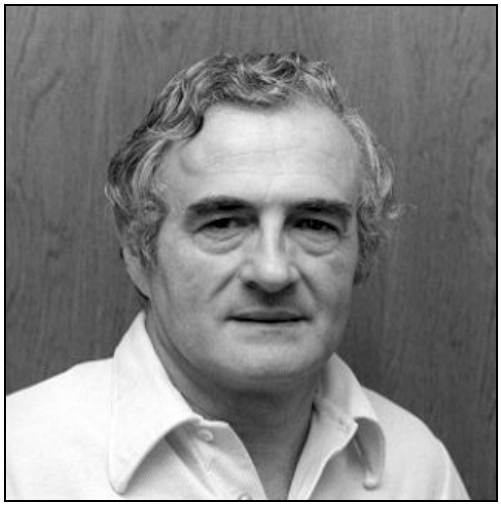

ROBERT L. SINSHEIMER
(1920–2017)

INTERVIEWED BY
SHELLEY ERWIN

May 30-31, 1990 & March 26, 1991

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Subject area

Biology, molecular biology, biophysics

Abstract

Interview in 1990 and 1991 with Dr. Robert L. Sinsheimer, who served as chairman of Caltech's Division of Biology for nine years (1968-1977) and later became chancellor of the University of California at Santa Cruz. He recalls his undergraduate education in the new biophysics program at MIT, his war work at MIT's Radiation Laboratory, and his graduate study at MIT in biophysics (PhD 1948). After a postdoc year there, he goes to Iowa State College as associate professor of biophysics; takes six-month leave in 1953 to Caltech, works on phage genetics with Max Delbrück. Joins Caltech faculty as professor of biophysics in 1957 and continues his work on isolating the virus Phi X 174; work with Arthur Kornberg of Stanford on *in vitro* synthesis of DNA. Receives California Scientist of the Year Award in 1968 and is elected that year to the National Academy of Sciences. He recalls his tenure as chair of the Biology Division, the growth of molecular biology, and his awareness of potential risks involved in the new technology of recombinant DNA. He discusses his concern over low level of public understanding of science; his involvement in the Asilomar Conference of February 1975 and creation of NIH guidelines for recombinant DNA research; and his part in initiating the Human Genome Project. In 1977, Sinsheimer left Caltech to become chancellor of UC Santa Cruz, a post

he held until 1987, when he moved to UC Santa Barbara, where he became professor emeritus in 1990 and where this interview takes place.

Administrative information

Access

The interview is unrestricted.

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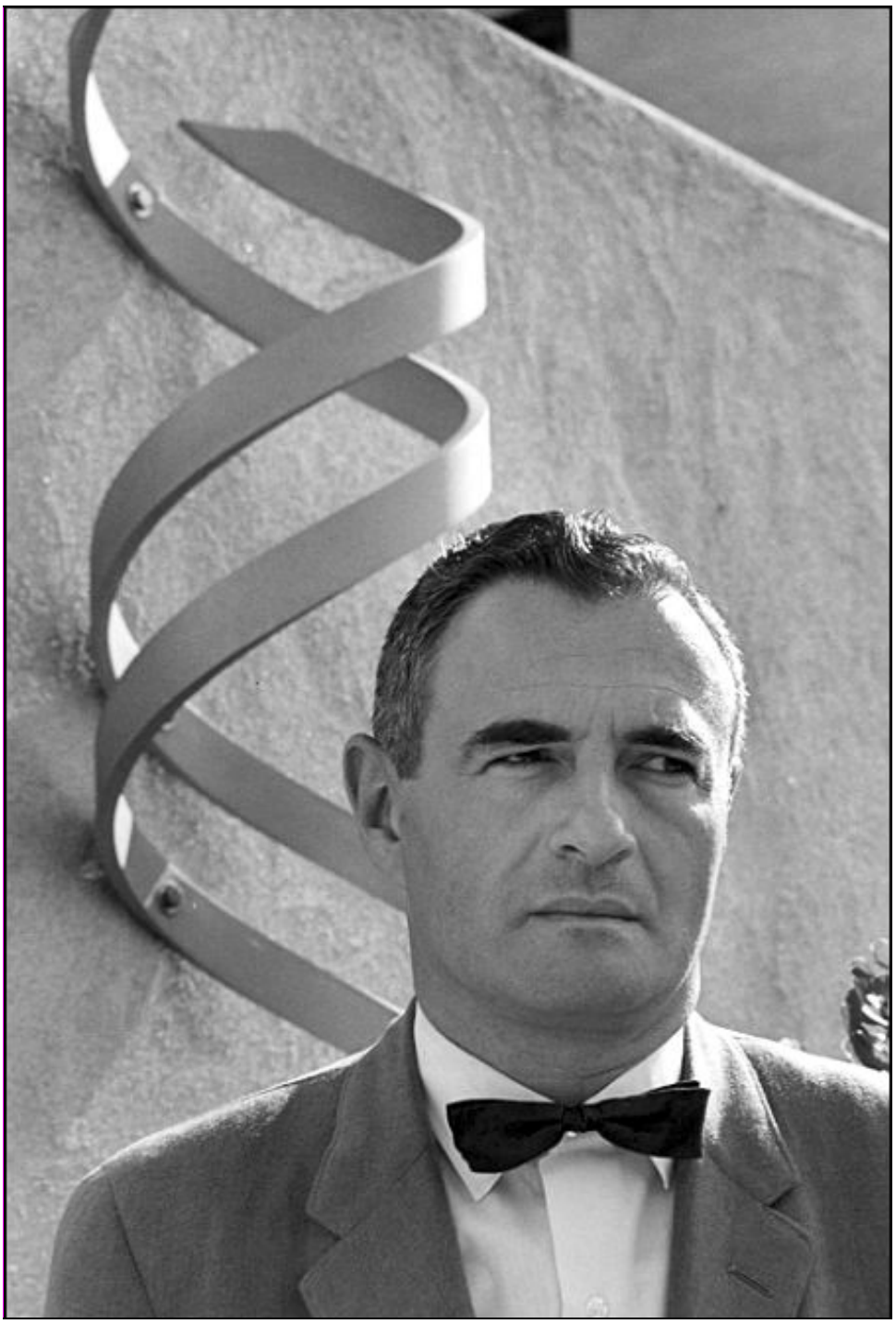

Robert Sinsheimer in May, 1967, after he and Arthur Kornberg succeeded in synthesizing DNA *in vitro*.

California Institute of Technology

Oral History Project

Interview with Robert L. Sinsheimer

by Shelley Erwin

Pasadena, California

Caltech Archives, 1992

ROBERT L. SINSHEIMER

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CALIFORNIA INSTITUTE OF TECHNOLOGY
ORAL HISTORY PROJECT

Interview with Robert L. Sinsheimer By Shelley Erwin
Santa Barbara, California

Session 1	May 30, 1990
Session 2	May 31, 1990
Session 3	March 26, 1991

Begin Tape 1, Side 1
Erwin: Could we begin by talking a little bit about your family background and how you got into science and your early education?

Sinsheimer: I grew up in Chicago. My father was at that time the editor of a trade journal. He didn't have a great deal of education. He went through grammar school, and then one year of high school, and then went to work. My mother went through a sort of secretarial high school. She was from New York. My father was pretty much a self-taught person. He did a lot of reading. They had a great deal of respect for education, and obviously they encouraged that in their children.

Erwin: So there were more children than just you.

Sinsheimer: Yes, I had two brothers. My older brother, who was six years older than I am, went to the University of Chicago and ultimately to law school.

I was always sort of interested in math and science. I'm sure I was influenced a great deal by some of the teachers in high school. I had a pretty good math teacher and an excellent chemistry teacher. In some ways we benefited because that was the depression; people couldn't get jobs, so we had some teachers who would otherwise probably have been doing something else, but they were teaching because that was the only kind of work they could get. So I thought about going into science. You know, some of these decisions, you look back and you marvel. Anyway, my mother was from New York, as I mentioned. She always retained the impression that eastern schools were better. I should say I did very well in school. I was the highest boy, anyway, in my high school class.

Erwin: It seems to me, from the chronology, that you were young when you graduated from school.

Sinsheimer: Yes, I was. I had skipped several grades. A friend of mine who was also interested in science was thinking about going to MIT.

Erwin: Had you heard of MIT?

Sinsheimer: Yes, I had heard of MIT. I didn't know a lot about it, but everybody had heard of MIT, a premiere engineering school, I guess you could say. So I applied to go there. Money was not in abundance, as you can imagine in the depression. So my father said that if I could get a scholarship, he would send me for a year. This would have been 1937. Otherwise, he didn't think he could afford it.

Well, I did get a scholarship, and so I did go. But then, there was also the question of what would be my major. Because of this teacher--McClain was his name--I was generally interested in chemistry. But my father didn't quite understand how a chemist would get a job. But MIT also had chemical engineering, and that sounded more practical. So we compromised that I would enroll in chemical engineering. But it didn't make any difference, the first year was the same for all freshmen.

Well, that was my first time away from home. MIT was a very difficult school at that time; it's changed a lot. But the motto was, MIT was "a place for men to work and not a place for boys to play." And they lived up to it, I can assure you. You really worked very hard.

Erwin: Was that a shock to your system?

Sinsheimer: Yes. I hadn't had to work very hard, actually. And here you had to work all the time as a freshman. Plus, as I say, it was the first time away from home. Yes, it was a shock. But, again, I did well. So, at the end of the first year, it was agreed that I would continue, and I would continue to get the scholarship. In those days, scholarships were awarded on merit.

Then, in the second year, you began to get some chemical engineering courses, as well as continuing basic courses. Everybody got two years of physics, two years of calculus. And I got to realizing that I didn't want to be an engineer. Well, then, what did I want to be? Physics seemed sort of attractive. But it was just at that time that MIT was completely renovating their biology curriculum. They had had a biology department a long time, but it had been essentially a service program. They had had a program in public health. You might ask, Why did they have a program in public health? Well, they had civil engineering, and somehow a subcomponent of

that was sanitation. And somewhere that developed into public health. This went back into the 1890s. It had been a very successful program. And they had had to have some biology as, really, a service course for this public health program. But by this time, by the 1930s, things had changed, and you really needed an MD if you were going to work in public health. So the program wasn't attracting very good students. So MIT reviewed the whole program at this time and decided to do away with public health. And they decided to completely revise their biology program into a program which would make some sense at MIT, which would emphasize biophysics and biochemistry.

There was a lot of publicity about that. And I had been interested in biology for some time. I know at least one thing that significantly influenced me, and that was reading this book--I think it was called *The Book of Life,* by Huxley and Wells [*The Science of Life*, by H. G. Wells, Julian Huxley,and G. P. Wells, pub. 1929--ed.] which was a fascinating book, because it was written for the public. I could understand it. I read this in high school, and it was the first time I'd read something that made me realize you could think about living processes in physical and chemical terms, not just sort of abstract, vague life, but you could really begin to analyze, as well as you could in those days. And that was fascinating to me.

Erwin: Was biophysics relatively new at that time?

Sinsheimer: Oh, yes, it was very new.

Erwin: How new?

Sinsheimer: I don't think the term was used much before the 1930s. Biochemistry went back a long ways into the nineteenth century, but I don't think biophysics as such was a recognized field until probably the thirties.

Erwin: But you're not using the term retroactively. It would have been a legitimate field in 1936.

Sinsheimer: Well, this would be '39. Yes. As part of this complete renovation of biology, they brought in a whole new faculty. One of the people they brought in was John Loofbourow. He had written probably the first major review of biophysics, which appeared in *Reviews of Modern Physics* in 1939 or '40, in which he reviewed what were then the several aspects of the field. And to my knowledge, that's the first review; the word may have been used before then.

Anyway, MIT launched this new program just at this time, and I decided to transfer into

it at the end of my sophomore year. I'm sure my father had his doubts about it, but by then I was doing so well. The program, as you might guess, had its--as a student, one didn't quite appreciate it--it had its settling-in period. There were a lot of changes in the first few years, and new people were being brought in. So it probably wasn't an ideal education, but I learned a lot. Part of this is relevant, because one of the areas that they initially concentrated on was applications of electronics. This was the period of the first electronic pH meter.

Erwin: Arnold Beckman's pH meter?

Sinsheimer: Yes. Some of the first faculty were people who were jointly in electrical engineering. Consequently, along with advanced physics courses, I also took a year of electrical engineering. I also took a course in X-ray diffraction and spectroscopy, as well as biology and chemistry.

Erwin: At what point did you feel that you had found what you wanted to do in science? When did you begin to get on the track that you stayed on?

Sinsheimer: Well, that would really be a little later, probably, because here I was still an undergraduate, exploring a lot of different things. And then, of course, everything got distracted by the war. And the question was, what should I do then?

Actually, it got resolved in a curious way. I should say that I had teamed up with John Loofbourow; I was doing research with him. And his field of interest at that time was, broadly speaking, wound healing. That is, put in simplest terms, when you cut yourself, what happens that causes it to heal. And that's a very complicated situation. So he was damaging cells, and specifically yeast cells, with ultraviolet light. And he had found, when he did that, that substances were released into the medium that accelerated the growth of other yeast cells. So that raised the question, What was the ultraviolet light doing? He had come from research in spectroscopy. But the point is, when the war broke out, he was asked to take a major position in the Radiation Laboratory that had been established in 1940, and it was the center for microwave radar development. It was a secret, but it was there at MIT. And he asked if I would go with him. And I could do that, because I did have this background in electrical engineering--I knew a lot about electric circuits and basic physics--and I was then assigned to airborne radar. I was in that for four years.

Erwin: As a civilian, though.

Sinsheimer: As a civilian. I was designing and flight-testing radar, and then I would go off to navy and army and air bases and work with the air force. It was not my major interest in life, but it was something I could do and it seemed useful.

Erwin: Did you, at that time, have any interaction with any of the people that you would later know at Caltech?

Sinsheimer: Well, Lee DuBridge was the head of the Radiation Lab. He was the chief. He was up there, and I was down here. Of course, I knew of him, because he was the director. [Robert] Bacher was there before he went to Los Alamos. And probably some of the other physicists, if I thought about it.

When the war ended, I had to make a choice again, because by then I was sort of an electronics expert, you might say, particularly on microwaves. I could have gone into the electronics industry, which was just beginning to emerge at that time. But I decided that was not what I wanted to do with my life. I wanted to be a biologist. So I went back to graduate school. Fortunately, I found money. The American Cancer Society was just getting going, and they set up a fellowship program, particularly to fund people who wanted to make this kind of transition from wartime research to biology, and I was able to get a fellowship from them that supported me in grad school.

So I went back to graduate school in biophysics. It was at that point there were some really basic decisions made, which turned out to be very fortunate. One of them was, What do you want to focus on? And I decided to focus on nucleic acids, which was not an obvious choice. Why did I choose nucleic acid? Well, partly fortuitous. I mentioned that Loofbourow had been interested in this wound-healing business. Because of that, he became interested in the effects of ultraviolet on cells. It was known that ultraviolet radiation could be mutagenic. When one obtained what we call an action spectrum, which is the effectiveness of different wavelengths, it gives you a clue as to what's absorbing radiation. That turned out to match the absorption spectrum in the ultraviolet for nucleic acids. So that was a clue--certainly not a proof, but a clue. You see, at that time, we didn't know what genes were, let alone know what the nucleic acids did.

Erwin: When was the term "genes" used? Does that go back to Mendel?

Sinsheimer: Well, Mendel didn't call them genes. I think the gene term came in early in the 1900s, 1905. Genes were rediscovered by [Walter] Sutton and [Theodor] Boveri. And there was [Thomas Hunt] Morgan's work, and so on. So the term was certainly used. But nobody knew

what they were. And, indeed, while chemicals known as nucleic acids were known, nobody had any idea what they did. But the UV action spectrum was really at that time a very suggestive link for genes having something to do with nucleic acids or vice versa.

And then the other thing, of course, was coming back after the war and knowing what had been done during the war. The famous experiment of Avery, McCarty, and McLeod showed that the so-called muta transforming factors, which behave like genes, were . . . of DNA. This was completely unexpected for a lot of reasons. Nobody had thought of genes actually being DNA, and second, nobody even thought that DNA was that complex. We were sure genes had to be complicated, and the most complex molecules that anybody knew at that time were proteins. It was generally assumed for a long time that genes had to be proteins. There was a lot of skepticism, I have to say, about the Avery experiment, of several kinds. Maybe there was some protein contamination, and secondly, maybe this was just a special case of some kind. But anyway, I was sufficiently convinced that I decided to become interested in nucleic acid. And that was a fortunate decision. And that was my graduate work.

Erwin: You said it wasn't an obvious choice. Could you perhaps give an example of what, let's say, another biophysicist might have chosen to do? What were some of the other problems?

Sinsheimer: Well, there are a lot of areas. If you were going to be tied in with biochemistry, you probably worked on proteins. Proteins were the "in" things. Proteins were enzymes, proteins had structure. And there were people working on that at that time, in X-ray diffraction, particularly in collagen, and myosin, structural proteins. They were doing studies on membrane surface structures; that was a different area of biophysics. Still another area was the whole area of electrical phenomena--nerve impulses and that whole area. Another area was electron microscopy, ultraviolet light spectroscopy. Another was the effects of radiation--high-energy radiation, ion radiation, radioactive isotopes. So there were a lot of possible choices.

My PhD thesis had two different parts. One was developing an ultraviolet microscope to be able to study the different absorption spectra of small parts of cells. The second part concerned studies of absorption spectra at low temperatures. UV absorption spectra are valuable but they're fairly broad. They don't always give you the kind of resolution one would like between different kinds of substances. And the question was, could you sharpen them up? And the reasons that they're broad at room temperature are two: One is just thermal motion; the other is interaction with surrounding molecules. And it was known that if you took something simple like benzene and lowered its temperature, really cooled it down, you could sharpen up its spectra. So we tried to devise ways for looking at compounds of biological interest at low temperatures. And we did, particularly purines and pyrimidines, and nucleotides of liquid

nitrogen and liquid hydrogen temperatures.

