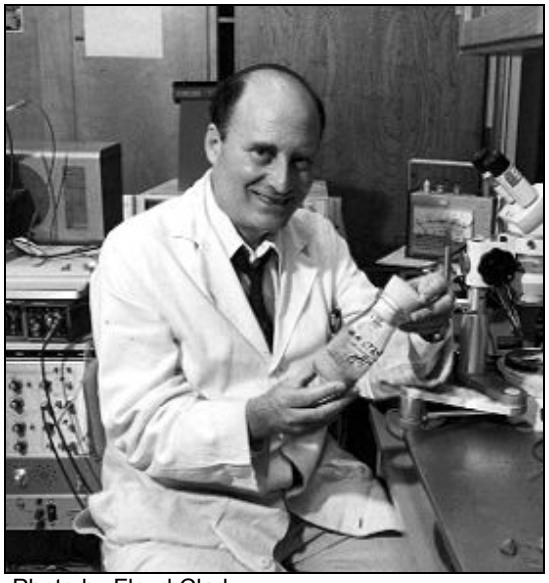

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SEYMOUR BENZER
(1921-2007)

INTERVIEWED BY
HEIDI ASPATURIAN

September 11, 1990–February 1991

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Pasadena, California

Subject area

Biology, biophysics

Abstract

Interview conducted in eleven sessions between September 1990 and February 1991 with Seymour Benzer, James G. Boswell Professor of Neuroscience in the Division of Biology. Benzer received his PhD in physics from Purdue in 1947. His interests had already turned to biophysics, after he read Erwin Schrödinger's *What is Life?* In this lengthy interview he recounts his peripatetic life visiting Oak Ridge National Laboratory (1948-49); Max Delbrück at Caltech (1949-51); the Pasteur Institute with André Lwoff, François Jacob, and Jacques Monod (1951-52); the Cavendish Laboratory at Cambridge, with Francis Crick and Sydney Brenner (1957-1958); Roger Sperry's lab at Caltech (1965-67); and intermittently Woods Hole and Cold Spring Harbor—all while he was also a member first of the physics and then the biology faculty at Purdue (1945-1967). In the early 1960s, he participated for a while in the establishment of the Salk Institute. In 1967 he became a professor of biology at Caltech, meanwhile spending summers in the early 1970s at the Salk Institute; recollections of the Biology Division and of Salk during that time. He discusses the early years and flourishing of molecular biology, including recollections of such pioneers as

Salvador Luria, Renato Dulbecco, Francis Crick, James Watson, Gunther Stent, and Delbrück's phage group. He discusses his own work on *r* mutants of bacteriophage, genetic fine structure, behavioral mutants of *Drosophila,* and monoclonal antibodies.

Administrative information

Access

The interview is unrestricted.

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Seymour Benzer with mega-*Drosophila*, 1974.

California Institute of Technology

Oral History Project

Interview with Seymour Benzer

by Heidi Aspaturian

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Caltech Archives, 2002

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CALIFORNIA INSTITUTE OF TECHNOLOGY
ORAL HISTORY PROJECT

Interview with Seymour Benzer By Heidi Aspaturian

Pasadena, California

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Aspaturian: Tell me your parentage and background.

Benzer: My parents came from Poland, from a small Jewish shtetl, west of Warsaw, called Sochaczew, which I am told is now an affluent suburb of Warsaw, although the original town has completely disappeared. I've never been there. My father's father—my grandfather, whom I knew—was a tailor. My mother's father was an orchard grower—apples and other fruit. My parents emigrated about 1910 into New York City, the Lower East Side; and although they had known each other in Sochaczew, apparently they became close only after coming here. My father worked all his life in the needle trades in the garment district—first as a sewing machine operator, then later he went into business for himself; then came the Depression, and he went back to the

sewing machine. My mother—I think actually before they were married—had established a dress shop where she made her stuff and it was fairly successful, but she had dropped that to be married and have children.

My mother was the first sibling in her family to come to the U.S., although she was not the eldest. She was skilled in dressmaking, so she was able to make money in the Old Country to get her fare to come over. And she was the one who was responsible for bringing over her whole family, one by one.

I was born in the South Bronx, where I don't dare go back to see my birthplace; it's changed. I'd be curious to see it, but everyone warns me it will be my death place, as well. We immigrated to Brooklyn when I was four years old. This was on the edge of a New York State development in Bensonhurst.

Aspaturian: Were you the oldest child?

