objectively think I am not charismatic. And it required things like getting funds, since the NIH was not interested yet. I called together at the faculty club at Washington University, a group of the major professors at the medical school. The chancellor, William Danforth, few other people. Especially the professor of medicine was important at that time, Dave Kipnis. Different medical schools have different dominant programs, and that was medicine at Washington University at that time. The -- and I explained what we were up to. I wanted their approval to go ahead with this initiative. And they agreed.

So, I then went to the McDonnell Foundation, and to Monsanto, the head of Monsanto research. And each of them gave me $1 million to start with. The McDonnell Foundation was headed by Old Mac, Mr. McDonnell, who had founded McDonnell. Brought in Douglas, to try to direct it away from missile, and just jet production; an interesting character in himself. He was a kind of real life Andrew Undershaft, who was the major force supporting the U.N. initiatives in the Saint Louis area. And was very interested in science generally, had set up the foundation. His wife came from a family in which there were many Hopkins physicians, and that helped too, so he was behind it. Howard Schneiderman at Monsanto could see the potential, and again contributed money. And so, we had money to start. I then had to recruit staff. I was a complete non-entity in human genetics, or any of the relevant fields. And yet, I had to be able to mount this program. So, the program had these two major unique features, which again are Maynard's thinking, largely. One was that it was clear that we needed a substantial group doing the mapping, and that we would also need -- and bioinformatics, which -- a word that hadn't been coined. But we were going to have lots of data, we would have to get together the appropriate people to analyze it and keep track of it. So, we also set up another unique feature at that time, a technical development lab. Maynard and I both agreed on that one. That we came to the same idea that the technology wasn't ready. So, we were setting out to do a Human Genome Project when there was no way to do it. And so, that would certainly require either the adaptation of new -- of techniques developed by others, or by us. And either we would stand in line trying to get help from experts who were already saturated. Or, we would have our own technical development core. And so, we went that route. Of course, both Maynard and I knew that from chemistry and physics, where large programs and technical development groups are the rule. But, it certainly was not the case in biology. And there were so many decisions that had to be made. I managed to recruit appropriate people for the positions. I found Ladeana Hillier, who was working at a -- in a lab studying the mechanics of the inner ear. And she was gifted for computer work and set up a lot of the mapping and organization of maps. Both for the nematode project for -- and for the Human Genome Project. I recruited Rick Wilson later from Caltech, where he was a graduate student with Lee Hood, maybe a post-doc with Lee Hood at that time and gave him to Bob Waterston to begin the sequencing center. And I found a whole array of people. We had lots of experimentation on techniques. Many, many steps I could describe that had to be done. But in any case, we got it started. A lot of the scut work of the endless reactions that were done to find where clones fitted in the map. We did with a series of lab work for a large number of undergraduates. They would get a recommendation for graduate school or medical school, and a temporary job. And we would have very active, lively people in the lab doing, you know, the bulk of the work. So, we had a core of technicians who were locally recruited. The -- and it was great fun. I had some terrific post-docs who took on much of it. The -- I could go on and on about the technical things we required. The major technical achievements -- advances, were from Maynard's lab; Maynard and his associates. They developed a workable pulsed-field gel electrophoresis method that enabled us to size the clones accurately, which was critical. They later developed the PCR based sequence tagged site formulation, which was the way we did the mapping. I recruited Phil Green from Boston, who had been -- who had done the genetic map that was available at the time. To have someone who could develop the theory for mapping for us, STS content mapping, which was what we used, and which worked [laughs], fortunately. The -- and so, we had a core of people. I had two spectacular post-doctoral fellows, Euna Kerri [spelled phonetically], who is now simultaneously a professor at Helsinki, and a professor at the Karolinska, and now running the human medical genetics at Kings College in London. And

Giuseppe Pallia [spelled phonetically], who later started with me the Sardinia Project as well, and did a lot of the mapping work; unfortunately, died young. And Remai Nagorage [spelled phonetically], who's been my dearest, closest associate now for almost 25 years. Anyway, we put together single-handed from huge varieties of data, a map of the X chromosome. So, there was a lot of talent that we managed to recruit, and that we put together. When we started we chose -- the X chromosome was the logical choice. Because at that point, 50 percent of the available clinical pathology was on -- genetic pathology, was on the x. Because males have one x, and it's exposed, and happens more easily. And, there was a sizeable community that were interested. The -- most of them, of course, were interested in diseases. And so, byproducts of the project were among the first genetic diseases to be cracked. First, fragile x, then Simpson-Golabi-Behmel, ectodermal dysplasia, and hidrotic. A number of these diseases were part of what my lab was doing, and some of the people at the center were doing it at the same time. So, we had this thing which I named, "The Center for Genetics and Medicine." I sold it by telling people that the sequence of the human genome, once available, would be parallel to the periodic table in chemistry. It would be the starting point for biological research for the rest of time. And that, of course, is true.