Then the third thing that I got interested in was following up on this business that UV irradiation of nucleic acids produced mutations. So I started taking the components of nucleic acids--in this case, purines and pyrimidines--and irradiating them with UV and seeing what happened to them.

Erwin: Was there, is there a difference between biophysics and molecular biology?

Sinsheimer: The name "molecular biology" had not been coined. That came ten years later, in the mid-fifties. Biophysics and biochemistry, particularly when they were applied to macromolecules--proteins and nucleic acids--increasingly overlapped, and they needed a term to refer to the combination. And that was called molecular biology. I think probably the term really became popular after we founded the *Journal of Molecular Biology* in 1957. John Kendrew was the first editor-in-chief, but I was one of the editors. It was at that point that the term became widely used.

Erwin: Did you have the sense during these years that you were working on something really new? You were in the cracks between the traditional sciences.

Sinsheimer: Yes. It's interesting. Take this low-temperature work, for example, which from our point of view didn't turn out to be terribly useful. It must have been ten or fifteen years later when I was talking to John Platt. He was working in Chicago in [Robert S.] Mulliken's laboratory doing physical chemistry research. Anyway, they decided they wanted to do some low-temperature work. He said he was astounded to look in the literature and find out that the most advanced work was this work we had done in a biology department fifteen years earlier.

Another way of realizing that you were doing something quite novel was you had trouble getting it published. There weren't any journals for it. We submitted our low-temperature work to the *Journal of Biological Chemistry*--where else would you get it published? And they had a hard time with it, because it just didn't fit into what they published. And indeed, a little later on, when we had done light-scattering work on tobacco mosaic virus RNA and wanted to get that published, the *Journal of Biological Chemistry* wouldn't consider it. So I sent it to the *Journal of Chemical Physics*, and they wouldn't consider it. They said, "This is too biological for us." Finally, they published it, but I mean, really, I had to practically plead with them and point out that nobody else would publish it. There was no problem with the work. And that was one of the reasons we founded the *Journal of Molecular Biology*, because we couldn't get work of this kind published.

Erwin: I noticed your bachelor's degree was awarded in quantitative biology. Was that the early name for biophysics?

Sinsheimer: Yes. MIT at that time wanted somehow to distinguish this from the conventional biology, which at that time was still largely descriptive. So they called it quantitative biology. And in fact they even instituted a program they called biological engineering, believe it or not, in 1940. That was ahead of its time, because we really couldn't do biological engineering. So the name died after five or six years. Today it might make some sense, because you can begin to do genetic engineering.

Erwin: Were there any other people at MIT with whom you worked closely?

Sinsheimer: Well, there's Frank Schmitt, who was the chairman. He was a physiologist. His field was nerve and nerve conduction. But he was also a biophysicist, and he brought Dick Bear, who did X-ray diffraction work; and he brought Dave Waugh, who did surface chemistry work. And there was Kurt Lion; he was more into electronics. And Stanley Bennett; he was an MD, who was interested more in biochemical problems. Irwin Sizer was an enzymologist. Charlie Blake was a good old-fashioned naturalist, one of these people who has just an encyclopedic mind. Another person I had contact with was Charles Warren in X-ray crystallography. I had a course in radioactivity, radioisotopes, from Robley Evans. He was well known. Evans was a leader in applying radiation to biological systems and in medicine. Another person, Vannevar Bush, was inventing computers; they weren't electronic, they were analog. I didn't have any courses from him. MIT was a very innovative place.

Erwin: How did you choose your academic career?

Sinsheimer: Well, you've got your PhD in biophysics, at that point there wasn't anything else you could do. Actually, it was sort of surprising and a little disappointing. Back in 1938 or '39, there was really not much demand for biophysics; it was too new. Schools didn't have programs in biophysics, so schools weren't looking for biophysicists.

Erwin: Today, would a biophysicist have a very wide choice?

Sinsheimer: He would certainly have a wider choice. I don't know how many schools churn out pure biophysicists.

Erwin: Could we talk about when you went to Iowa State?

Sinsheimer: Yes, let's talk about that. As I just started to say, I was somewhat disappointed that there weren't that many opportunities. But then this opportunity at Iowa State did come up. It wasn't the only one; there was another position at Washington University, St. Louis. Or, in fact, I could have stayed at MIT, but I didn't think that was the best idea.

Erwin: Why?

Sinsheimer: Why? Well, you'd be a junior person, one of their own products. I thought it was better going out on your own, establishing your own identity. Actually, I really believe one shouldn't do one's graduate work where one did one's undergraduate work. You should get another point of view, another way of looking at the world, see how somebody else functions. In my case, it probably wasn't as crucial, because I had four years in between, doing something very different. I did think of going somewhere else for graduate work, but there I was in Boston. I was married and my wife had a job. And there weren't many other places I could consider. So anyway, at that time I felt I should go somewhere else. And there really were only these two opportunities.

Iowa State, believe it or not, had had a biophysics program. It was in the Physics Department--and biochemistry was in the Chemistry Department. But they had had a chair of physics who had had some interest in biological problems. And they had had a biophysicist, a man named Fred Uber, who actually had done some of the experiments that I had mentioned before on the UV effects on producing mutations of corn. He had moved to Missouri and had left a vacancy in the Physics Department in biophysics. And then it did turn out that a number of the physicists at Iowa State had been at the Radiation Lab [at MIT] and I had known some of them. That's not surprising, because physicists from all over the country came to the Radiation Lab during the war. But this had the virtue that, in a sense, they recognized that my four years of experience at the Radiation Lab were of value. And they were willing to recognize that in their initial salary and faculty position and so on. Whereas the position at Washington University, which was in the Biology Department--they just wanted a fresh PhD, starting out at the bottom level. Plus, I visited the two places and, frankly, at that time Washington University was just an old-fashioned Biology Department, whereas the Physics Department at Iowa State was a lively place. It had machine shops and a whole variety of physical equipment. You also have to recognize that Iowa State had had an important part in the Manhattan Project. It was a strange, odd part, but an important part. Many of the fission products were rare earths, and nobody knew

anything about rare earths--a very exotic field of chemistry--except that Frank Spedding at Iowa State was an expert on rare earths. And so the Manhattan Project had enlisted him and other people there and had set up a lab there during the war. And then after the war, when the Manhattan Project became the Atomic Energy Commission, they set up a whole research laboratory at Iowa State. Many of the faculty in physics and chemistry there had joint appointments--part-time in the AEC laboratory, and the AEC put a lot of money into it. So it was a thriving place. I got a lot done there. I did some of my best work there.

Erwin: When did you actually start the work on Phi X phage?

Sinsheimer: At Iowa State I first set up to continue radiation studies. And that had an interesting development. Initially, I started to work with purines and pyrimidines. And then I thought, Well, I really should get things that are more like the way they are in the nucleic acid, in the DNA. And DNA is made of nucleotides, I knew that much. So I wanted to irradiate nucleotides. Well, in those days, you couldn't buy nucleotides; you had to prepare them. And I have to say, the methods were terrible--very long, very tedious. You had to go down to the slaughterhouse in Des Moines and get some thymus glands from cattle, which were relatively rich in nucleic acid, and bring them back and grind them up and extract the DNA you needed and then . . . that, chemically. You got maybe a one-percent yield of purines and pyrimidines if you were lucky. So I thought, Well, this is ridiculous, and I started to apply some more modern methods.

Begin Tape 1, Side 2

Sinsheimer: So we prepared the DNA, and we wanted to prepare the mononucleotides from that. It seemed the way we should do that was enzymatically. It was known that there was an enzyme, deoxyribonuclease, which would partly digest the DNA. And then we found that there was an enzyme, phosphodiesterase, which would degrade the partial digest down to mononucleotides. But the only source of that was snake venom. You could buy snake venom. But then the problem was that the enzyme in the snake venom was contaminated with another enzyme, called phosphatase, which would cleave the phosphate off the nucleotide. We didn't want that. So the first thing I had to do was to invent a method for purifying phosphodiesterase. Fortunately, about the second time I tried it, it worked. I got pure phosphodiesterase. And with that I could degrade the DNA completely to mononucleotides. But then the problem was how to separate them. I had become acquainted with chromatography in some chemistry courses I took, so I applied a whole new technique that had been developed during the war, called ion exchange

chromatography, for separating the mononucleotides. And to make a long story short, I was able to get 100 percent of it.

Erwin: It sounds like you really overcame quite a formidable technical problem.

Sinsheimer: Right. And that solved that problem. But it also did something else, which really turned out to be very interesting. As I said, the first enzyme, deoxyribonuclease, gave you a partial digest. One could know by titrating the digest that only about twenty-five percent of the phosphate bonds were cleaved. But what was in that digest, nobody knew. So I decided to look at that again. I said, "Well, what if we put that on ion exchange, what would we get?" Well, to make a long story short, it turned out to be a mixture of dinucleotides, trinucleotides, tetranucleotides, and on and on. We were able, by controlling the conditions, to fractionate all of the dinucleotides. Nobody had ever isolated a dinucleotide before. So this was the first time we had any dinucleotides. We had to separate all of those. And then we were able to determine which was which--and there are sixteen possible dinucleotides--and that gave us the first crude information about sequences. We couldn't do that with trinucleotides; we couldn't really frationate them very well, and beyond that, we were lost. Also, I might say, we discovered a fifth nucleotide. It turned out it had just been identified as a pyrimidine base the previous year, which is the 5-methyl cytosine.

The other thing I undertook. . . . It seemed to me that if I was going to work with nucleic acids, one had to get beyond just working with them in a test tube and study them doing something. By that time, it was known that viruses had nucleic acids. There were still some arguments as to whether it was a protein or nucleic acid that was the functional part. Tobacco mosaic virus had been purified by Wendell Stanley and semicrystallized in the 1930s; that had RNA in it. So I started working on that, learning how to grow it in greenhouses and purifying it. There was a lot of dispute about the size of the RNA tobacco mosaic virus. Well, the only way I could resolve that was through a new technique called light scattering--a biophysical technique, which could give absolute molecular weights. So we set up a light-scattering apparatus.

The Iowa State Atomic Energy Laboratory had some money for inviting distinguished speakers. I was able to get some of that for biophysics, and one of the people I invited was Max Delbrück. He had to go to Washington a couple of times a year, and he agreed to stop in Iowa. He was at Caltech then. And he came to Iowa and gave, I guess, three lectures. It was spectacular, it really was. He just blew us away with his phage work. It was absolutely glorious. So I got to know Max at that time and I was impressed. I decided I really wanted to learn how to work with phage, nucleic acids, doing something. And the obvious way to do that would be to go out and spend some time in Max's lab. I could take leave from Iowa, but I needed money,

because I hadn't been there long enough to qualify for a sabbatical. So I applied for a fellowship. Then I ran into a problem, because I only could get leave for six months. I remember I applied for the fellowship and they were willing to give me a fellowship for a year, but they wouldn't give me money for six months.

Fortunately Max came to my rescue. He had money that he could use. So I came out, and this was in the beginning of 1953, and spent six months with him learning phage.

Erwin: And that was your first contact with Caltech?

Sinsheimer: Yes. And I have to say, that was very exciting, not merely because I was working with phage and Delbrück and a lot of other people at Caltech. What I realized was that Caltech was one of the world centers, and everybody came through Caltech. So you were really in the loop. In a year there, or six months, by going to seminars you could learn what was going on everywhere. And obviously that was not true in Iowa, which was completely out of the loop. It hadn't been true at MIT either. It is now, but it wasn't in the biology loop at that time. That was really a great awakening for me. And, of course, it wasn't just biology. There was Linus Pauling. Linus had previously come out with the alpha helix and all that with protein, and he was working on DNA, and he came out with this triple helix, which was wrong. And then it was a couple of months after that that the Watson-Crick thing came out.

Erwin: Were you at Caltech when the announcement was made?

Sinsheimer: Yes, there was a letter to Delbrück. And then I was at the Cold Spring Harbor symposium that June. Then I went back to Iowa State and started to do some phage work. Now, while I had been at Caltech, I of course had thought about what I would do after I came back, and I intended to start studying some phage nucleic acids. But it was obvious that most of the work was being done at that time on so-called T-even phages--T2, T4, T6. It was obvious these were big and complex. And you have to realize that at that time we didn't have the techniques to work with really large nucleic acids. Also, it seemed to me they were too complicated, and that what would be desirable would be to work with a small virus, which had presumably less nucleic acid and fewer genes. So I looked in the literature to find the smallest phages that anybody knew of. That wasn't very precise at that time, because there hadn't been a lot of very quantitative studies made on viruses. There were two particular lines of evidence as to which viruses were big and which were small. One was the size of plaques. The idea was that a small virus would diffuse faster and so make a bigger plaque than a large virus. But obviously, that was not perfect evidence, because it would also depend on the length of each generation--how long it would take

to find a cell, infect it, lyse it, and make more. The other line of evidence had to do with how much, in this particular case, ionizing radiation it took to inactivate it, the idea being that the smaller it was, the more radiation it would take before one of the gamma rays would hit the particle and inactivate it. But that wasn't clean-cut either, because everybody knew that some of the effect was direct and some of the effect was indirect through ions produced through the medium, radicals produced in the medium. You could change the dosage by changing the medium. And I should say, there was a third line of evidence, which had to do with filtration through cellophane membranes. Presumably the smaller virus would go through faster. By those criteria, the two smallest bacterial viruses one could find in the literature were one called S13, which had been discovered in England, and Phi X 174, which had been discovered in France. And you might say, "Well, how were they discovered?" Well, people were just sort of categorizing viruses. They would take some sewage from the Paris sewers and find how many viruses they could find and which hosts, or cells, they would plate on and what the plaques looked like. The name Phi X 174 means it was the 174th virus in the tenth series of phages that they got, that's all. No more meaning than that. This was the tenth set of experiments they'd done--X was actually ten.

Fortunately enough, they had kept samples of these viruses, and I was able to get one from England and one from France. When I got back to Ames, I started doing phage work. First I started working on T2 and T4, because I had those available, trying to degrade their DNA, and that led to an interesting discovery. It was known that instead of cytosine they had hydroxymethylcytosine. But then I discovered that there was something odd about that. And to make a long story short, it turned out that the hydroxymethylcytosine was substituted with glucose, and in some cases, with two glucoses. There were differences and different strains, which you could correlate with different properties of the viruses. It sounded more interesting at the time than it really turned out to be, because it clearly is a question of which glucosylating enzymes they have. It isn't all that clear why they do it, but it was interesting at the time. They called them sweet and sour phages.

I thought we should look at one of the smallest viruses. So much was being done with the T-phages. We also looked at the T7 virus. But then, after I got the Phi X and S13, I focused in on those. First of all, it seemed that one ought to make a choice, which of those two. It just turned out that cultures of Phi X were more stable. You could make a lysate that would hold its titre, whereas S13 would die very quickly. So we said,"OK, we'll work with Phi X." Then, of course, whenever you start with a new virus, you have to domesticate it first. I had to find a host for it. It was originally grown on salmonella, and I didn't want salmonella, because it's toxic. But I was able to find a *coli* strain. And then you have to try different media, find out what will give you high titres, lots of virus. So you find out what media and what conditions will do that.

And then you have to learn how to purify it. So you go through a variety of procedures, try this, try that.

Erwin: What does that mean, to purify it, exactly?

Sinsheimer: You'd like to end up with a test tube with only virus in it. You see, you start with a lysate, which has all the bacterial debris. It's got whatever you had in the culture medium to enable the cells to grow. And you want to get rid of all of that other stuff and just have the virus, because otherwise you've got the host nucleic acid, you've got all of the host's proteins. So you want to learn to purify it. And that usually involves some chemical steps and some centrifugation steps, which we did.

Erwin: Are we in 1954?

Sinsheimer: This is by '54, '55, probably. When we wanted to know really how small it was, we could measure the sedimentation. Well, that's sort of an interesting little bit in itself. The technique you really wanted at this point would be an ultracentrifuge. And at that time, there was not an ultracentrifuge in the state of Iowa. There was one at Caltech, but there was none at Iowa. But I was able to get a grant from the National Science Foundation. It took $25,000 to buy one. There was no way I was going to get that from the university. I could get $5,000 a year, but I couldn't save up for five years.

Erwin: So you were going to buy your own centrifuge.

Sinsheimer: Yes. We got this set up, and we were going to use it, and we were going to measure sedimentation coefficients and things like that, which proved that it was probably pretty small, but again, sedimentation coefficients aren't perfect unless you know the shape, because that could lead to certain changes in the sedimentation. But we did have an electron microscope. I learned how to use that. And after I had a pure preparation I could look at, lo and behold, there it was, little particles, and they were only twenty-nine millimicrons in diameter, and obviously it really was small. Then we set out to extract the nucleic acid from it and study that and also to determine its molecular weight by light scattering. I remember in the spring of '57, we were just starting to do this. I had good sedimentation data on it (the nuclear acid). I remember I gave a paper at the Biochemical Society meeting. And it was obvious there was something anomalous. If you took the sedimentation rate, which we'd measured, and assumed it was a normal DNA, it was really obviously too big to fit into a twenty-nine millimicron virus.

And I commented on this at the meeting, but I didn't know the answer, of course. Didn't have the light-scattering data yet.

Of course, in the fall of '53, after I'd come back, I'd kept in touch with Delbrück, and we had a fair amount of contact about the unusual bases in T2 and T4. Also, by that time we had measured the light-scattering weight of TMV [tobacco mosaic virus] RNA and concluded it was a large RNA. That was interesting, because that was the first really large RNA that had been isolated.