Benzer: No, I had two older sisters. I had a sister Ruth, now deceased, who was about ten years older, and I have a sister Rose, still living, who is about eight years older. I was the first boy, and I had a younger sister as well, who is ten years younger than I am. So there's a very wide spread. As my friend Jean Weigle used to say, I was the egg with two yellows. [Laughter] That's apparently a European expression for being the only boy.

I grew up in this neighborhood, which was quiet, residential, and on the border between a Jewish and an Italian neighborhood. I grew up thinking there were only two types of people in the world, Jews and Italians. Bensonhurst is now almost entirely an Italian neighborhood, and it became famous in the news just recently when some black kid made the mistake of wandering in there. So it has a reputation now, unfortunately. But until then, nobody ever heard of Bensonhurst. I go back there occasionally. We still have the family house there, which my sister manages. The only real change in the neighborhood is that the street's full of cars. You can hardly walk on the street, whereas when I grew up, it used to be open, because the street was the playing field for stickball, and the sidewalk was the park. It was a quiet neighborhood, so I had a relatively unruffled childhood. Even during the Depression, I was never really made much aware of it.

Aspaturian: Did the Depression have much effect on your family?

Benzer: Well, it meant that my mother had to work. My father was bringing home boxes of clothes, which she had to work on far into the night. I'm aware that there was a period of great struggle, but they largely protected me and the other children from it. The only real work they put me to—I feel now I should have done much more but they didn't demand it—was delivering the bundles of clothes, sometimes, on the subway to Manhattan or Brooklyn. I did some delivering, but not much when I think back on it.

Aspaturian: Did you have both sets of your grandparents there with you?

Benzer: My father had five brothers, and their father lived with one of them. They were in Brownsville, which I think now is an all black neighborhood but was then Jewish, and we would go to visit them. My father was a bit exceptional in having his own car, which was unusual for that neighborhood, and certainly also unusual in his family. I don't think any of his brothers had a car. We had a DeSoto. Often the main outing would be to go visit cousins in the Bronx or in Brownsville on Sunday.

Aspaturian: How about the cultural/intellectual environment?

Benzer: My parents could read Yiddish, and they read the Yiddish newspapers regularly; but their English was minimal all their lives. They went to school to a certain extent, but they never became fluent in English. As a result, I learned Yiddish at home. I went to Hebrew school like a good boy up to the Bar Mitzvah, and after that I wouldn't have anything more to do with it. I didn't have any religious feelings at all, but out of respect for them, I went that far. Out of respect for my father, I used to go to the synagogue with him for the High Holy Days like Yom Kippur and sit in the synagogue, but I'd take along a physics book that I would hold over the Bible and read surreptitiously. This was already when I was somewhat older, past the Bar Mitzvah, but that was the one thing I would do because it was a shame for the father not to have his son accompany him. He looked the other way while I was reading. [Laughter]

Aspaturian: At what point did you become conscious of not being religious?

Benzer: I can't remember specifically. But I just remember it all seemed like nonsense. I was interested in science quite young. It used to be the custom back then for Jewish families who could afford it to go to the Catskills for the summer, and during the affluent years we'd go there and stay at a hotel. But during the Depression years, my mother still insisted that we had to get out in the country in good air—the city got pretty stifling in the summer—we'd go to cheaper places where you cook yourself and just rent a room. I would sometimes work delivering newspapers to the hotel. But I have memories back then as early as eleven or earlier of catching frogs and dissecting them.

Aspaturian: What did you use for instruments?

Benzer: Scissors, needle, thread. When I think back, I was interested in nature and biology even at that age.

Aspaturian: What about teachers and outside reading?

Benzer: Not so much. I remember in high school and junior high school, there was not much. In elementary school, Public School #48 in Brooklyn, there was a biology club—sixth grade, I guess—but it was very primitive. It was just a matter of taking care of the snake and the terrarium and stuff like that. By that time, I had begun to use my basement. We lived in sort of a duplex house, two stories and a basement—which was a blessing, because that was my laboratory. The turning point was on my thirteenth birthday, when my brother-in-law—this was my older sister's husband, named Harry, who was like a big brother to me—bought me a microscope. And that opened up the whole world. My father thought a ring, but Harry said no, a microscope. [Laughter]

Aspaturian: What was Harry's profession?

Benzer: He was a package-design artist.

Aspaturian: Was he American-born?

Benzer: Yes, he grew up in Newark. And he rose quite high in his profession. He, at one point, was art director for the Seagrams Company package design department. But what he really was interested in was photography. He did marvelous work as a photographer. When he retired from Seagrams, he was able to give his whole time to that. He was a big influence on me, in terms of support of a type that my parents were not able to give. He only published one book of photographs—of Coney Island. He died before he became as recognized as he ought to be. There was one gallery here in Los Angeles that took him on—G. Ray Hawkins, which is one of the prime photo galleries in Los Angeles. But people in Los Angeles were not interested in Coney Island pictures. Even the bookstores here wouldn't carry his book, because they said, "That's East Coast stuff. West Coast people are not going to care about it."