I believed it if we could do it. It was a matter of, in retrospect, enormous naivety it started out, especially with the opposition of most of the community. Once we got started, there was a meeting called by Don Fredrickson at NIH at the time, to discuss whether there could be a program, and a leader of the human genome project. I had jointly run with another of Jim's former students, Julian Fleishman [spelled phonetically]. His retirement party at Coal Spring Harbor at the time, so I knew he had time and effort available. And the discussions at the meeting obviously came to him as the logical choice if he would do it. The backup was Danny Nathans, who would have done a great job too. But Jim accepted that. He came out to St. Louis, he liked what we were doing, and that was one of the reasons why the center notion was adopted as the basis for the project. It was a natural development. The -- so at the time, everything was always unsteady. An interesting sideline, Jim told our chancellor, William Danforth, who told me this much later, that his one doubt was that I was being given a great deal of responsibility without authority. He was quite right. The medical school -- doing anything at a university made sense to me to have a center for genetics and medicine at a medical school, because those would be the people would be interested. But of course, it took a long time for genetics to penetrate into the curriculum. The curriculum was full, and no one gives up contact dollars at a medical school. I had no space, no money, no positions open. Everything had to be created on the basis of funds that were raised. And that was a constant problem. You can contrast that, for example, in the history of the project, with the development after that of the center in Baylor, where Tom Caskey had clinical practice funds, jobs. He was the head of the department, and a huge enterprise; money from the university, and so on. I had none of that.

He was a parallel career at that point, and of course, very, very impressive. He immediately was interactive with people and charismatic. And in fact, the agreement that we'd had at the -- with the Genome Institute was that we would try to do chromosomes. We took on x, and Eric Green -- with Eric, with Maynard took on chromosome seven. Similar size, and having the cystic fibrosis gene, that Eric had worked on with Maynard in the start of official chromosomes. And so, we thought that was our assignment. When Baylor started, they also wanted to work on x. And so, I was contacted by the Genome Institute to ask whether that was all right with me. And

I said, "Of course it is, we'll get there faster." [laughter] They -- so, the division of chromosomes made sense, because these were the physical elements, and the initial focus was on mapping.

Well, let's say it's a matter of asking Macy's about Gimbels. The -- because of the medical relevance implicit in the project, it made sense for it to be done at the NIH. The Department of Energy was very good at some technology developments. But, they did not have the intrinsic biological thrust or background that we naturally had, doing it at universities. And so -- and that's the way it played out. I would say that the tools they used, and the progress that they made, which were significant, were largely derivative of the ones that were developed in the -- through the NIH funding mechanisms and centers. But they did have a role to play. They were definitely very important in convincing the public. I think they had a comparable impact. They were much earlier, as I remember it, on the ethics questions for example, which were then picked up by the -- more by the NIH as well. So, it's a matter of history how it went, and I only know the part of it I know in the tale. I couldn't comment on that, we had good friends in the -- at Los Alamos. Bob Moises [spelled phonetically], who's one of their best researchers, and others who were involved. But Bob, for example, is interested more in certain features like telomers, then he was in a mapping project, per se. The -- as it turned out, the technologies were strong enough to sustain the mapping until the sequencing developed to the point where it could be handed over.

Well, to be -- to be honest, we were responsible for the -- for much of the discussion. Both technically and in the goals, and I'm very proud of that, and I don't know how much of it would be acknowledged by others. But, for example, in setting up the center, one of the things I did, was in addition to adding in the X chromosome, doing the targeted mapping projects for local individuals who could use them. We isolated the compliment complex for a top rheumatologist, John Atkinson. We isolated the 18Q cancer locus for Stan Coursemeyer [spelled phonetically] and his post-doc Ed Solon [spelled phonetically]. And so, we were not only aware of the likely relevance, we were actually functioning to try to initiate it. The -- and I think that caught the attention of everyone progressively. I -- others may have had other sources of motivation, but that was ours.