Anyway, in the fall of 1955 they had the dedication of the Church Laboratory at Caltech. I was asked to give the keynote speech. And while I was there, I also gave some seminars. And then in June of '56, there was a big meeting at Johns Hopkins on nucleic acids. I was one of the speakers. George Beadle was there, and George cornered me and asked if I might ever be interested in coming to Caltech. And I said, yes, I might be interested. I'm not entirely sure of the chronology. Anyway, it was after that that Beadle contacted me and essentially offered me a job at Caltech.

It was not an easy decision. Professionally, it was clearly to my advantage for a number of reasons. One was the distinguished department. Teaching loads were much lighter; you had more time for research. You got better graduate students. And particularly, there was the fact that, as I brought up earlier, at Caltech you were in the loop. At Iowa that just wasn't true. Obviously, you could keep up by reading the literature and so on, but that's always six months to a year behind the real action. But on the other hand, I'd been in Iowa for seven years, and my children were born there. We had lots of friends there, and we'd sort of set down roots. And it's hard to pull all that up. And in many ways, it's a very pleasant place to live. It was just a university town; there's nothing there but the university. It's a small town; it's changed now, I'm sure. When I first went there, there wasn't a stoplight. There was no crime; we didn't lock the doors. The kids could go anywhere in town with no fear. It was a university town with an excellent school system. These kinds of things.

Anyway, obviously I did move. I came out to Caltech on July 1, 1957.

Erwin: Did you at that time foresee where your work was taking you? You had solved so many technical problems. But things were going to change as far as what then becomes your attitude toward your work.

Sinsheimer: Well, we've skipped over a number of other things I also did at Iowa State. I was doing some infrared spectroscopy. You're in a physics department; you're in a more physical type of environment. I should also say, the last year I was there, I was asked to, and I did, become part of the biochemistry faculty as well. In retrospect, that didn't offer any particular

advantage. The disadvantage was you had twice as many committees. [Laughter]

Anyway, coming out to Caltech, of course, the environment changed. You're in a biology department, particularly a department famous for genetics, and so your emphases are going to change somewhat. Obviously, when I first went there, they brought me there for the kind of expertise I could bring them. My plan, of course, was to continue my initial work with Phi X and with tobacco mosaic virus. But as I said, originally my intent in working with small viruses was to try to be able to study what was going on, what they were doing in the cell, *in vivo*. I wanted to be able to push my analysis into the cell. That was still ahead of me, and in a sense, nobody had ever done that.

Now, things did change, there's no question. Being in a new environment changed the direction of one's work. But I think what I want to say is, in part it was the environment, in part it was the natural evolution of the problem. Plus, the evolution of techniques. For example, the centrifuge. In the last year I was at Iowa, in the course of learning to use it and learning the problems, I sort of stumbled on to the density gradient technique. But then when I came out to Caltech, I found that they had just developed that whole technology--[Jerome] Vinograd and so on. So I didn't have to develop it; it was all there. I think what you're asking me is what direction would my work have taken if I had stayed at Iowa compared to moving to Caltech. I don't think anything would have changed immediately, and I think even the next things would have followed in a fairly logical sequence. But then, undoubtedly, as you go further on, my directions change.

Erwin: Yes, well, I was thinking ahead, I was skipping ahead to, let's say, 1966, when you gave your talk, "The End of the Beginning." And you certainly had this feeling that your discipline, biology, had reached a point in a long history.

Sinsheimer: Yes, but that wasn't just *my* dream.

Erwin: I realize that, but did you foresee coming to that point earlier? I mean, even during the Iowa years, did you have a sense that you were going to arrive at that great turning point?

Sinsheimer: I'd probably have to say no. That is, obviously the purpose of, the goal of my going into biology was to try to be able to understand biological phenomena in terms of physics and chemistry. I think it came much faster than I would ever have imagined it could. It may sound curious, but I don't think, until that particular talk that you're referring to, I had ever stood back and asked, "Where is it taking us?" I think my feelings at that time were purely scientific. I wanted to know the answers. I was trying to solve scientific problems. And, as I say, it all

came so fast.

For example, if you go back a little, when I came out to Caltech in 1953, I remember, I had only been there a few weeks and I was asked to give a seminar. And I talked about our preparation of mononucleotides and the digestion of DNA and the dinucleotides. I had been thinking about DNA, of course, and I knew the Chargaff rule. From a lot of sources, [Erwin] Chargaff had analyzed a lot of DNAs--this was about 1949--and he had shown that in all of them, the proportion of adenine equaled that of thymine, and the proportion of guanine equaled that of cytosine. And the question was, Why was that? Nobody understood why. And one possibility, of course, would have been that somehow A was always followed by T or preceded by T or G. And our dinucleotide work proved that that was not the case; it couldn't be the case. So that still left us with a conundrum. It had occurred to me that there had to be two DNAs, one with A and one with T. I mean, there had to be two DNAs which we would now call complementary. I had no idea what they would be for, frankly. And it never occurred to me to think it was a double helix, because I wasn't thinking in those terms. I wasn't thinking structurally. If I had been at Caltech, maybe I would have been, because that was what Pauling was doing with the alpha helix. That's what started people thinking about a helix, the alpha helix, and then the coiled coil with seven strands. So I just had this idea and I didn't know what to do with it.

So [in the seminar] I talked about dinucleotides, and I mentioned this concept--that maybe there were two DNAs and they had this complementary composition--but I didn't know what to make of it. That didn't arouse any interest, it seemed to me, but everybody was very interested in this numerical data on the dinucleotides. And I didn't know why. Then I realized that they were already thinking about the code: How could information in DNA specify proteins? They were already thinking about that. And this was the first sequence data they had. Now, it didn't tell you much, for two reasons. One, it wouldn't tell you enough even if you knew *all* the dinucleotides. Secondly, we didn't know all of them; we only knew the fraction which turned up in the digest as dinucleotides, usually about a sixth of the total. And I couldn't even know if that was a random sample of dinucleotide sequence.

Anyway, the point I'm trying to get at is this. After Watson and Crick came out, that sort of stimulated more discussion about the code. Everybody's an amateur cryptographer, it turns out. All kinds of codes were proposed--overlapping codes and comma-less codes and error-correcting codes. And the point is, it seemed like this was a very hard problem to solve, the relationship between DNA and protein. And it looked like the most promising way was going to be to try and get a whole bunch of mutants, where we could analyze the change in the protein sequence and a change in the nucleic acid sequence. For TMV there was a bunch of mutants one could analyze, but one didn't know what to analyze. You could analyze the proteins,

determine the amino acid changes, but then you would have to determine the corresponding change in the RNA. And as I said, in the late fifties it just seemed like this was going to take a long time to solve. And then it was solved overnight--or virtually within a year--by [Marshall] Nirenberg discovering that he could get an *in vitro* system to translate polynucleotides. You could put in poly U [uridine] and it would make polyphenylalanine. You could put in other nucleotides and make poly A, poly C, or a mixture of adenine and cytosine and see what polypeptides were made. Then you could work out the whole code within a year this way, and that was done, which was completely fortuitous. It was fortuitous because it shouldn't work. People don't realize that. It only works because you're using very nonphysiological conditions. I mean, in the cell, the cell could not translate polyuridine into polyphenylalanine. You'd never get polyuridine onto a ribosome. You'd have to have a sequence that the ribosome binds onto, you have to have a starting triplet, which is always AUG, and so on. But *in vitro* it'll work because you've got nonphysiological concentrations of ions and other components.

Anyway, I only go into that to point out that these things came so much faster than we had reason to think they would.

Erwin: I think that's a very interesting observation.

Sinsheimer: So, by the mid-sixties, one had really solved so many of the basic questions about DNA replication and transcription and protein synthesis in broad scale. One could begin to see how the system worked.

Begin Tape 2, Side 1

Sinsheimer: Coming to Caltech was, of course, both inspiring and a little intimidating. Here were really giants. George Beadle was the chairman; Max Delbrück was there. Linus Pauling was chairman of chemistry. Frits Went, who was a leader in plant biology, was there. Roger Sperry, who was certainly a leader in psychobiology was there. [Alfred Henry] Sturtevant was still active and teaching. In genetics, [Sterling] Emerson was still there. Norman Horowitz was there; Ed [Edward B.] Lewis, Herschel Mitchell, James Bonner. There were a lot of great names. And then, of course, in physics, there was [Richard P.] Feynman, [Carl] Anderson, and [Murray] Gell-Mann. And [Lee A.] DuBridge was president. So you could say it was pretty deep company.

There's funny things you remember. Church had been built, Kerckhoff was there, but the connection--Alles--wasn't there. So you had to go outdoors to get there, or else go through the basement to get over to Church. We had the phytotron across San Pasqual, which was a

greenhouse. Frits Went built it, but it may have been Bonner who named it. It was a greenhouse, but it was temperature controlled, CO_2-controlled. Very elaborate precautions were taken to prevent insect infestation with a change of clothes when you went in.

Erwin: Is that where Braun is now?

Sinsheimer: No, it's where Beckman Behavioral Biology building is now. Then there was another little greenhouse, the Dolk Greenhouse. I wanted to grow TMV but I couldn't do that in the phytotron; I could do it in the Dolk Greenhouse. Anyway, I got set up. Beadle was very helpful, and he was able to get money. It didn't cost as much as it does now, but we had an ultracentrifuge and light-scattering equipment and so on. I worked in Kerckhoff then.

Erwin: So you felt that you were in a pretty cohesive, supportive environment.

Sinsheimer: Yes. And I brought a couple of grad students from Iowa and got some new grad students and later some postdocs. In the first year there, we got Phi X DNA purified, did the light-scattering measurements on it, established its molecular weight. The most convincing thing was that I was able to use my earlier methods, which I mentioned, the 100-percent degradation of mononucleotides, to determine the mononucleotide composition and prove that it wasn't Watson and Crick, and therefore could not be double-stranded. And that fit with the sedimentation coefficient and the light scattering, which gave now a molecular weight of 1.7 million daltons. All that said it was single-stranded. And then the only question really was, Was this somehow something we had done in extracting it from the virus? I was able to show spectroscopically and in other ways that it was a single-strand in the virus itself. So it clearly was single-stranded DNA, and we wrote this up and published it in the first issue of the *Journal of Molecular Biology*. And that, of course, was for a time a sensation. We had never seen a single-stranded DNA. And, of course, once that was published, there were lots of people coming as postdocs. Success breeds success.

Of course, that immediately also raised a number of obvious questions of great importance. We had this model for double-stranded DNA, but how did the single-stranded DNA reproduce? Indeed, how would it even get transcribed? And that meant having to pursue the thing into the cell. So we developed ways of labeling the DNA and following it into the cell. There are several ways of doing that. First, you had to be able to extract it from the cell, and we learned how to do that. But we wanted to be sure we got it out intact. Then immediately that was one of the virtues of choosing a small bacteriophage, because we knew how to handle DNAs of that size. So we could label it with radioisotopes and follow where the isotopes went. But

that wasn't conclusive. We could still have had something happen to the infecting molecule as long as the radioisotopes stayed in some DNA. So we also used density labeling. You could label the infecting virus with heavy isotopes and see what happened to the density of the infecting DNA.

I have to go back a second. By that time, the doctrine was that DNA was the genetic material and the protein was just sort of a protective coating. If that were true, the DNA should be capable of performing an infection by itself, if you could get it in a cell. But nobody had ever been able to demonstrate that, because they hadn't had a complete DNA. So we set out to try and prove that and we succeeded. We learned how to make protoplasts, which are cells with part of the cell wall removed. We could get DNA into that with reasonable efficiency and grow virus from pure DNA. So, on the one hand, that was the first time that had been done, to verify the principle. But it also meant that we could assay the infectivity of DNA we extracted from the cell. And clearly, if it was infective, it had to be pretty much intact. So, we had these three ways of following what happened to the DNA in the cell. And to make a long story short, we were able by these methods to show that the first thing that happened to the single-stranded DNA after it went into the cell was that it became a complementary-stranded DNA--it became a double-stranded molecule. And then, obviously that could be transcribed. And then, that double-stranded form multiplied as such--we call that a replicated form--multiplied as such for a time, and then later in the infection it started to make the single strands of DNA. It went back to the single-stranded form to put into the progeny. Not only was it really novel in itself, but what was really novel were the techniques to follow it into the cell.

Next it occurred to me that this was the first time we had a complete, infective DNA. And this raised in my mind the question, Was there something special about the ends? What do you have at the ends of this DNA strand? So we tried to determine chemically what was at the end of the single strand. We had enzymes, which we thought should chew off either end. There's a polarity to DNA, so that there was a three-prime end and a five-prime end, as we called it. And we had enzymes that were chewing from the five-prime end, and you could determine what they would chew off. And if they were chewing from the three-prime end, you could determine what they could chew off. We couldn't do it! We were baffled for some time, but we just could not get any--we could get only a little bit of degradation.

Erwin: You mean they didn't chew?

Sinsheimer: They didn't chew. We could get a few mononucleotides, but we couldn't get any kind of systematic release. And it seemed like the enzymes didn't affect the infectivity at all. We were sort of puzzled by this. And we had sort of laughingly at one point said, "Well, maybe

it doesn't have any ends. Maybe it's a ring." That wasn't the only possible answer, because obviously another answer might be that there were *things* on the ends, X, unknown, that could block the enzymes. But it also occurred to me it was a ring. Then, one day, it all fell together. We had made an observation and reported it in our very first paper, that in the ultracentrifuge, there were two sedimenting species of DNA, different only by ten percent or so in their sedimentation rate. And that, after we learned how to do infectivity, we could see that the infectivity of different preparations varied some. And that the more infective ones seemed to have more of the faster component and somewhat less of the slower component, although by that time we had learned how to make preparations that were almost entirely infective.

Erwin: You're still talking about the same virus? Two types of DNA from the same virus?

Sinsheimer: Right. All Phi X. We extracted DNA; we put it in the centrifuge, and there were two sedimenting components, a faster one and one that was about ten percent slower. That puzzled us; we didn't have any explanation. We recorded it in our first paper but had no explanation for it.

Erwin: So you would think that they would be the same, that there would be no difference. Is that what you mean?

Sinsheimer: Well, why would we get two different sedimenting components from the same virus? We had no explanation at all. But then it occurred to me that if you took seriously the idea that this was a ring, some of these [rings] might be broken, in which case you have a linear model--same size, but linear. And that would sediment more slowly. The ring is smaller; it has less frictional resistance, so it will sediment faster. And actually, you can calculate; the difference should be about ten to twelve percent. If the ring was infective and the linear one was not, that would explain these infectivity fluctuations. So that immediately put to mind an experiment. And Walter Fiers, who was a postdoc, was the one who had been trying all these efforts on chewing the ends. He carried out the experiment. We took a preparation which was almost all fast component and treated it with a very low concentration of deoxyribonuclease, which would cleave it. And at various times we took out samples and put them in the centrifuge and measured the ratio between the amount of the fast component and the amount of the next component and also measured the infectivity. What we saw was that with increasing time, the amount of the fast component dropped, the amount of the slow component increased. And then it decreased and you got slower sedimenting material. Then the infectivity dropped off exponentially. I worked out the equations, assuming you had a ring and you first cleaved it to a

linear, and then you cleaved that again to slower sedimenting components. And you could measure the number of enzyme hits from the falloff in infectivity. On an average of one hit, you should be down to thirty-seven percent infectivity. And then from the number of hits, you could calculate how much should be in rings, how much linear, how much in the smaller [units], and it all worked perfectly.

Erwin: When you say a hit, you mean cutting it, breaking it?

Sinsheimer: One cut. So the equations all fit. So we had a ring. And I published that. It was interesting, because people who were biophysically oriented understood the experiment and were very excited about it. And some of my friends who were biochemists didn't believe it. You see, until then everybody had always worked with fragmented DNA, and so the idea of a ring had never occurred to them. This was the first time anybody had a complete DNA, a whole DNA, and it turned out to be a ring. And then, I remember I went up and talked at Stanford about this ring model. And [Arthur] Kornberg felt there must be some other explanation. They didn't quite believe it.

Erwin: Now this didn't undo the idea of the Watson and Crick model?

Sinsheimer: No, not at all. It was just a ring! Then presumably the question was, Was the replicative form, the double-stranded form of Phi X DNA, also a ring? We did the same kinds of things, the same kinds of enzymatic tricks to show it was a ring. This was spring 1963. In the summer of '63 I was invited up to Berkeley; they have a special summer course; they bring in some distinguished person. So I was up there for six weeks to teach this course. While I was there, I became acquainted with Kleinfelter [name unverified]. Kleinfelter had just developed the first technique to look at DNA in the electron microscope. It had to be double-stranded; you couldn't look at single-stranded.

Erwin: Why?

Sinsheimer: The single strand just all balls up into a little clump; you couldn't see anything. The double strand was rigid, and you could see something. So, after I finished there, I came back down to Caltech. Then I went back up there and took some of our double-strand replicative form to look at. And I'll never forget it. We took the pictures, developed them, took them out. The first plate we looked at was full of little rings. I wasn't surprised, but you know the old "Seeing is believing." That convinced everybody, that you could actually see it.

That was 1963. It was '62 when we had done the single strand. By '63 we had done the enzymology and satisfied ourselves. And in fact we published the enzymatic paper at the same time we published the electron microscope paper.

Erwin: Now, the *in vitro* synthesis didn't come until after that?

Sinsheimer: That came later, yes. And actually, a couple of years later, techniques were worked out so that you could see single-stranded DNA, you could see the single-stranded rings. There were some classic pictures; they've been published. But at first, the techniques weren't available to do that.