Aspaturian: So you said this microscope opened a whole new world for you.

Benzer: Yes. I just looked at everything that I could find. And then I started to do chemistry experiments, making frog legs twitch with electric wires.

Aspaturian: Were you reading things that gave you these ideas?

Benzer: I don't remember consciously reading an awful lot of stuff. I can't think of any specific books that turned me on at that time.

Aspaturian: What about structured educational experiences? Did you have any high school classes that were helpful?

Benzer: Yes. I went to New Utrecht High School, which was quite a large neighborhood school. I'm always amazed at the number of distinguished people I meet in my profession who graduated from the same school. I was still very interested in biology, but I think my biggest influence there was a chemistry teacher toward the end of my stay. And I was active in the chemistry club. Then

I went to Brooklyn College. It was the only place we could afford. I had the Regents Scholarship—$500 a year.

Aspaturian: What year did you start?

Benzer: 1938. I graduated just before the war. The Depression was pretty deep at that time. I got twenty-five cents a day for expenses and ten cents for bus fare round trip and fifteen cents for lunch.

Aspaturian: Were you the first person in your family to go to college?

Benzer: Yes.

Aspaturian: Your older sisters did not?

Benzer: They did not; they got married and had children.

Aspaturian: How did your parents feel about your going?

Benzer: Well, I was the egg with two yellows, so they certainly wanted me to go to college. There was an issue over whether they could afford it or not, and whether I shouldn't go out and earn some money. And I think the saving grace there was the Regents Scholarship, which would be forfeited if I didn't go to college. I have a feeling that may have tipped the balance. [Laughter] Although my parents were certainly prepared to sacrifice, I don't know how much they were really able to. I once asked my father, "Suppose I wanted to go away to some other college, would you be able to give me twenty dollars a week?" And he said, "I couldn't even give you ten." So it was clear there was real hardship there. But I was largely protected from it.

Brooklyn College was a commuting school. Although I was interested in biology, I felt I knew enough about it—you know, the typical arrogance of youth. I thought I wanted to go straight into the more advanced classes and not take the general biology, which seemed boring—a survey of all the plants and all the animals. It was mostly taxonomy. But the Biology

Department refused to let me take anything advanced without that prerequisite. So I said to hell with that and I concentrated on chemistry instead. I went quite far along in chemistry. Then I discovered physics.

At Brooklyn College, the Chemistry Department was excellent. I don't know how the Biology Department was; I never found out. The Physics Department had, remarkably, a group of young dedicated teachers who also had a good background in research and who were closely united in their efforts on the curriculum, and they created just a wonderful physics environment. The best part was the so-called advanced laboratory class, where they had all the equipment set up for doing rather sophisticated experiments, one of which was the Millikan oil-drop experiment. You would spend a month or two on one experiment and then write up a detailed report. So I learned a lot there.

Aspaturian: What was the atmosphere like socially or culturally at Brooklyn?

Benzer: Well, as I said, it was a commuter college, so there was nothing like fraternity life. I did make some good friends there. Most of them were other physics majors that I would know from classes. But the social life was really quite minimal.

Aspaturian: How about liberal arts training? Did you get much exposure to that?

Benzer: There were required courses, so I was forced against my will to take those things because I really wanted to come straight on the science. And in general, I got poor grades in the other courses. I did very badly in things like history and economics, not realizing then how important they were, and not having the good luck to have inspiring teachers to get the point across. Whereas, physics was real stuff—problems and solving problems. In economics there are no problems, or in history; just a narrative. I realize now that there's so much depth in those subjects that it's a real challenge and they are very important to know. But—you know how kids are. So I would not say I got a very broad liberal arts education in college. I was turned on to classical music. Art, not really; that came later.

Aspaturian: Literature?

Benzer: Not so much. I think most of my intellectual development came in graduate school—on my own, not the courses. The graduate school I went to, Purdue, was recommended by my professors as one with a young developing Physics Department, as the place to go.

Aspaturian: Did you choose Purdue just on the basis of their recommendation?

Benzer: Yes. I think I had three choices; I don't remember exactly what they were. And they said, "Go to Purdue; that's a good developing place."

Aspaturian: By the time you graduated from Brooklyn, Pearl Harbor must have happened.