It -- the irony was quite present to me all the time, that 25 years later I was working for Jim again. [laughs] But, the critical thing was there was no one with his name and reputation who could have the impact that he did on Congress. That was critical. And on the public. This was a notable occasion, on which an obvious in retrospect. And even then, an obvious extension of his original discovery was about to be able to lead if done adequately, to the sequence of the human genome. So, that was enough. He also realized that the center set up would work. And that was quite critical. The -- and so, he fostered that. He early on caught on about the importance of ethical questions of having ELSI, and so on. And that was also important. So, everything was in place by the time he left for the continuation of the project. It was development, implementation, expansion, and so on, and then, the big turn to sequencing, that were the critical events. Early on, I might point out, that when we had the early game in town, we were doing side projects and finding clones for everybody. Including people at the University of Michigan, who found Francis's center, budding center to be unable to service them. We were getting a lot of work from other places, the X chromosome community. Contention, and envy, and people who were eager to be important are not rare in any a field, including science, and that was certainly true for the X chromosome community. For example, one of the first targets that -- there was an X

chromosome every year, and the community of people, many of whom were splendid and very interactive -- some of whom were quite selfish and self-interested. They were more interested in finding the important gene then having the gene found. The -- and so, one of the first targets was Fragile X. We were trying to find clones and distribute them to all the groups that were interested. When we got close enough, the consortium fell apart, and everybody went their own way. And so, you got several independent publications from different groups, all of whom participated in the first patent, the patent of the genome. So, in many ways it was like usual competitive science. But there was an overarching feeling that there was something bigger that was being constructed.

Well, of course, everything depended on reviews. Usually, those were very good. In the last reviewing cycle for the center -- so that would have been 1992 -- I made a significant part of our proposal based on our looking at the structure of linkage and equilibrium. And trying to get a handle on how recombination effected the -- was affected and worked with structure of the genome. And everything depended, as usual not on the extramural staff, but on the reviewers. An expert linkage of equilibrium, who can remain nameless, was on the board and said this would never work, it was far too difficult to do. So, that part of it never got off the ground. Fortunately, Eric Lander, who had a much more persuasive capacity than I started the HapMap some time later that went ahead anyway. But, we were subject to the same constraints, the same problems of reviewing that every grant has. And we all know the problems of the peer review system, and nothing better has been found. The -- so, that was our major contact with the -- with the extramural program, was being reviewed. Yeah. To be honest, we knew what we were about, and we knew what to do. We were usually setting up things that would be adopted also by others.

Of course, we were curious about it, who would lead it next. And the -- by that time, the program had momentum, and it was clear it was going to go ahead; how well, or whether it could be stymied in some way, wasn't clear. So, yes, there was uncertainty. And Francis was a wonderful choice. He's such a brilliant teacher and persuasive speaker. And he had so many credentials that were excellent. So, he was the natural choice. Of course, it's worked out very well.

I think my feeling was that everything remained in a pilot level, and that it was always important to be able to walk before you tried to run. So, that we were early enough to continue the mapping. And again, the question was when the transition point would come. All of us in the field had been dominated by the development of technology, and everything runs by Sangers rule; that anytime you get technical development that’s two to threefold or more efficient, accurate, cheaper, a whole range of experiments opens up. So, the question was, "Would these be incremental, or completely transformative?" And it turns out that simple changes, like the development of automatic loaders for capillary electro freezes were enough to start bringing the cost down and make things feasible on a large scale. Again, it was Sanger and Washington University, rather than Sanger at that point, who were making decisions for box sequencing. The real question was the point at which one decided that mapping could be dispensed with. And in the historical record, I think that's unclear. We did get to the answer, but it wasn't an obvious choice. The -- how can I put this? The -- one feature of the mapped clones that is -- that remains and has never been completely exploited, is the fact that they reproduce large sections of the

genome in a form that can be manipulated in a study. So, for example, the A.C. clones we made at the time remain the only source of a complete factor eight gene, a complete factor nine gene. These have both commercial and medical implications. And, they're only available by actually having the clones, which are still achievable in 3D yeast artificial chromosomes at this point. There's the group led by Vladimir Larionov at NCI, which does recombination-based cloning. That's got help with that as well. So, that remains something of great interest.