Now, what you're referring to was the *in vitro* synthesis. Well, in the mid-fifties, Kornberg had isolated his DNA polymerase, which initially was thought to be the replicating enzyme for DNA. It isn't, but it was then thought to be. You could certainly make DNA with that; starting with DNA, you could make more DNA. But there's always the question, Was it really making accurate replicates? And so the obvious question then was, once we had learned how to determine the infectivity of Phi X, could we replicate Phi X and would the replicas be infective? If they were, then we would know the enzyme replication was accurate. We first tried this in 1960, actually, and it was a failure. We could make DNA, but the infectivity just died. We tried a few variations. This was a collaborative experiment with Kornberg.

Erwin: At Stanford?

Sinsheimer: Well, we prepared the DNA, he replicated it, and we took it back and did the infectivity studies. It died. So, as I say, we tried a few variations and nothing worked. We tried again, it must have been in '63 or '64. We had a purer enzyme by then. We also knew it was a ring by then, so we knew that if we started with preparations we knew were all rings, all of the initial DNA molecules would be infective. But again we failed.

Then, I guess it must have been about '65, another enzyme was discovered, DNA ligase. If you have got double-stranded DNA and you've broken one of the strands, one of the phosphodiester bonds, ligase can seal that up.

So it occurred to us and Kornberg that maybe that's what you had to have, that maybe polymerase could make the complementary strand, but it could not seal it up into a ring. After you've made it, you need ligase to seal it up, or otherwise. . . . As we know now, polymerase also has some exonuclease activity, and it starts degrading the strand it made and you start getting fragments, and then you start to replicate those, and so on. So, in 1967, we took this up again. Mickey [Mehran] Goulian was a postdoc with Kornberg. We gave him the DNA, pure

rings, then he replicated them. And then we introduced some new tricks. I don't remember the exact sequence of events. But basically we put in bromouracil, which is heavy for thymine, so we could separate the replicated DNA from the original. And this time we got an increase in infectivity, and we could show that it was in the replicated DNA because of their different density. And the second trick was incorporating ligase along with the polymerase.

Erwin: Did that make the ring close?

Sinsheimer: Well, you start with a single-stranded ring. You make the complement of it. You close that with the ligase. Then, what we did was to nick with a nuclease, an enzyme which would only cut one strand--we didn't want to cut both--separate those two strands now, isolate the complementary strand which is heavy, use that as the template to make another strand, which is the original viral strand. Make that light, nick again, and again separate, because you're separating the heavy strand and the light strand. Now you have the second-generation light strand which is like the viral strand, and you show that that's infective. And it was. So the enzyme could make the infective strand. That proved it. And that was the experiment that, I guess you could say, was considered astonishing. In a sense, it's an artifact. It's not the way it happens *in vivo,* but it worked. It was the first in-test-tube synthesis of something that was infective. Those things could infect and make progeny indefinitely. Now, of course, we know how to do all kinds of other things. You can introduce mutations and all kinds of things. So, in effect, you felt like you'd made a living thing, if you want to call a virus living. You'd made an infective object able to replicate in a cell indefinitely, although it isn't the way that it really works in the cell. And in fact, of course, all we had done was copy something that already existed.

Erwin: But the cell does that, too.

Sinsheimer: The cell does the same thing, makes a copy. Today, in principle--nobody as far as I know has ever done it--we could today chemically synthesize DNA.

Erwin: You mean from scratch?

Sinsheimer: From nucleotides, which is scratch. In principle, you can make the nucleotides from carbon and hydrogen and nitrogen and oxygen and phosphorous. So, in principle, yes, we could make the whole thing from scratch. Nobody's ever done it.

Erwin: The thought of somehow manipulating these little molecules, it's very astonishing.

Sinsheimer: I know. I always have this problem in talking to nonscientists about recombinant DNA. They have this picture of somehow going in there with scissors and cutting the DNA and pasting it together. [Laughter] And, of course, it's all done with enzymes. You never see the molecule.

Erwin: It's a matter of imagination. A scientist with a good enough imagination eventually could work up a feeling for it.

Sinsheimer: Well, it also takes practice. In my class--I teach the third quarter of biochemistry; it's a course on nucleic acids--I start off the first few weeks talking about nucleic acids and different structures. And they have trouble with that; they're not used to thinking in three dimensions and thinking about helices and right-hand helices and left-hand helices. So it's a matter of getting used to it.

Anyway, that's the Phi X story pretty much up to 1966, I would guess. We did a lot of other things. We were still interested in UV effects on a virus. I was interested in learning about the mechanism of DNA replication. And one thing that we showed was that if you inhibited protein synthesis, you could make the double-stranded form. But you couldn't make any more viral DNA. So the virus itself had to make some proteins in order to go on to the next step. And at about this point--and being at Caltech--we realized that to get much further we were going to need to do some genetics.

Erwin: Could you elaborate on what that means?

Sinsheimer: Sure. But let me say before that, once we knew we had the DNA--we knew how big it was, knew it was 5,400 nucleotides, knew it was a ring--obviously one thing we would have loved to know was the sequence. But we didn't have the technique.

Erwin: A sequence being the exact arrangement of nucleotides?

Sinsheimer: Yes. We simply didn't have the techniques to determine that. We could determine all the pyrimidine sequences, all the tracts. In other words, as you go along, there's a pyrimidine, a purine, or maybe there's two pyrimidines, then a purine. So we could determine how many tracts there were with one pyrimidine, how many with two, how many with three, how many with four, how many with five, up to the largest, which turned out to be thirteen

pyrimidines in a row. But we couldn't sequence; I couldn't tell you what the sequence was for the pyrimidines in those tracts. And we'd do the same for purines. But that's as far as we could go.

OK, genetics. What does that mean? Well, it means that you get mutants of the virus. There are various kinds of mutants. The first kind we got were delayed lysis mutants. The virus infects the cell, and after a period of time normally it lyses and releases progeny. But we got some that were late in releasing progeny. And these were useful, because if they didn't lyse, they kept making more virus. So we got higher yields of virus. And then, when we really set out to make mutants, we were fortunate. We borrowed the technique of conditional lethals, which had been worked out for the T-viruses by [R. H.] Epstein, [R. S.] Edgar, and Bill Wood at Caltech. The conditional lethal viruses are viruses which can't grow under one condition but can grow under another. You know you have a mutant because it can't grow under one condition, where the wild type can. It's conditional lethal, which means the mutation is lethal to the virus in condition A but not condition B. And you need condition B, because otherwise you can't multiply it and you can't propagate it. Actually, this goes back to *Drosophila*, the idea of conditional lethality. But its application to phage was really first worked out with the T-phages by Epstein and Edgar and Wood. There are two general classes. One is temperature conditional lethality. The most common are temperature sensitive; they can't multiply at high temperature; they can multiply at low temperature. That's usually because you've made a protein which is mutant and which is inactive at the high temperature because it doesn't necessarily have the right configuration, but is active at the lower temperature. The rest of them are the other way around; they're cold-sensitive.

Erwin: How much difference is there in the temperature?

Sinsheimer: You would use maybe forty-two degrees for your high temperature and thirty or twenty-five for your low temperature.

The other type are suppressible mutants. There are three general classes, which are called ambers, ochres, and opals. The explanation of these is that you have had a mutation, in the middle of a gene for a protein, to a stop codon, a codon which says, "Stop translating." So, in your normal host, you're going along making a protein and you stop in the middle at that gene. And obviously, then you don't make an effective protein. But, in suppressor hosts, you have a variant tRNA that enables you to read that stop codon as some amino acid. It may or may not be the one that was originally there, but if it's in a region that isn't critical, you can still make an effective protein. So, all your amber mutants will grow in a host with an amber suppressor, but will not grow in the wild one. And actually, the amber suppressor reads the UAG stop

codon. And then there are the ochres, which read the, I guess it's UGA, and the third type, the opals, read the UAA. You can get lots of these mutants; you can generate a whole set of mutants of the virus.

Then, you want to group them into what we call complementation mutants. And the idea here is you do an infection simultaneously with two different mutants--two separately isolated mutants. You do this in the wild type (nonsuppressing) host. If they're mutant in the same gene, then neither of them can make that protein, and so it doesn't work. If they're mutant in different genes, they can complement each other, and the infection will be successful. So that way, all those that can't complement each other are mutant in the same gene, or what we call the same complementation group. And in that way, we were able to assort all the mutants in nine different complementation groups, labeled A through J.

Then we could further order them by genetic crosses. We would infect with mutant A and mutant B. You have the possiblity of getting recombination between mutants to produce a wild type. This again goes back to *Drosophila*. And you can measure the frequency of recombination, and that way you can order the genes. In that way we were able to produce a genetic map. Gene A here, and gene B here, and gene C here, and so on.

But then the next question, of course, is to find out what each of these things does. Well, some of them were fairly obvious. It turned out that all the mutants in gene E either didn't lyse at all or were delayed in lysing. That was clearly the lysis gene.

In the meantime, we had been studying the proteins of the virus itself, the particle. It turned out there were four proteins in the virus. And in some of these you got mutants that would change the electrophoretic mobility of the virus particle or of the protein itself as you got it out of the particle. So you could associate those mutations with, let's say, the forty kilodalton protein in the virion. And that might be, say, the G complementation group. Anyway, it turned out that F, G, H, and J were the four proteins in the particle. And we could identify each of those proteins. And then it turned out that A was the protein that you had to make in order to get replication of the DNA.

Erwin: So it's sort of a process of elimination?

Sinsheimer: A process of elimination and studying what's going on in the cell. In other words, you infect with the mutant and see what doesn't happen. This takes us now into the seventies.

Erwin: You mentioned Walter Fiers. Who else at Caltech was involved? You were really the head of this group.

Sinsheimer: Oh, there were a lot of students and postdocs.

Erwin: Did any of them subsequently go on to great things?

Sinsheimer: Well, practically all of them are now in universities and teaching. Dave Denhardt was a grad student. He's now chairman of the department at Rutgers. And Arnie Levine was a postdoc. He's chairman of the Biology Department at Princeton. Walter Fiers went on to do some beautiful work on RNA viruses and more recently on tumor necrosis factor. Remember, many of these postdocs came from abroad. Bjorn Lindquist is head of the Biology Department at Oslo University. Rolf Knippers, who was a postdoc, is the dean at Konstanz University.

Begin Tape 2, Side 2

Sinsheimer: Larry Dumas is the Dean of the College of Letters and Sciences at Northwestern University.

ROBERT L. SINSHEIMER
Session 2
May 31, 1990

Begin Tape 3, Side 1
Sinsheimer: I think we had taken the story up to the early seventies, when we were doing the genetic mapping. At that time, restriction enzymes were used to cut DNA at specific sites. This was a new way of being able to break DNA up into fine pieces.

Erwin: At this point you still didn't know the sequence?

Sinsheimer: No, we did not. But this was actually the necessary prerequisite to the sequence. We did apply that restriction enzyme technique to Phi X, and we got the first complete restriction fragment map for any DNA. And by using two different enzymes and partial digests, we could order all the pieces so that we knew their relative positions but still not the sequence. And actually we did some kind of cute things, where you could take one fragment and in the electron microscope you could see the single strand. You could connect a specific restriction fragment to the single strand and then see the double strand region. You could take two restriction fragments and put them both on and see if they would be adjacent to each other or separated. This confirmed visually the order of the fragments, but we still did not have the sequence.

But then, about this time, in the early seventies, Fred Sanger was developing his method of DNA sequencing in Cambridge, England.

Erwin: Had you had any contact with him prior to this?

Sinsheimer: Well, I had known of Sanger for many years, from the fifties, when he was doing protein sequencing. He had chosen as a test object for his sequencing effort Phi X, because it was the best understood DNA. We had sent him strands. And then Clyde Hutchison, who was my graduate student, completed his thesis and went to work in Sanger's lab as a postdoc to help on this project. And that was very successful. Using Phi X, using all the mutants we had, using the restriction enzyme technique, they were able to sequence each of the fragments, and by 1977 they worked out the complete sequence. And this was, again, the first DNA that was sequenced.

Erwin: That meant knowing the precise order of the 5,400 nucleotides.

Sinsheimer: And in many ways that was very satisfying, because our earlier physical measurements back in the late fifties said it was 5,400, so it was very accurate--actually 5,386. And it also revealed a number of interesting facts. It showed that there were two small genes we had missed; we just hadn't gotten mutants in those genes. Also we had had a great deal of difficulty in trying to order unambiguously what we called genes D and E. The mutants are different complementation groups; there are mutants in both. But we were unable to get a consistent map order.

The explanation became clear with the sequence. The two genes were using in part the same sequence of DNA but reading it in different frames. That is, the genetic code is a sequence of triplets of DNA. Obviously, depending on where you start, there are three possible ways you can read that. And each of those will produce a different set of amino acids and different proteins. It had been recognized very early that that was possible. But it was thought that it probably wouldn't ever work, because once you've defined one set, you've placed enormous constraints on the second set. So it seemed unlikely that you could do this and make two different proteins, both of which would be functional. But, in fact, it turns out Phi X did that. It subsequently has been shown in some other viruses that the same thing occurs. You see, the amount of DNA you can package into a Phi X particle is fixed by the structure. And so there's a lot of pressure to make the maximum use of that DNA. The same is true of some other viruses. And apparently it has proved possible to make the maximum use by reading the same DNA in two different frames.

Erwin: Pressure by the virus?

Sinsheimer: Evolutionary pressure on the virus. Now, to my knowledge, this has not been observed in cells, because cells can contain a lot of DNA and thus are not nearly so limited. So it's easier for a cell to make two different genes rather than seek to use the same DNA twice.

Erwin: Instead of an overlapping arrangement.

Sinsheimer: This was not just a simple overlap; the E gene was totally contained within the D gene but reading part of it a different way. So that was an interesting phenomenon we discovered. The sequence clarified some other things about Phi X. And in a way, it sort of brought the Phi X work to an end.

Erwin: There wasn't anything else left to do?

Sinsheimer: Well, not that one fully understood everything. There's still, in fact, some aspects of how the viruses are put together that aren't understood, but that's rather specific to this virus. And this virus, per se, is not a particularly interesting virus. It's not causing any diseases. It was useful because it was small and you could analyze it in great detail. It therefore served as a sort of leading wedge for molecular biology for almost twenty years. But there really wasn't that much more interesting to do with it.

Now, in a sense, one of the arguments that we used for studying Phi X proved to be slightly fallacious--that is, the idea that it was small and simple and easy to understand. It's true, as far as the virus goes. But you have to carry out a certain number of functions to reproduce any virus. And if the virus provides less functions, then the host has to provide more. And so, in contrasting, say, Phi X with a virus like the T-even virus, Phi X is much more dependent on host enzymes to replicate its DNA than the T virus. But that conversely proved to be a virtue, because it enabled Kornberg to use the Phi X replication as a way of studying DNA replication in *E. coli*, since it's using the same host enzyme system. And Phi X provided a well-defined, small system. And he pursued that for another ten or more years and found a whole set of host factors that are involved, and he has pieced together how they work, using Phi X as the paradigm.

Basically, from our point of view, we had learned the interesting and important things that we wanted to know about the virus. So I was really in the process at that time--in the mid-seventies, after the sequencing of Phi X--of phasing out much of this work. I thought, What would I want to take up next? I considered a lot of things. But what I had actually chosen to do was to study nitrogen fixation, obviously an extremely important problem for the world and one which--it seemed to me, with the new techniques--one could make significant inroads on. By understanding the molecular biology involved, one might hope to extend the range of organisms which can fix nitrogen. This is basic biology but potentially very significant to agriculture. And I was just gearing up to do that. I was reading the literature and I outlined some experiments that I thought would advance the field.

In a sense, that made it easier to move to [the University of California at] Santa Cruz, because I was in transition anyway. These things, I should tell you, on the one hand are driven by science, and they should be. But they're also driven in other ways, and it was obvious by then that the interesting things had been done on Phi X, and there were fewer graduate students around interested in working on Phi X and fewer postdocs--which probably showed good judgment on their part.

Erwin: Let's back up to the period of the middle sixties. Some of your concerns were ethical

ones.

Sinsheimer: Yes. And it came about in a curious way. At Caltech they had what they called the Monday Night Lectures--I think they're now called the Watson Lectures. These were lectures for the public, really. Every Monday night there was some Caltech faculty member to talk about his field of research and where it was going and what interesting things were going on. And they had--and still do, I suppose--a very loyal audience.

In 1965 I was asked to give one of these, and I did. And what I tried to do was talk about DNA and present this like a book of instructions which we were trying to learn how to decode. I used the analogy to the Mayan codices, and that was *The Book of Life*, and it was later published.

I remember, that Monday night came, and it was a deluge. Just pouring--it was one of those nights. I didn't think there'd be anybody there [laughter], but it was a loyal audience. The lecture seemed to go over very well. I'm sure as a consequence of that, I was asked to talk at the seventy-fifth anniversary celebration in the fall of '66. Caltech was planning a whole series of talks on the future of the various fields of science and technology, and they asked me to talk on the future of biology. I had a lot of lead time, six months. I'd never given that kind of a talk before. Well, that led to "The End of the Beginning." That was the name of the talk, because I realized that all these advances in microbiology had coalesced to give us a really, not detailed, but clear outline of what constituted a living cell and how it reproduced. It was pretty clear that out of that knowledge was going to come no end of medical and environmental innovation. We had penetrated in biology down to the basic genetic level, and we didn't have to penetrate any further. You start with the organism and you follow it down to the cell, and then parts of the cell, and then the molecules and so on. And now you have gotten down to the absolute genetic basis—which really determined the nature of the cell and of the organism. While there were a lot of aspects of that we didn't understand, clearly we knew we'd be able to understand them, and then, once you understand, you can intervene in the process. It would give us a control over animate organisms similar to what had been acquired over inanimate objects. And that was a completely new phase. Before that, we'd just sort of taken animate organisms as they came. We'd done a certain amount of breeding of crops and so on, but that's still just taking what you have and crossing it.

Erwin: I think you made the point in that article--and maybe elsewhere, too--that now that man's evolution is in his own hands, an evolutionary Rubicon has been crossed.

Sinsheimer: Yes. As I said, the development was faster than I had anticipated. Obviously, for

example, the recombination of DNA took place through processes we didn't fully understand. But then, in the early seventies, recombinant DNA came, not by the way cells do it, I'm sure, but by human ingenuity using enzymes and other things from cells. We still don't know exactly how cells do it, but we can do it in a test tube in a shortened way. Then I was asked to give a number of talks deriving from that talk ["The End of the Beginning"]. And in some of those, I tried to point out both the potentials and the difficulty that this would bring. The potentials were clear for human genetic diseases. But at the same time, you were going to have the potential for determining the genetic characteristics of the next generation. How would you do that? Who would do it? Who would have the responsibility and the authority? And according to what criteria? And then when you talk about genetic disorders, where do you draw the line? Everybody might agree that cystic fibrosis is a genetic disorder, but is myopia a genetic disorder that you want to cure?

Erwin: Now this is really what was--and still is, I suppose--called eugenics, is that correct?

Sinsheimer: Well, yes, it harks back to the old eugenics.

Erwin: And this had a bad odor.

Sinsheimer: It does, for several reasons. One, there was the assumption in it that somebody knew what was best. And then, of course, the Nazi misapplication to create the master race. People were sterilized, the mentally incompetent. Which again implies that somebody knew what was best. So there were all those kinds of questions. As you say, eugenics had a bad name. And indeed, if you look at the history of human genetics, it really goes back to [Francis] Galton. He was the first one--he was a cousin of Darwin--who took up the point of view of genetic determinism in human beings. This was back in 1870. He invented the word "eugenics." And then there was some interesting human genetic work done early in this century by just identifying genetic traits. But then, because of these eugenic aberrations and the Nazis and so on, the whole field fell into disgrace. And it only revived, really, in the sixties, I think, through medical understanding of a number of these disorders, diseases that were in fact genetic. One could begin to give genetic counseling. So it revived through the medical field.

Erwin: I think there has always been and still is this feeling of uncertainty about to what extent you could advise people, for example, not to have children if there was the possibility of a disorder.

Sinsheimer: Of course, or to counsel abortion after amniocentesis became possible and you knew if you had a child with Down's disease or something like that. Each step becomes a little more interventionist, and each step raises its questions. You could raise the possibility of abortion because you know the child is going to be afflicted with a terrible disease--Tay-Sachs or something like that. But then people want to use that to decide whether they're going to have a boy or a girl. So each step brings new problems. And likewise, it was thought, for example, that we would be able at some point, through recombinant techniques, to produce growth hormones, and that would be useful for children who might become dwarfs. At the same time, people might want to use it to create basketball players. You've opened up a whole gamut of possibilities. It really gets into what I've come to think of as almost an ideology, because a lot of people simply don't want to believe that we are genetically determined. They prefer to think it's all social and cultural. And it's obviously both. I mean, it isn't pure genetics. There were these tremendous arguments about whether IQ is genetic or social, and that disintegrates because your measurement of IQ is very difficult and somewhat arbitrary. It's almost astonishing to me that you can show that there is a genetic correlation, but there definitely is, if you compare identical twins and fraternal twins and siblings and so on. It's clear there is a genetic correlation, even if they're reared apart. And people have applied this to alcoholism, schizophrenia, things where it's not absolute. If one identical twin becomes schizophrenic, it isn't certain that the other does, but there's a much higher chance. So that somehow there is a genetic and an environmental component, as there is for alcohol.

Then there are the questions of not only what does the society want to do, but you also have to consider what the offspring are going to feel. How are they going to react if they think that they've been programmed to do this or programmed to do that? There was some discussion of cloning. It fortunately turned out to be more difficult than they thought. How would a clone feel, if he knew that he'd been cloned from a particular individual for that purpose?

The point is, it's such a change from all human history. It's outside the boundaries of our ethics, which have really been developed to deal with other kinds of problems.

Erwin: Certainly these things haven't been beyond the human imagination. Take something from literature, a book like *Frankenstein*, to give an example.

Sinsheimer: Oh, the creation of life, yes.

Erwin: Yes, but also the creation of an unnatural creature that thinks and feels like a human being, which the creature does in *Frankenstein*.

Sinsheimer: Well, it goes back long before that. The myth of Galatea. The sculptor makes the statue so beautifully, and some god blows the breath of life into it, so it does come to life. This goes back--in *Frankenstein,* too, for that matter--to not understanding the difference between living and nonliving. If you could just put something, some spirit into it, it would become living. Biology now tells us that's hopeless. You've got to have DNA and RNA encoding proteins and all the rest of that stuff. But then, also, the Frankenstein myth is not really that you have created life. It's that, having created it, it is not subject to its creator.

Erwin: In the sense that it, he, [the creature] becomes loose, roams around.

Sinsheimer: Yes, he's an autonomous creature and can live on beyond his creator. I guess it was, maybe not the first, but one of the first novels in which the product of science is evil. And, of course, that's become kind of cumulative.

Historically it seems to me that what has happened is, life was really pretty bad, so almost anything you could do to improve it was welcomed, even if it had some side effects. But we've gone beyond that time, and for most people--at least in the Western world--life is pretty good. So the side effects loom larger sometimes than the potential improvements. Accompanying that is the fact that the capacity to do things has been augmented so greatly through machinery. You can move whole mountains. I'm always astounded--I've forgotten what product it was, but after it was introduced, within five years it was being made in a billion pounds a year, or something like that. We have this kind of capacity to turn out immense quantities of a new material and to perform many other feats on a vast scale. It wasn't possible many years ago; we had nothing like the factories or the machines. So the capacity certainly has been enormously augmented, together with the acceleration of technology.

There, again, I think science started working on the surface of things. I said that in respect to life, but it's true for inanimate matter, too. You worked at the surface of things and then you gradually worked down to the atom and the molecule. That's the basic level--at least as far as we're concerned. Sure, there are subatomic things, but that doesn't affect us, really. But, there again--just as with biology, once you got to the genetic level you tried to reshape life, similarly in physics and chemistry--once you got down to the molecules and atoms, new chemicals were made, new arrangements of matter in transistors and things like that. So that the whole pace of change has accelerated.

Erwin: At what point do you think you started to feel a certain sense of alarm?

Sinsheimer: I wanted to raise some of these issues that sort of became apparent in the late

sixties. It wasn't alarm, but I felt that these potentials were surely coming, and we needed to have thought beforehand about how to use them and who would control their use. Another thing that happened during this time was that in '68, I became chairman of [the Biology Division], so that had several consequences. It got me involved in thinking about the future. Also, it put me on the Institute Administrative Council, so it got me planning and thinking about the future for the institute itself.

Also at that time, I was elected to the National Academy of Sciences and then to its Council. I was on that for three years, and that put me in contact with the policy issues and so on at the National Academy in Washington. And I have to say, and this may sound bizarre, but until that time I had been what I can only call a naïve academic. Washington was a shock when I first went there. It was just so foreign. The Academy isn't an ivory tower, but compared to Washington it surely *is* an ivory tower. Washington is this immersion in this totally political environment. And it is *totally* political. The merit of an issue is not irrelevant, but it's surely secondary to the politics of who you know, what you know, your relationship to people in power, and your understanding of the tricks of political maneuvering, how you're going to [wield] political influence. I'm not saying it should or shouldn't be that way. I'm just saying that's the way it is. And that takes some getting used to. And the first time, I really found it to be unpleasant. Then I came to realize that, Hey, that's the way it is, and it probably can't be any other way, because in a certain way Washington is the place where noncommensurable issues get resolved by compromise. I mean, there are definite choices. And they're resolved by political compromise. That is a whole art in itself.

So that made me realize that, however we might want to discuss these ethical issues abstractly, they're going to be resolved politically or legally, and probably also commercially. When you have the free enterprise system, if somebody can make a buck, they will. So that there was on the one hand, if you like, the abstract question of what *should* we do. And then, in particular, as things started to move faster, you didn't have the luxury of waiting for a long time while you thought this business through. And then still another complication, starting in the sixties and the seventies--it started broadening. Then you realized that not only do you have all these conflicting points of view in the United States, you have the rest of the world, with their different cultures and their different points of view and ideologies, their different religious perspectives. And these problems were just as real to them as they were to you. But they didn't go at them in the same way.

Erwin: Around the period 1969 and '70, do you think that any outside influences play in at this time? It was a rather turbulent period, shaping what then became an ever widening debate over biohazards?

Sinsheimer: I think yes, in the sense that, as you know, the late sixties were a turbulent period--the civil rights [movement], Vietnam, and so forth. Fortunately Caltech was relatively spared, for which I'm eternally grateful. Caltech students were scientifically oriented. There is only one occasion I can remember with students really being upset, which was the invasion of Cambodia. We had to close classes for a day and have discussions with the students. But I do think that whole era--personified, I'm sorry to say, by Nixon--led to a great distrust by the public, which still persists, particularly among young people: You remember, "Don't trust anyone over thirty." They still have this distrust of authority and of the government particularly. But of all authority--university authority. In some ways, you could say that's good, they should distrust. But at the same time it's become a form almost of paranoia. They don't believe anything. I remember a discussion with people up at Santa Cruz about various technological problems, and they just won't believe anybody. If they want to believe this is bad, it's bad. No matter how much data you show them, they don't trust it. And, of course, it's taken even more extreme forms, like the animal rights movement. But you're right, that period certainly [was significant].

Coming back to the bioethics issue, these are subtle problems, they are not easy problems. At the same time, this total distrust of authority makes it even harder to achieve a consensus. And of course, I have to say I think TV has made things worse.

Erwin: Why? You think the issues are presented in too superficial a manner or there's sensationalism?

Sinsheimer: All of the above. [Laughter] Plus, it's too immediate. By reading, you have filtered the information. We're primarily visual creatures. I mean, if it's on the damn TV screen, we believe what we see. We don't realize how hokey that is. We see what the guy behind the camera wants us to see and that's all we see.

I first realized that back in Iowa. They had a TV station there, and they asked me to appear once to talk about, I've forgotten--something in biology. And they had this program where they did an interview just like we're doing here. They had a set with bookcases, it looked like you were in a nice library setting, about as big as this office. [Laughter] And really it was in a big barn. [tape ends]

Begin Tape 3, Side 2

Sinsheimer: I'd like to talk a little about the [biology] chairmanship and the Institute Administrative Council.

Erwin: And that began in 1968.

Sinsheimer: The paper with Kornberg on the synthesis of DNA came out in '66 or so. ["Enzymatic Synthesis of DNA. 24. Synthesis of Infectious Phage PHIX174 DNA," M. Goulian, A. Kornberg, R. L. Sinsheimer, *Proceedings of the National Academy of Sciences*, 58 (6): 2321-27,1967] Anyway, in '68 I got the California Scientist of the Year Award for that year. By pure accident, as far as I knew, Lyndon Johnson was giving a talk at the National Institutes of Health, and he needed something to say. Somebody apparently put on his desk something about this [DNA synthesis] being the closest approach to the synthesis of life yet. And he mentioned it in his speech, so of course it made all the newspaper headlines.

Erwin: Did he mention your name?

Sinsheimer: No, he just said this discovery in California--I've forgotten exactly. But because it was in his speech and at NIH, it got an enormous amount of publicity.

I still remember the year before, I guess it was, that Watson wrote *The Double Helix* [published 1968—ed.], in which he portrayed himself and Crick as being in tremendous competition with Pauling in discovering the secret of the structure of DNA. Actually, they had information about what Pauling was doing, but he didn't have any information about what they were doing. He [Watson] had portrayed science as a rather cutthroat business: They were stealing data from [Maurice] Wilkins--all this kind of thing. And I always felt that that was greatly distorted and exceptional, because it was not my experience. And I still remember, when I got this California Scientist of the Year Award we had this press conference, and I explained that I had done this work in collaboration with Dr. Kornberg. And a reporter asked me, "How did you ever do this?" His understanding of science was that people never collaborated, they just competed. I had to try to explain to him that collaboration was much more common than this kind of cutthroat competition.

As chairman, there are several things [to say], but the most important is this. We had had quite a bit of discussion in the department about the future direction. At Caltech, it was always felt that you concentrate on key areas. And there was a general feeling that there were two such areas we should concentrate on: One was molecular genetics and the other, neurobiology. We had Roger Sperry; we had a couple of older physiologists, who were approaching retirement. So it was thought we should really make a big push in neurobiology.

Erwin: Was that conclusion reached while you were chairman?

Sinsheimer: Yes. So then it was my job to do that. So my first job was to get acquainted with neurobiology, and I organized a conference, "The Biological Bases of Behavior." I had people from all over the world. I thought it was a great conference when I put it together. And then, partly as a consequence of that, Arnold Beckman was persuaded to donate money for building the new building [the Mabel and Arnold Beckman Laboratory of Behavioral Biology].

Then I knew what I needed was somebody to lead this enterprise. In a way, Roger Sperry would have been ideal, but Roger Sperry, as you probably know, is really a very difficult kind of person. He could never lead anything; he rarely comes out of his lab; he does his own thing. At this conference, I had been very impressed with Jim Olds at Michigan. He was the one who had discovered what were then called pleasure centers. He was, I guess, head of the Psychology Department at Michigan. Fortunately I was able to persuade him to come out to Caltech to head up this program.

Erwin: Was he a psychologist?

Sinsheimer: He was an experimental psychologist. He worked with rats, planted electrodes in their heads; he was studying learning in rats.

Erwin: Did he have the rat in the maze that you described, who got his "charge"?

Sinsheimer: Yes. He did that. He was trying to trace learning back, all the paths of an auditory or electrical signal into the brain. He was clearly a major person in the field, had a lot of insight. He was a rare person--and still would be, if he were alive--because he had a good background both in neurophysiology and psychology. The psychologist presents the problems that need to be solved and the neurophysiologist presents how you might approach them. So he came out and we put together, I thought, a really very good group of people--Dave Van Essen, Jim Hudspeth. A couple are still there, I think--John Allman, Mark [Masakazu] Konishi. I thought it really got off to an excellent start.

And then--it was tragic. The year after I left for Santa Cruz, Jim Olds drowned. I guess they tried for a while to get somebody to replace him but without success. They've brought in some good young people since then. But that was, I would say, probably my major accomplishment as chairman. I also brought Seymour Benzer.

Erwin: He was in the molecular biology area.

Sinsheimer: Yes, he had been in that, and then he decided to get into behavioral genetics with *Drosophila*. He's done some beautiful work there. I also brought Eric Davidson in developmental biology, James Strauss in animal virology, Jean-Paul Revel in electron microscopy, Henry Lester and Jack Pettigrew in neurobiology.

The IAC [Institute Administrative Council] was interesting. I'm trying to remember how often it met.

Erwin: Under [President Marvin L. (Murph)] Goldberger, it was once a month. I don't know how it was under [President Harold] Brown.

Sinsheimer: It was probably once a month. I was on it first under [President Lee A.] DuBridge in his last year [1968]. And I'd say DuBridge ran it very autocratically. He set the agenda and he didn't put anything on the agenda that he didn't want. I still remember, one time there was a delicate topic, and I thought it at least should be discussed. And I sort of kept after him to have it on the agenda, and he complained but reluctantly put it on the agenda. But he was pretty sharp. The meeting went on and on. Finally, at five minutes to twelve--we would break for lunch at twelve--this comes up on the agenda. He just sort of dismissed it; it was a lesson.

Anyway, Harold [Brown] ran things more democratically, I would say.

Erwin: Did he, for example, solicit agenda material?

Sinsheimer: Yes. His modus operandi was that he would sit there very quietly. Of course, it was clearly understood he had the final decision. I said it was democratic; it was democratic in the sense that there was discussion, but we didn't take a vote. Although sometimes we did take a vote, but it didn't matter, he had the final decision. We would take a vote, for example, on tenure decisions. The way that worked was if someone came up for tenure, then the department would have its tenure review and the department would vote, and that would be brought to the IAC, along with the case.

Erwin: Wasn't there a committee intervening between those two levels?

Sinsheimer: No. It went from the department to the IAC; the case went to all the other division chairmen--at least at that time. And they would read the material, they really would. And you'd get some pretty tough comments in the IAC. And then, finally, there would be a vote. It became

pretty clear--and I think appropriately--that the standard was and should be very high. Basically, unless the candidate got at least seventy-five or eighty percent voting favorably in the division, you would never get tenure. Which I think was probably appropriate for Caltech. It's probably not as appropriate at a place where the standards are not quite the same.

Erwin: Appropriate in the sense that it had to be that high?

Sinsheimer: It had to be that high, and it had to be somebody who was clearly distinguished. It had to rest on accomplishment, not promise. Now things have probably gotten a little more complicated, with the affirmative action issue.

Erwin: That was just starting to happen at that time.

Sinsheimer: It was just starting to happen when I became chairman of biology. Jenijoy La Belle, that was just about the time I left.

Erwin: That became a rather celebrated case.

Sinsheimer: Yes. And Caltech got hung out to dry. I learned more about affirmative action at Santa Cruz, in the UC system. I mean, the fact was that in biology we would solicit a lot of outside letters from other people, and unless this person would be ranked in the top five of his age in his field, we wouldn't recommend him. Even then there might be some dispute.

Erwin: That probably worked well in the sciences. But I wonder whether in the humanities it worked as well, because the top five in the country in the humanities are not at Caltech. They're at Princeton or Yale.

Sinsheimer: Well, it's more complicated than that. In the sciences, you get a pretty sharp distribution. In other words, the evaluations will be pretty uniform. In the social sciences, they'll be much broader. In the humanities, they'll often be bimodal. I'm serious. It became very clear that there were different schools of thought of literary analysis, like ideologies. People in one school thought you must be an idiot if you were in the other school; regardless of whether you were the best protagonist of that school, you were still an idiot. And so you literally got bimodal distribution. And I saw the same thing up at Santa Cruz. And the worst were the arts. Arts people are totally unwilling to evaluate anybody. Everybody's equally good, as far as I can figure out. One artist feels totally unwilling or incompetent to evaluate another artist.

But to come back to the IAC--what I came to realize also was that the institute was pretty smart. It's a great place, and it knows it; and it's quite happy. [Laughter] And it doesn't want to change. And suggestions for change of any kind did not fare too well. Let me give you a couple of examples.

The American Academy of Arts and Sciences decided that it would be good to set up a national center for the humanities. There were some foundations that were willing to support this. I was at the time somewhat active in the American Academy and still am. And I conceived the outrageous idea that we could put a national center for the humanities at Caltech. It sort of fit in with my concerns about bioethics. Interestingly enough, that intrigued the committee of the American Academy. I obviously also had to propose this to Harold [Brown]. And they came out and they looked at Caltech, and I think they were sincerely interested. But Harold wasn't very interested. He wasn't negative, but he wasn't about to go out and raise any money. And it was clear the other division chairmen--again, I don't think they were negative, but it didn't enthuse them. Except humanities, of course.

Erwin: Do you think at a different time, maybe? I mean, budgets were awfully tight for a period of years there.

Sinsheimer: This was later than that. Budgets were very tight after Harold first came. I think by the last DuBridge years, things were running in a deficit. But he got that straightened out pretty quick. And by this time, as far as I know, [David] Morrisroe [then director of financial services] was there. And I think they were in a reasonably sound state. It would not have been a huge drain on the institute; we probably would have had to raise a few million dollars to help to match other funds to build a building. At least Caltech had the land. It's just that it didn't appeal; they didn't see how it would fit into their conception of the institute.

Erwin: Well, how would you present this? How would you move on this plan?

Sinsheimer: Well, I presented it from the point of view that science and technology were increasingly posing problems that affected society, and not just affected society economically but affected society in terms of culture and ethics. In a sense, it was the responsibility of an institution that was constantly, I use the word "spewing forth," changes in society to have some concern for the effects of these on society. That was my argument.

Erwin: It became a theme with you.

Sinsheimer: Yes. And that this was kind of an elegant way to do it. I didn't want Caltech to try to develop a whole school of humanities.

Erwin: This center would have been permanent?

Sinsheimer: A permanent center, yes, with a small, permanent staff. It actually finally got established, at Duke [University]. And it has a small permanent staff and then each year twenty-five or thirty people come, and they spend a year there doing research and talking to each other and talking to people around the university. They have weekly seminars. I think they pick a theme for a year.

The second way in which I encountered that kind of problem [i.e., reluctance to change]--we had created this program in behavioral biology which was oriented, if you will, towards a neuronal basis of behavior. We had in the institute the program in humanities and, to some degree, social sciences--and increasingly social sciences. And I felt the institute needed a bridge between those, and the proper bridge was psychology--particularly experimental psychology. So I proposed that we should have a division of psychology. But then I realized how hard that was. I mean, you've got six divisions, and how do you create a seventh? There's nobody to speak for it. You're there in the IAC, and each chairman is defending his department, which he should do. But there's nobody to speak for the seventh. They all see a seventh department as another claimant on the institute resources. So I was never able to get that.

Turning back to Harold, who I think was highly intelligent and a great administrator--he had no educational vision. I don't say that because he didn't think these were great ideas. But I can't think of anything he did for education. He was happy enough to keep the institute running. And you know, that's not bad; it's a great place. The division chairmen, of course, varied a lot in their ability to take a larger view. Some of them were able to look at the institute as a whole. Others were just appropriately the representatives of their division. Of course, I found the same thing later on at the University of California, where the analogous group was the council of chancellors.

Erwin: Were you finding that you were becoming increasingly frustrated with Caltech as an educational institution?

Sinsheimer: Oh, no. I always enjoyed Caltech. I did feel that those kinds of changes I mentioned would be beneficial, but not only, as it were, for the institution. I did think--and I still think--that the educational opportunities for students at Caltech are too limited. The institute needs to be more creative. It's not really that they don't have available courses in arts and

music. It's more than that. They don't have contact with students who have majored in the arts or humanities, whose whole outlook on life is different, with people who think the arts indeed are the most important thing in the world and not science or technology. And I think it's important to realize that there are these other people in the world who have other goals, other values. And if you don't have contact with them, you tend to be sort of scornful of them and you don't understand them. I think it's something of a deficiency in one's education. I don't know really the solution to that, because I think Caltech would lose itself if it became a university.

MIT has been able to do a better job, probably because it's bigger and it's much more diverse. It has a school of architecture, for example, and that has led into things like city planning. And they've been quite interested in, not the conventional arts but the more modern--How can you describe them?--arts. They have some very creative programs. They're much more diversified in many ways. They're about thirty-five percent women, and they have an immense variety of activities. Of course, it's five times the size. So you have enough students to put on dramas, to make an orchestra, to do that kind of stuff. And then there's another thing: They can take courses at Harvard, which is just down the road.

Erwin: Well certainly, at Caltech, some concessions have been made to broaden the whole base of the education. There's the possibility of taking courses at Occidental. And of course, the advent of women undergraduates--do you think that's changed things?

Sinsheimer: A little. They've never been able to get up, it seems to me, a high enough proportion to make a real difference. At MIT, they do; thirty-five percent means one out of every three is a woman. I have to be honest and say I think there have been some negative aspects at MIT, and they're worried about those: That in the effort to diversify the student body and to diversify the offerings, they have had to dilute the basic core science. There's not enough time, and not all the students are interested in it, and it is now much more diluted. When I was there, everybody had two years of physics and two years of math; there was no choice.

Erwin: Now is that true at Caltech?

Sinsheimer: Yes, I think it's still true at Caltech. It was when I was there.

Another thing, for example, when I was at MIT--as a freshman, you spent practically every afternoon in the lab. Now that's been eliminated. And there's a serious concern about that; they're reviewing that whole thing now. I think it was a mistake. You need some kind of hands-on experience to make this real. It's one thing to read about a reaction; it's another thing to see it.

Erwin: I wonder if this was not simply an MIT problem but a tendency, a sign of the times.

Sinsheimer: I must say I was on the accreditation team that visited MIT last fall--even MIT has to have some accreditation. [Laughter] You know you're not going to take it away, but they go through the motions. It's a valuable exercise, because they have to review everything. Another thing they're doing there, they're planning to make a semester of biology required. Biology is now a respectable science. But still more important, if they pull it off, is [a change in the engineering curriculum]. MIT is much more of an engineering school than Caltech. Traditionally, I think, two-thirds of the students at MIT are in engineering. They have many varieties of engineering that Caltech doesn't have at all. And it's the engineers who have been the dominant group at MIT, and they're the ones who are the most dissatisfied with what they regard as the dilution of basic physics. But the problem is what to do about it. They recognize that some of these other things, the broadening courses, are valuable. And they have, among themselves, pretty much come to the conclusion that four years is no longer sufficient for an engineering degree. And they are really proposing to go to a five-year program. You'll still get a kind of a degree at four years, but it won't be what they call a professional degree. You'll have to go a fifth year to get that professional degree, because that's the only way they feel they can put in more of the rigorous training and still allow the broadening of the curriculum.

Now, that's, of course, a major break. If MIT does that, other engineering schools will have to at least consider it, if not follow it through. It raises all kinds of problems. It's costing. They're thinking MIT might be able to raise enough scholarships and so on from industry to support the students a fifth year. But this has been recommended by the engineering division. And that might be something that people at Caltech will have to consider.

Erwin: When you were chairman of the division, did you find that it was a full-time occupation, and should it have been?

Sinsheimer: I think, no, it shouldn't have been, in the sense that I was able to maintain a research program. And it was desirable to do that, for several reasons. One, it should not be a lifetime occupation. It was a five-year appointment [1968-1973], and then a second five-year appointment, though I left after four years [1973-1977]. I told Harold when I met with him that I felt that you should get somebody new, somebody who's different, somebody who's fresh. I think the five-year appointment was so that you at least got reviewed every five years, and renewal wasn't automatic. It had been too difficult to fire [chairmen], because they thought it was for life. Going back to George Beadle, nobody wanted it. He was the chairman when I

came, and then in '59 or something like that, he became, I think it was called dean of the faculty. We didn't have a provost in those days, and he was sort of second in command. When he took this on, he said, "Well, I really shouldn't do that and try to be chairman, so you guys select another chairman." Well, we never could select another chairman. We were quite happy to have a third of Beadle. [Laughter] But then, of course, he went to Chicago [1961]. So I think it shouldn't be a full-time job. And I think as long as the institute doesn't get any bigger, it doesn't have to be. But I will say, one thing which Caltech did and which makes that possible is to give the chairman more hands, more support--executive officers, administrative officers. I have to say honestly that UC doesn't do as good a job in that. It's costly, but it relieves the chairman of a lot of nitty-gritty things. Because I think the chairman should keep up with research programs. Otherwise, what's he going to do when he's no longer chairman? And he should keep active and alive in research if he's to represent the division outside. In biology, I represented the Biology Division at the National Academy. You're called on to do that, make speeches.

Erwin: The chairmen of the Biology Division have typically been drawn from members of the division. Was there ever any discussion about getting someone in from the outside to be chairman?

Sinsheimer: Yes, particularly after Beadle left, it was seriously discussed. I think the job was actually offered to someone from outside but they didn't take it. [Ray Owen was chairman] when Harold came in, and then I think Ray just got tired of it. And then when I left, there was Norman Horowitz. Then when he retired, I think there was again a serious discussion, but they ended up with Leroy Hood. It's the usual problem--how to get somebody from the outside who understands the distinctive features of Caltech, particularly Caltech biology, who is also at the same time a very good scientist and can operate his research program and bring it to Caltech, versus "Who have you got available at Caltech?"

Erwin: Have other divisions looked outside? I believe so, on a few occasions.

Sinsheimer: I believe so, particularly engineering. They brought in [Francis] Clauser and then they brought [Robert] Cannon. Those were both from outside. [Tape ends]

Begin Tape 4, Side 1

Sinsheimer: In 1977, I was in transition in several ways. First, my research was in transition. I was winding down the Phi X research and trying to get started in the nitrogen fixation research.

I was in my ninth year as chairman, and I had decided that I didn't want to be considered for another term. And then, quite out of the blue, really, I got a phone call one day--I think it was in February--from David Saxon, the president of the University of California. David Saxon had been a classmate of mine at MIT, and I had known him off and on for years, but I'd had very little contact with him in the previous probably fifteen years. Well, to make a long story short, they were looking for a chancellor at UC Santa Cruz and could I be interested. Well, I knew something about UC Santa Cruz; my daughter had gone there some years before. Also, I knew George Hammond, who had been chairman of chemistry at Caltech. And actually, that's really curious in a way, because George Hammond and I go back a long way. We were both at Iowa State. We both came to Caltech, separately. And then he had been chairman of chemistry while I was chairman of biology. And he had gone to Santa Cruz as a vice chancellor. But then he had stepped down from that and gone back to being a professor. And I'm sure he must have been one of the people [who recommended me]. Anyway, Saxon said I had been proposed as a candidate for chancellor and would I be willing to consider it. Well, I hadn't thought about this at all. So I said, "I don't know, but I'll think about it." And then, I guess, partly because I was in this transitional stage, I said, "Well, I'd be willing to go up and look at it." I understood that he wasn't offering me the job; I knew they had some other candidates. So I went up there and looked at it and met with a number of people and with the students. It's just a beautiful place, truly beautiful. And I must say I was in all honesty intrigued in many ways. I knew it was one of the new campuses, and I thought it would be growing. I mentioned before, I'd come to realize that a university that is established and not growing is very hard to change. But in a growing university, you can impress some new concepts and programs on it. Also at this time, because of my concern with bioethics and with the social impacts of science, I'd come to feel that we had a serious problem--and we still do, it's even worse--in that we have a scientifically illiterate populace. In a democracy, they have to decide on these issues that have more and more scientific and technological content. And I felt that some serious efforts were needed to develop programs that would provide some kind of background for the general student--not the Caltech kind of student, other students. And Santa Cruz might be a place to do this.

Well, I met with Dave Saxon, and the people up at the central administration assured me of their support if I were chosen. And then a few weeks later, yes indeed, I was the choice. Then I really had to decide, not just play with the idea. And it seemed like a challenge, I guess. I mean, I could stay at Caltech and go back to professor and do what I'd done, and that was fine. I had a great life. Or I could take on this new challenge. Also, at that time I was fifty-seven and I wouldn't make many more life changes after that. If I was going to do it, this was the time. So I said yes, with frankly a lot of hesitation. And if I had been better informed, I probably wouldn't have said yes. [Laughter]

Erwin: It wasn't a particular thing at Caltech?

Sinsheimer: No, it was no particular unhappiness. I was happy at Caltech, I really was. I'm sure if I'd stayed as a faculty member there, I would have continued to be very happy. Let me preface that by saying, in the twenty years I was at Caltech, particularly after the first couple of years, I probably got three or four offers a year to go somewhere else. I don't say that bragging. Practically every university in the United States. And I never said yes, because I could see no reason that I would be happier there than I was at Caltech. It had everything I wanted. You could do research, have wonderful colleagues, great students, and so on. So there was no reason for me to go to Harvard or to Yale or to Florida or to wherever. So it wasn't that I was unhappy at Caltech; it was just that this was a new and different kind of challenge. And it was more of a challenge than I realized.

Erwin: How long were you at Santa Cruz?

Sinsheimer: Ten years.

Erwin: And then you retired?

Sinsheimer: Yes. They have a mandatory retirement age for administrators; but I could still be professor. And I came down here [University of California at Santa Barbara] because I felt that it's a bad practice for a chancellor to stay on as a professor where he's been chancellor. It's difficult for the new chancellor, because you're always looking over his shoulder. And you're bound to not always agree, but he's the chancellor, it's his responsibility; you should stay out of it. At the same time, since you *were* the chancellor, people who may disagree with the new chancellor inevitably try to bring you and whatever prestige you have into the issue. And you shouldn't do that.

And in part, frankly, I had some problems with the founding chancellor, who's still there, who sort of butts in from time to time. So I really felt, both for my own peace of mind and for the new chancellor, I should not stay on. I was able to arrange to come down here. Actually, my status here is anomalous, in a sense. I'm a professor at Santa Cruz, but I'm on loan to Santa Barbara.

Erwin: At Santa Cruz, in your pursuit of a more balanced program, were you able to realize any of your educational vision?

Sinsheimer: Yes and no. To answer that, I have to point out that at Santa Cruz the situation was almost the other way around. Caltech is science-dominated and, with all due respect, rather limited in humanities and social sciences. At Santa Cruz, they have some good science programs, but it was really dominated by the humanities and social sciences. And so one of the things I had to do was to build up the sciences and start some engineering.

Erwin: Is that why, for example, they were interested in you, in a scientist?

Sinsheimer: Well, it may be why Saxon was. I'm not sure why the campus was. The Regents is another whole story.

Erwin: They don't come into that?

Sinsheimer: Oh, they do come into that. The Regents have to approve the choice. No, the other problems at Santa Cruz were a variety of things.

Erwin: Did your feelings about education in general change?

Sinsheimer: No. As to what I think is desirable in education, I don't think my feelings changed. I think I acquired perhaps a much more realistic sense of what's possible, and of the real limitations posed by resources. With Caltech, you're remarkably insulated.

Erwin: So you were spoiled at Caltech, in a way?

Sinsheimer: In a sense. [Tape ends]

ROBERT SINSHEIMER
Session 3
March 26, 1991

Begin Tape 5, Side 1

Erwin: Who blew the whistle on the DNA controversy?

Sinsheimer: Well, Paul Berg is largely associated with it. Although, it seems to me that Dr. [Robert] Pollack at Columbia really also played a significant role.

Erwin: And Berg was at Stanford.

Sinsheimer: Right. In the early seventies, several laboratories were beginning to try to do experiments which involved combining different genomes for various reasons: One purpose was to move genes from higher organisms into bacteria where one knew how to manipulate genes readily. Also one wanted to try to introduce, in one way or another, genes into higher organisms via viruses. The problem was, How could you splice genes? And as I said, a number of labs were trying to do it. In my own lab, we were trying to see if we could, with Phi X, work out something of that kind. The obvious trick was to somehow be able to find some gene that the virus didn't need that you could then replace with something else. In the case of our own work--actually Tony [Anthony J.] Zuccarelli did much of his thesis on this problem. We thought that the gene that we could probably do without was the gene that is responsible for lysing the cells. Because we could do that (lysis) artificially. And we knew where that gene was. The idea was that if we could get a virus that didn't have it, then we might be able to insert something else. Actually, Tony put a lot of effort into this. And it turned out negative, for a reason that we didn't understand at all at the time, which we now understand, because it turns out that the gene for lysis overlaps another gene which is essential. So it was doomed from the beginning. But we didn't know that, and we were misled down a number of pathways.

Anyway, Berg was going at this more systematically, as before. Berg sought to combine genes from the SV40 virus with genes from the lambda bacteriophages. It was known that portions of the lambda DNA were not necessary under certain conditions. And then I really think it was Pollack who pointed out that you might be producing something that was hazardous. And Berg, as I understand it, sort of backed off and didn't do anything for a while. But then the whole issue really came to the front again with the Boyer-Cohen experiments with plasmids.

[Stanley] Cohen was at Stanford, [Herbert] Boyer was at UCSF [University of California at San Francisco]. That was really the beginning of recombinant DNA. What they showed was that they could cut open a plasmid and insert another DNA, seal it back up, put this back in cells, and it would grow. That was about '73.

Erwin: I know you were on sabbatical for some of that year. Were you actually gone when this happened, or were you pretty closely in touch?

Sinsheimer: Oh, I'm sure I was aware of it, because I was in Switzerland in a lab. But this really broke it all open. Then there was a Gordon Conference that summer--and I wasn't at that because I was on sabbatical--at which there was some discussion of were there any possible hazards, because it seemed clear this was going to make possible an introduction of practically anything into bacteria, at least. My understanding is that some group, or the conference, wrote a letter then to [Philip] Handler, president of the National Academy [of Sciences], saying that there was this concern and would the Academy look into it. And Handler appointed a committee, which included Berg and some other people, probably [David] Baltimore and some others. And they finally wrote this letter back to Handler and a statement was issued at some time in the summer of '74 which, in effect, pointed out that there was a possible danger here, that it needed to be evaluated--there might not be any--but calling for caution in these experiments and that a conference would be held to review this in more detail.

Erwin: What were your feelings at that time?

Sinsheimer: I think initially I kind of passed it off.

Erwin: You mean you thought it was an overreaction to the possible dangers?

Sinsheimer: I think initially I thought this wouldn't call for any more precautions--and I guess I was initially thinking in terms of hazard to the people doing the work itself--than were required for other kinds of work in the lab. You work with dangerous materials all the time. But then, for whatever reason, I got to thinking more about this.

There was another set of experiments going on, which somehow did not get much in the press, but which I remember perturbed me. And this had to do with tumor viruses. At that time, there were no known human tumor viruses. In fact, even now only a few are known and they are not a major problem. But there were well- known animal tumor viruses, a feline tumor virus and a baboon tumor virus. And people were doing experiments with these. They were mutating

these; they were doing genetic crosses between them.
Erwin: Where was this happening?

Sinsheimer: Well, one place I knew was at Saul Kit's lab, some place in Texas [Baylor University College of Medicine in Houston—ed.]; and at NIH, I think. It seems to me also evidence was coming out at that time that the baboon tumor virus and the cat tumor virus were related. And it seemed probable that there had probably been some species jumping at some time.

Erwin: Now does that mean that those viruses only cause tumors in respectively cats and baboons? And were not known to cause them in any other species?

Sinsheimer: Right. But that somehow the cat virus had mutated into the baboon virus. There was evidence, at least, that it was sufficiently closely related to the baboon tumor. So that obviously gave me the concern that in playing around with these different viruses and mutating them, you might somehow create a virus that was a major problem for humans, where one didn't naturally exist. But nobody seemed to be worrying about this. Well, that joined with the other [issue, i.e., recombinant DNA]. And then I got to thinking more seriously about the recombinant DNA experiments. And what concerned me particularly was the fact that these were being done in *E. coli*--which was understandable, because we knew far, far more about the genetics of *E. coli* than any other bacterium, because it had been studied for twenty-five years, and we knew how to introduce viruses into it and plasmids into it and all that kind of thing. But, of course, the fact was that *E. coli* is an organism that lives naturally in the human intestine. And in a certain sense, we live in a world surrounded by bacteria, which you really can't avoid. And if we did produce some kind of dangerous organism, a dangerous form of *E. coli*, it could easily spread very widely through the population.

Then there was the question, Was one likely to produce such an organism? Well, we know that many organisms have genes that produce toxins, and somehow these might get into the *E. coli* and that wouldn't be a very happy thing.

I think a second aspect that particularly concerned me was—and you might say, "Well, nobody would do that purposely," and that's a different issue, possible misuse, but I'm thinking of accidental. But what particularly concerned me was that people were doing a lot of what were then called shotgun experiments, where you took a random piece of genome from some organism--you didn't know what the heck it coded for--and put it into *E. coli*.

Erwin: Why? Was it just to see what would happen?

Sinsheimer: To see what would happen, or maybe you knew that somewhere in that piece there was a gene you were interested in, but you had no idea what other genes were also in there.

Erwin: Was that done at Caltech?

Sinsheimer: Yes, probably. It was being done at Stanford, at SF, at Berkeley, lots of places. So that particularly concerned me because--well, you'd say it's accidental, and it is, but you're putting things in that you simply know nothing whatsoever about. And could some of these be toxic? How do you know?

Erwin: I recall there was sort of a voluntary moratorium.

Sinsheimer: Well, the statement that came from the Academy, that the Berg committee put out, called for. . . . Now I've forgotten the language, because it's interesting how attitudes seem to have changed. Berg's become very defensive about this whole thing. And I thought it called for a moratorium, but it seems to me I've heard him say in recent times he simply called for caution, or something like that. But certainly the word "moratorium" was commonly used.

Erwin: I don't think the letter does call for a moratorium. But someone at some point voluntarily used that word or said, "Let's have a moratorium," and it seems to have been widespread, the idea.

Sinsheimer: The idea that it called for a moratorium, yes. The Asilomar Conference was held, I think, in February '75. I was there; I was invited.

Erwin: Was that by invitation?

Sinsheimer: Yes.

Erwin: And it was sponsored by?

Sinsheimer: I guess NIH, I don't remember now. It was a very curious conference, unique, in that we'd have one session devoted to scientific results and then have another session devoted to possible concerns and dangers. And then they even had a session where they had invited some lawyers to talk about possible legal liabilities. And then, of course, there were sessions as to

what should we do. And my impression clearly was that the sessions on scientific results aroused by far the most interest; that's what the scientists were interested in. And also, one has to say, that it was clear that certainly there was no moratorium. People were using the technique and getting scientific results. I remember Dave Hogness from Stanford talking about shotgun experiments of the type I mentioned with *Drosophila* genes and so forth. So it was clear that whatever had been called for, there had not really been any moratorium.

Erwin: How could one, in effect, have a moratorium? Can you just all of a sudden stop what you're doing?

Sinsheimer: Well, that's the problem. Indeed, that became very evident, when one started to think about what to do, that the science has a momentum. After all, this technique was invented by scientists to help them solve their scientific problems. And so here was this new way of going at things for which there was no real alternative. And you could hardly ask the scientists to just turn away from it--particularly, I would say, younger scientists who've got seven years to get tenure. You have all of this momentum that's built into the system; I don't know how you could turn it off. And then of course there was a lot of uncertainty about the extent, the magnitude, of the possible hazards. It was thought that the *E. coli* strains that were being used had been kept in the laboratory for many, many years and might not be able to compete in nature anyway. But nobody really knew that. Then there was the possibility that even if they couldn't survive, they could exchange plasmids with other bacteria that could survive. And nobody knew really how dangerous it would be to have *E. coli*, even if it survived in your intestine, if it did have certain types of genes in it, leaving aside the fact that it might secrete a dangerous toxin. There were immunological concerns; even if it just produced certain proteins that might cause an immunological reaction of some kind, that was another possible concern. And then, of course, the concerns about if they were tumor genes. But nobody knew; it was all very amorphous. Not so amorphous that you couldn't sketch out a lot of different scenarios, but you couldn't give any kind of quantitative estimate as to how much danger there would be.

Erwin: Did people seem to be falling into different camps during the conference?

Sinsheimer: Oh, there were some who felt there was no possible hazard. And some were much more conservative than others. And some were much more troubled by the prospect of liability than others; some felt it wasn't their liability or the institution's liability.

Erwin: Who else from Caltech went to that conference?

Sinsheimer: I have to believe Lee Hood was probably there.

Erwin: Actually, I know that [Jerry] Vinograd attended.

Sinsheimer: Jerry was probably there. It's possible that [Giuseppe] Attardi was there. I have to say, up until almost the last day, there were huge disagreements as to what to do. And somehow, over the night before the last day—well, [Sydney] Brenner came. They [in England] had been debating the same issue and had come to certain conclusions. And he really, I think, furnished the basis for the final recommendation, based to a considerable degree on the experiences they were having in England. And what they worked out were two things: One was that there was to be what they called physical containment, which is just the sort of practices you'd use in dealing with pathogens at different levels. But then the idea came up—and again, I really think this was something Brenner brought over from England—of biological containment: That is, OK, we really needed to do this with *E. coli* because we knew so much about it, but we could develop strains of *coli* which would almost certainly be unable to survive outside the laboratory, by introducing appropriate mutations.

Erwin: Was that a relatively new thing at that time?

Sinsheimer: That was a new suggestion, yes. And everybody was very happy with that, because somehow it was thought that that could probably be done in a month or two--develop the strain. And then you wouldn't have to worry about building the elaborate containment facilities.

Erwin: So that was perceived to be an easy thing to do.

Sinsheimer: That was perceived to be the easy fix. So I think people left with the feeling that, yes, we would have these two forms of containment, and biological containment would be available shortly. And in the meantime, they would go ahead with the kinds of experiments they'd been doing.

Erwin: What about the tumor viruses?

Sinsheimer: That didn't come up. This was recombinant DNA. There were certainly different camps in terms of the extent to which people felt that there was or wasn't anything to worry about here. Certainly at that point I was in the school that thought there *was* something to worry

about, because I felt that we were venturing into quite new ground. In biology, generally speaking, the definition of species is that they don't interbreed, so that genes don't normally cross between species. And that's certainly true, otherwise you wouldn't have species. We've learned since then, of course, that there are occasions when that does happen; sometimes viruses can carry genes between species. It's not that it never happens, but it's certainly not very common.

After the meeting, several things happened. First of all, it proved to be much more difficult to develop these crippled strains than had been imagined. Roy Curtis was the leading person to do this. It took him a year, year and a half to develop anything, and even then they were hard to work with. Secondly, it was sort of left then to NIH to draw up the real guidelines to govern the work.

Erwin: Backing up for just a minute, there had been a committee formed at NIH somewhat prior to the Asilomar Conference--the Recombinant DNA Molecule Program Advisory Committee. You were not involved with that.

Sinsheimer: No.

Erwin: Were you ever invited to participate in actually forming the guidelines?

Sinsheimer: Only to comment. After the committee finally drew up the guidelines, they had a big meeting in Washington and I was invited to participate and comment.

I think once this NIH committee got into it, they found it was much more difficult to do than they had anticipated. NIH was quite unfamiliar, if you want, with being a regulatory agency. Obviously, when you get into regulation, you find yourself bogged down in a whole mess of things. You have to have definitions of terms. There are so many possible kinds of experiments and so on, that you had to think of. They eventually built this whole framework combining different levels of physical containment and biological containment. There was P1, 2, 3, and 4 protection. The P1 facilities were just sort of the standard thing; and P2 was a little more than that; and 3 was significantly more than that, where you had airlocks and things of this kind. And P4 was of course the highest, where you had the most hazardous pathogens. But then if you used biological containment, you could use a lesser physical containment and so forth.

But what struck me about it was that after they came out with this sort of matrix, in reality, the question was, Where would you float this? I mean, you could take different kinds of experiments and say, "Yes, these are probably more hazardous than these, and those are probably more hazardous than these," and so on; but you had no way to set an absolute level of

hazard, so you really had no way a priori to decide where should you put this, at what level should you put the moderately hazardous experiments. In effect, what they ended up doing was to allow the experiments that people really wanted to do at that time to be done under very modest facilities, so that the research really would not be inconvenienced. Because it didn't require constructing any laboratories—that is, P1 or P2. And whether that was really justified or not seemed to be quite arbitrary, but that was what they were doing.

So I remember at this meeting at NIH I expressed a lot of concern about the proposed guidelines. It seemed to me that it was still quite possible we were doing something that was really far more hazardous than anybody was thinking about and that the guidelines should be more stringent.

Erwin: Of course, compliance with the guidelines was essentially voluntary, isn't that right? I mean, how could they be enforced?

Sinsheimer: Well, the only way they could be enforced would have been NIH could have cut off funding. There was no law, but obviously NIH could cut off funding. Whether they were right or wrong, it's a classic situation where NIH has, like many agencies, become partly the captive of its clientele. It would be very hard, almost impossible, for them to take a position on a major matter which differed from the majority of its clientele.

Erwin: So who could have taken that position?

Sinsheimer: Well, Congress did get concerned about this, and there were hearings; I testified. And there were bills in Congress to regulate, which would set up agencies to regulate this.

Erwin: I think you testified somewhat more than a year after the guidelines were published, so there was some time lag there.

Sinsheimer: Well, it takes a while for Congress to catch on. I don't know about NIH, but it was clear that there were a lot of scientists really lobbying intensely against it; they didn't want anything with the force of law involved. They weren't too happy with the guidelines, but they could live with those. But they certainly didn't want the possibility of legal penalty.

Erwin: How did you feel about that?

Sinsheimer: Well, I felt that if there was a real hazard, which I thought there was, that you did

need someone to enforce it. I was well aware that people were not necessarily obeying the guidelines. I tried in some minor ways to increase the ability to enforce them. For example, at the time I was chairman of the board of editors for PNAS [*Proceedings of the National Academy of Sciences*], and we did put in a proviso that work done with recombinant DNA, if you were to publish it, would require a statement that it had been done in accordance with the guidelines. And we got some other journals to go along with that. It's a pretty minor kind of sanction, but it seemed to me it was in the right direction.

And then, of course, almost as soon as the guidelines were promulgated, pressures began to develop to weaken them, particularly as people started to want to do experiments that would require more containment. Now, I have to say that I was personally put in a kind of awkward position, because while I had my position on it, there were people at Caltech who certainly had other positions. And they wanted to do some of this research. And so I felt that I should make it possible for them to do so within the guidelines, so we went ahead and actually built a P3 facility.

Erwin: Where was this?

Sinsheimer: In Kerckhoff. I was the [division] chairman. And some people asked, How could I do that when I didn't think the guidelines were strong enough anyway? And I said it seemed to me it was my responsibility as chairman to foster their research. And I certainly would insist that it be done in accordance with the guidelines, but it wasn't up to me to single-handedly impose a higher set of guidelines. And there were people like Tom Maniatis and some others who were very anxious to do experiments that would require such a facility.

Erwin: What were they aiming at?

Sinsheimer: Why did they want to do it? Well, this was the way they wanted to go about their research. They were trying to study genes from higher organisms, putting them in viruses like SV40, which under the guidelines required P3 facilities. In fact, it required an investment of $120,000, building a laboratory with airlocks. Nothing could go in or out except through an autoclave.

As I said, almost immediately it seemed like pressures began to build, as people wanted to do experiments which under the guidelines called for containment facilities and various other kinds of precautions, which in a sense inhibited research. And I have to say, we really were doing things that were kind of sloppy. People in molecular biology came into it without necessarily a lot of training in microbiology. Basically, they were treating *E. coli* like another

chemical, sodium chloride or what have you, throwing it down the drain, and pipetting by mouth, and all kinds of things. You don't do it now, even for the most innocuous experiments; it's not allowed now. You cannot pipette by mouth.

Erwin: Now, did that come directly out of this?

Sinsheimer: I think it did, yes. All biological wastes like that now have to be put in a bag and incinerated, not just dumped down the drain. We should never have done it in the first place, but I'm just saying we did for many years. So that did come out of this.

In the late seventies, two things happened which gradually changed the whole picture. Frankly, I really believed there was a potential of a greater hazard, and I was really seriously concerned about the possibility of causing some epidemic or something, while I have to say, it seemed to me some of my colleagues were pretty cavalier about it; it was almost sort of "So what?" But the two things: Number one, it became clear that these strains of *coli* that we used really couldn't compete. You see, I had worried that they could, or could exchange a plasmid into what-have-you. So one thing I advocated was to try to attempt a crash program to work out the genetics of some other organism. I suggested thermophil, which could clearly never grow in normal conditions.

Erwin: Was that done?

Sinsheimer: No. The other thing I suggested was that the work be confined initially. I thought maybe the government could set up ten really high containment labs around the country, and people could go and do their work there. The second thing that developed, which I think no one could have anticipated, was that it then turned out that most of the genes in higher organisms are so structured that they cannot be simply translated into protein. They have spacers—introns—between the coding regions, the exons. And the higher organisms have a whole apparatus for splicing out these introns, and splicing the exons together, which *coli* don't have. So, if you just take a raw gene from a higher organism and put it in *coli*, it almost certainly will not produce anything meaningful. But that was not known until the late seventies. Most people still don't understand that, because you read all the time about how the gene for growth hormone or whatever has been put into *coli* and you can now make growth hormone in *coli*. And that's true. But what they've done is taken the processed gene, after all the introns and so on have been taken out, and put that into *coli* and attached to it a proper promoter, so that it will be translated and make correct protein. But that wouldn't happen in nature, and it can't happen readily by accident; it can only happen because somebody deliberately worked on that gene to do it.

Erwin: It seems that at the time of the Asilomar Conference, people's concerns were, I think as you said in an article you wrote after that, very much in the practical vein but not running along ethical or philosophical lines perhaps as much as you would have liked.

Sinsheimer: Well, you're quite right. Nobody was thinking at that time about the longer-term consequences, that this was going to open up all kinds of possibilities, creating genetic hybrid organisms, or organisms with all kinds of properties that never existed in nature, and ultimately would affect ourselves . . . . [tape ends]

Begin Tape 5, Side 2

Erwin: Were people thinking along lines such as there might be a right or a wrong here?

Sinsheimer: No. I don't think that was in many people's minds at all. Well, I have to take that back. The National Academy had a forum at which I spoke, and I tried to list all the reasons why I thought that one should go slowly on this. And I remember one of them was that "We don't know how much we don't know." Anyway, that meeting was interrupted by a group of religious zealots--I've forgotten what sect--that broke into the room and argued that what you were doing with this genetic work, this was blasphemous, should not be done. The guards ushered them out and the meeting went on, but when you say was anybody--yes, there were some such fringe groups. And of course there was Jeremy Rifkin. And he was taking what was ultimately a moral or philosophical position: that it was immoral to exchange genes between species; you shouldn't violate the species.

From my point of view, these were very extreme positions, and frankly didn't help me at all, because they were so far out, almost to the point of absurdity. I think Rifkin is not a dumb person, but initially he had no understanding of biology; he does now, but he just had no comprehension of biology or evolution.

Erwin: There were some other challenges to the report from the Asilomar Conference. For example, [Erwin] Chargaff and [Francine] Simring. Letters that were written, I believe, to *Science* magazine?

Sinsheimer: Well, Chargaff, I think, might have written some letter that the future will curse you.

Erwin: Was he a very imaginative person?

Sinsheimer: Chargaff was a very embittered person. Chargaff always felt that he should have shared the Nobel Prize with Watson and Crick because he discovered the equalities of adenine, thymine, guanine, and cytosine. And some of it went beyond that, because he had had some personal encounters with Watson, whom he regarded as uncultured and arrogant. So the end result of this was that Chargaff was very embittered. And I've forgotten about Simring.

Erwin: She was a representative of environmental groups, Friends of the Earth, or something.

Sinsheimer: I think so. And I think she may have felt that while we were worrying, if you will, about possible medical hazards, we weren't thinking about environmental hazards.

Erwin: And do you think that was a valid point?

Sinsheimer: Yes. Because in the long run, clearly you're going to want to apply this not just in the laboratory but in the world, to crops and what have you, and you need to worry about what the ecological effects may be. And, as you know, that subsequently came to a big tempest over the frost-inhibiting organism. You spray on these organisms that hopefully reduce frost damage. You spray them on leaves. There was a big fight about that. Because you're taking them out of the laboratory, and you're putting them into the field. And more and more, that's happening. Again you find yourself in a very amorphous situation, where there are conceivable hazards. We know cases clearly where species have been introduced that have caused great damage. But whether that could happen with any of these kinds of variants? I've talked to ecologists about this, and you get both sides of the issue.

Erwin: So it's still a question of not really knowing enough.

Sinsheimer: Not knowing enough, and not knowing how are you going to find out enough without actually doing the experiment. Now there, again, I would have thought that it might not be too foolish to try some of these things out on an island or something. You could confine the results, the organism, if it should prove dangerous. But people don't seem to want to do that.

Then it goes on into a whole variety of side issues, the question of patents. It strikes me as a little bizarre to think that you can patent an organism; the Supreme Court says you can. It seems to me it defies reproducing. In theory, if you can patent something, you should be able to describe it completely and reproduce it. And obviously you can't patent *E. coli* and describe it

completely. It seems to me it's just going to breed an infinite amount of litigation. If I'm going to patent an *E. coli* with one property, how different does it have to be before I can patent another one? Am I violating somebody else's patent? But that's a whole side issue.

The larger ethical and philosophical issues are, to some degree, attracting more attention, particularly now in the clinical field, for several reasons. One is they're localizing more and more and identifying more and more genes responsible for genetic problems. And that permits the possibility of diagnosis of carriers of the those genes, the fetuses that have those genes. Do they have the gene for Huntington's disease that will hit them when they're forty, with, in most cases, no possibility of doing anything about it? What do you do with that kind of information? Who is entitled to that kind of information? Should insurance companies have that information? Should employers have that information? All these kinds of questions. And, as you know, they are also beginning to try therapy for some kinds of genetic disorders. What sort of controls do you have on those kinds of experiments? And people can see that this is clearly going to expand rapidly. Not just a few, but dozens or hundreds of diseases of genes have been identified that are responsible in part or in whole for this or that disorder. How do you handle that kind of information?

Erwin: But then once you have the information, how close are we to correcting the situation?

Sinsheimer: That depends a lot on the disorder. If it's a single-gene disorder, it's much easier than with a multiple-gene disorder. And if it's a single-gene disorder--let's say, like the ones they're trying to treat now that affect circulating cells, like white blood cells--that's easier. You take them out of the body, you treat them, put them back in after you have modified their genomes in one way or another. On the other hand, if it's genetically more widespread, like cystic fibrosis, you can't really do that. You then have to treat the whole body, and then how are you going to do it? And there are various approaches that people are trying. But I have no doubt that sooner or later, it'll happen.

Erwin: You talked in our prior sessions about how, in the work you were doing, things came faster than you had predicted, your work with Phi X. Would you care to predict, say, over the next ten years?

Sinsheimer: Well, I have no doubt that over the next ten years we will have identified many, many genes involved in genetic disorders, and just in general. That poses problems for potential parents: How many of these do you want to be tested for? How many do you want the fetus tested for? To my mind, in the long run, it sort of changes the compact between the generations.

Nowadays, or until now, when a child is born it has a certain genome and that's the result of a mating. And there's been nothing anybody can do about it one way or another. But you've probably read about these cases where children have tried to sue for wrongful birth, so to speak. And to date, mostly that has not had much success. But where a test could have been done and wasn't done, is there a liability? And I don't want to discuss the legal aspects of that, but in a moral sense. And then, on the other hand, it always struck me a little strange, because when the choice was whether you should have aborted me instead of having me born with this crippling disorder, that's a difficult issue, it seems to me.

Once you have the knowledge, once you're able to do these kinds of tests, whether you do them or don't do them creates a problem either way.

Erwin: It seems that you saw ahead into this in a way that a lot of other people didn't, or weren't willing to. For example, the article you wrote for *Engineering & Science*, "Humanism in Science"--you wrote that not too long after the Asilomar Conference. And there you talked about a new educational model, to help people cope with the questions that they might have to cope with--just these things we're talking about.

Sinsheimer: Well, as you know, one comes to realize that most people are involved with their day-to-day activities, and it's hard for them to think more than a few months ahead, much less worry about problems that may come in ten or twenty years or thirty years.

Erwin: Did you have to take a certain amount of flak at the time over what you said?

Sinsheimer: Oh, I have no doubt I did. Particularly, a lot of my colleagues were very upset that I was taking what they thought would be too strong a position with respect to the specific hazards of recombinant DNA. That was their primary concern, because they were worried that things I was saying might cause some actual legislation or something, and they would have much more trouble subsequently dealing with and doing anything about that than if it was just an NIH committee that was involved.

Erwin: Caltech traditionally keeps a low profile, in a certain sense. For example, the University of Michigan had a big open debate on the subject of the DNA research. Do you remember that?

Sinsheimer: I sort of vaguely remember. Well, there were communities, La Jolla or San Diego, where there were concerns. Cambridge, Massachusetts, was the famous case. The community was worried about the potential hazards escaping the laboratory and so on. And other

communities, like Ann Arbor, may have been. Princeton had debates on this issue. That did, frankly, seem to me kind of foolish. You weren't any safer in Cambridge; if you banned it in Cambridge, it could be done in Boston, across the Charles River. It didn't make any sense to have local controls, which would be different in each locale. But there was no doubt that, as I think I said, a lot of my colleagues were upset, more particularly, I think, about my problems with the guidelines than about the longer-range issues. They may have felt that raising such issues would raise doubts in the minds of congressmen as to the ultimate consequences of this work, and they might become less willing to support this kind of work.

There's an interesting point in that, really. And I have seen this now many times, and I understand it better. Scientists work in a world that doesn't understand what they do, by and large. And yet they are dependent on that world for their resources. In other words, funded research depends on the largesse of Congress, which in turn depends on the willingness of the people to support what Congress does. And that, in turn, really depends on a basic assumption of congressmen that supporting basic research will in the long run produce benefits for their constituents. It's that simple. But they don't understand it. They don't really see why this should be true. They just sort of believe it, because they don't understand science. So scientists who have to work with Congress, through the Academy and so forth, are very leery of any kind of position or projection or whatever that they feel might tend to undermine the confidence of politicians in science, to impact on their willingness to support science. They don't want to hear anything that could be construed as negative--"This could be bad and could create problems." It's a very built-in defensiveness, and it comes from this awareness, as I say, that they are completely dependent on the goodwill of people who don't really understand. I understand that now--where that defensiveness comes from.

Erwin: But you were a person who made an effort to explain or to talk in a language that a layman or an educated person could understand.

Sinsheimer: Well, I certainly tried to do that.

Erwin: It seems to me that's how a scientist would try to bridge that gap, to be a publicist.

Sinsheimer: That's right. But then you ultimately come to realize you're talking to a very small audience--not zero, by any means, but small. And in a democracy, it's large audiences that ultimately decide what happens. You mentioned "Humanism in Science," and what I was coming to realize was the painful scientific illiteracy of the populace. As science becomes more and more powerful, and as the society becomes more and more technological, to my mind that's

a built-in recipe for disaster. People are more and more surrounded by technology, but they don't understand it, and they are confronted with, or will be confronted with, some of the kinds of issues that we just brought up.

Erwin: Will they ever understand?

Sinsheimer: Well, that gets back--we move from one difficult problem to another--to the whole educational system.

Erwin: Looking back, do you feel comfortable and justified in your position at the time? Would you have done anything differently?

Sinsheimer: No, I think that knowing what I knew at the time, I feel the position I took was to my mind quite reasonable. Obviously, we've learned more since then. But I think we were lucky, in that the hazard really was far less than what we might reasonably have projected or anticipated. Now, that's happened before. That was one of the arguments people made at the time. They said, "Well, you could have expressed the same concerns to some of the alchemists who were putting X and Y together and didn't have any idea what they would do." And I'm sure the fact is that some of them probably blew themselves up or blew up the neighborhood. But it didn't have the potential, it seemed to me, this had, because the one really novel hazard here was that you were dealing with a living, self-reproducing organism. And once it escaped, you couldn't recall it. You would never be able to recall it. And that to my mind put up a yellow flag. It wasn't dynamite; it wasn't even DDT. You could stop making DDT and in a little while it would go away. This would never go away.

Erwin: So in a sense, time was bought.

Sinsheimer: But we really didn't buy time. We put in guidelines which I don't think would have been effective if it had been really a major hazard. We temporized. We muddled through. And we were lucky. I hope we'll always be lucky.

I do think the longer-range issues that we sort of touched on--our ability to intervene in biological systems at a genetic level which includes us--are profound. How they'll be resolved, I have no idea. There'll be some time before we confront them on a major scale, but I don't think it's a century.

There are two things that I'd like to add. As you may know, I guess I was in considerable part responsible for what developed into the Human Genome Project. There was a

conference that I organized up at Santa Cruz. That was interesting, because Norton Zinder, who is the head of the NIH advisory committee on the human genome, had an article in *Scientific American*. And he said it was ironic that I, who had been sort of a negative influence--a pain in the neck is what he really meant to say--at the time of the recombinant-DNA controversy, would be the one to have now advanced this project, which, of course, relies on recombinant-DNA work. I wrote him a note and said that maybe it was ironic, but it seemed to me that the common thread here was that perhaps I was more imaginative as to the potential of this technique, both then and now.

The other comes back to what you were saying about humanism, humanism and science, and my realization that an outcome of all this would be creating situations in which people would be making decisions about their personal positions and their personal lives which require a fair amount of scientific knowledge, and that they were totally unprepared for this. Therefore, some educational developments maybe were becoming as necessary as scientific development. And that was in some way partly responsible for the fact that I went to Santa Cruz.

Erwin: So you felt, then, that this would give you an opportunity to work on these new educational issues.

Sinsheimer: Yes.

Erwin: Coming back to the genome initiative, that really was your idea from the start?

Sinsheimer: Yes.

Erwin: And now it's being worked on in lots of places. Can you explain a little bit about how the project is actually going along?

Sinsheimer: Oh, yes. Well, it's a big project now. It has a budget of over $100 million. There are two lead agencies--the NIH and the Department of Energy; both have big projects.

Erwin: Was that initially conceived as a project to be done at the University of California?

Sinsheimer: Well, my original idea was to set up an institute at Santa Cruz. I didn't think we could do the whole thing, but we could play a leading role in it, in that we would be the first institute.

Erwin: How did you come to this idea at the time that you did?

Sinsheimer: Several things. Obviously, for one, as chancellor, I was concerned with trying to put Santa Cruz on the scientific map, so to speak. And we were, in some areas. We had the astronomy program there. That and Caltech's, I think, are the two best in the world. We also had a very good high-energy physics program which takes advantage of our proximity to SLAC [Stanford Linear Accelerator Center]. And I wanted to do something in biology. So I had been thinking about what could we do.

Secondly, I had been, as chancellor, involved with projects one would think of as "big science." The University of California was playing a major role at that time in trying to get a superconducting supercollider accelerator for California. As a chancellor, I was involved in that. That's, as you know, a multibillion-dollar project. And then our astronomers were involved in the Hubble Space Telescope, a multibillion-dollar project. And even on a smaller scale, I've been very much involved in what has now become the Keck Telescope, which was originally a UC project. Also, of course, I was very familiar with the developments in DNA sequencing. As you may know, the first genome ever sequenced was the Phi X. I didn't do it; Fred Sanger did it, but it was Phi X. And I've followed the development of sequencing since then.

At the University of California, I was on the steering committee for the 10-meter telescope, as we called it at that time. We had gotten $36 million, and we needed another—we figured at that point it was supposed to cost about $70 million. So we had to raise the rest. And I had actually suggested that we should approach Caltech, that their astronomers would probably like to get in on this and they could help raise the other money. Ultimately, an arrangement was made with [Caltech president] Goldberger, that Caltech would try to raise $25 million and in return would get a share of observing time. Goldberger was in the process of trying to raise this money. And my present understanding is he tried to get $5 million from each of five trustees and had raised $15 million when he went to Keck. And Keck said, "I won't give you $5 million but I'll give you $70 million, but it's got to be the Keck Telescope." Now, of course, we had already named it the Hoffman Telescope [laughter]. So what do you do? Well, that was a problem. Keck also wanted it to be strictly a Caltech enterprise. I'll have to say Caltech was very honorable about that, and they realized that it was our idea and we had already designed it, and they wouldn't do that.

But to make a long story short, it ended up that UC was going to have to give back the $36 million for the Hoffman telescope. I knew this, so I wrote a letter—and it all gelled right there—well, maybe we could get this $36 million for another scientific project. And *voilà*, what should that be but the Hoffman Institute for the Sequencing of the Human Genome. I thought that might really appeal to them, because it was a colossal project. And I wrote a letter to David

Gardner, the president [of UC], suggesting this. I don't think he ever acted on it. He didn't see it; he didn't understand it. Anyway, that's where it originated. And then, after I realized we weren't going to get the $36 million, that I'd have to raise the money elsewhere, I still thought this was a sensible idea. More than sensible.

One obvious thing would be to go to NIH. But if NIH thought it was a good idea, they weren't just going to give Santa Cruz $25 million, which I figured was the minimum needed to get going. They would undoubtedly have to go out for bids, and there was no way Santa Cruz could compete with Caltech or Harvard or Berkeley at that stage. So I thought what I needed to do was to raise $25 million of private money, and then we could go to NIH and we could get grants or something. But, in order to do that, I had to have more than just the idea; I had to have some validation that this was really a feasible project. So that's when I decided we had to have this workshop. And I got together with some of the other faculty at Santa Cruz and invited about a dozen of the leading workers in the field and held the workshop and decided the project was feasible.

Erwin: What year was this?

Sinsheimer: I wrote to Gardner in the fall of '84, and then we actually had the workshop in the spring of '85. And then I wrote up the conclusions of the workshop, and that got distributed. And it seems pretty clear that it sort of took off from there. Not without difficulties. And I didn't succeed; I tried to raise $25 million from some people who could have funded it, I think. If it had been at Caltech, I would have succeeded.

Erwin: How did the work get shared out eventually on the project? I know some of it's going on at Caltech.

Sinsheimer: Well, they've set up a whole bunch of things now. DOE [Department of Energy], of course, is doing a lot of it in-house at Los Alamos, at Livermore, and at Berkeley. But they give some grants. And NIH does a lot of grants. They've also set up a number of centers; Lee Hood [at Caltech] has a center. They've set up, I think, eight or ten centers around the country.

Erwin: And did you see it evolving that way? Is that what you envisioned?

Sinsheimer: No, I don't think anybody would have envisioned the shape it has now. What happened was that the DOE picked up the ball. It clearly had to be a large, coordinated project. And NIH, I think, was pretty reluctant. They don't work in that mode; they work much more

with investigation-originated projects, with large, managed endeavors. Whereas the DOE is much more hierarchical. Their programs are from the top down. And they're used to running collaborative big science, with accelerators and nuclear reactors. So they picked up the ball and started to run with it. Then NIH realized they had to get into the act or they were going to lose out here on what would normally be thought of as their turf. Both of these agencies, of course, have their partisans in Congress. So the net result was that there really are two programs, and there's supposedly a coordinating committee which coordinates what they do. I don't know how well that works. I don't think that it would have been set up that way a priori, but that's the way it's evolved. It's going well. It's interesting, because looking back on the workshop, we anticipated remarkably well what needed to be done and what sort of scale it needed to be done at.

Erwin: And about how long?

Sinsheimer: Yes, about how long. I think we probably predicted twenty-five years. First we had to develop automatic techniques for sequencing. While this was being done, the gene mapping could go on, and then comes the actual sequencing. You'd also have to get started very early on developing computer techniques to handle all this information. [Tape ends]

Begin Tape 5, Side 1

Sinsheimer: We said, the first thing that needed to be done, and what should be done in the first few years of the project, was to develop the technology to automate the techniques, both to bring down the cost and to, in a sense, obviate what would otherwise be an unbelievably tedious kind of task, unless you could develop machines. And of course, that's what Lee Hood's very good at, what they're working on. So I think it's going very much the way we thought it would need to go at that time. I don't mean that we foresaw everything. I'm sure things will develop as it proceeds; there'll be innovations that we never thought of.

Erwin: Do you keep pretty close touch?

Sinsheimer: Yes, I do. Actually, last summer I served on an NIH study section in Bethesda which reviewed grant applications for human genome research. Also, I am giving a lecture next month at a symposium up at UCSF that is on the ethical issues.

Erwin: Do you feel that you're back where you started?

Sinsheimer: Well, I think I have a little better developed perspective than I did in the seventies.

I have written a description of the Santa Cruz workshop, who was there and what was discussed, which was published in the magazine *Genomics* last fall.