Benzer: Oh, yes, I can remember standing on the quadrangle listening to President Roosevelt's address after Pearl Harbor—the day that would live in infamy. It was just shortly after that that I started graduate school in January.

Aspaturian: You weren't drafted?

Benzer: I was drafted. I was already in graduate school when my number came up, and I went down for the physical exam and I was put in 1-A. It was a pretty degrading experience; I remember standing there naked and feeling absolutely helpless. But by that time I was already involved as a graduate student in war-related research. My research director, who was also the chairman of physics at Purdue, got me deferred.

Aspaturian: Did you have relatives who were trapped in Poland during the war?

Benzer: Yes, but none that I knew, because my mother and father and all their siblings had come over. But there were more distant relatives whom I never met and were completely abstract to me. They were all wiped out. But again, my parents protected the children from that.

Aspaturian: Even at that age, they were still sort of shielding you?

Benzer: Well, they didn't know very much, because I left home in 1942, and at that time there was not much known about what was going on.

Aspaturian: Where is Purdue?

Benzer: It's in Lafayette, Indiana, on the Wabash River.

Aspaturian: Was this your first encounter with the Midwest?

Benzer: Oh, yes.

Aspaturian: Was there any culture shock?

Benzer: Well, yes, but for the better, since I got married just before I left. I had been seeing Dorothy, my first wife, for almost four years, essentially all through college. She was a nursing student; then she graduated and worked as a nurse in a local hospital. She lived four blocks away, so we saw each other day and night practically. And then, when it became time to go to Purdue, my father said, "I want you to marry the girl." [Laughter] So we got married in January. We had an Orthodox wedding at her home, and we left the people dancing while we went to catch a train to Indiana. That was our honeymoon.

I didn't know what to expect. I thought that to get into Purdue we'd have to lift up the gates so the cows couldn't get out from the physics building. It wasn't all that different. We didn't have to go very far to the cows, but there was an honest-to-goodness campus. And for both of us, that was a complete liberation. I mean, living in Brooklyn is like living in a small town; I'd occasionally get into New York City to do this or that, but I had no money to partake of any of the cultural attractions. I went to the Museum of Natural History, some of the standard things, but certainly never to Broadway or to an opera or concert.

Aspaturian: So it's not as if you missed all the advantages of big-city life, in other words.

Benzer: Yes, none of that. On the other hand, there certainly was an advantage in growing up quietly without conflicts or violence—it was really like a village.

Aspaturian: By the time you got to Purdue, had you already decided you wanted to focus on solid-state physics?

Benzer: No, I knew I was interested in physics. And then they had a project. The chairman of the department's name was Karl Lark-Horovitz. He was a Viennese Jew who had come over quite some time before, essentially built up that department, and was still in the process of building it. So he undertook a project connected with the effort on radar.

Aspaturian: That was a British effort primarily, wasn't it?

Benzer: Well, the British seem to have invented the idea. And there was a big effort on it being established at MIT, sponsored by the Signal Corps, I think, under the National Defense Research Administration, or something like that. So Purdue had a contract with them. And our specific job was to develop crystal detectors for microwaves, to resolve a particular problem. The way radar works is, they send out a pulse of microwave signals and when it gets reflected back from the plane you have to be able to detect it. And the detectors they were using were the old-fashioned type that worked at these extremely high frequencies where you couldn't use microwaves. The only thing that worked was the old cats-whisker semiconductor that the original crystal radios used, and these would be burning out all the time. So the challenge was to develop a detector that was sensitive to the high frequencies, resistant to mechanical damage, and not going to burn out all the time—when you're in the middle of tracking a plane, the detector can't burn out. That was really our mandate, but Lark-Horovitz's approach was to get a basic understanding of how the semiconductors worked and how to quickly adapt to that need. I'd been at Purdue only a short time when I was invited to join that project as a graduate student.

Aspaturian: And you found it interesting?

Benzer: Yes. Interesting, challenging, and of course, it was connected to the war effort. I

worked very hard. Horovitz called me up once on Christmas Day, saying "Why aren't you in the lab?" I said, "But it's Christmas Day." He said, "Yes, but why aren't you in the lab?" [Laughter] I remember once I told him Heifetz was giving a concert in Chicago on a Saturday night. He said, "And you want to go?" I said, "Well, yes." He said, "Well, so go." [Laughter] Of course, the work was all secret, so we couldn't talk about it on the outside.

Aspaturian: How many of you were involved?

Benzer: We had a large room, and there were six people in this room and one in the basement. That was, for me, a very good experience, because three of us were graduate students and three were faculty members. So we had very close interaction and cooperation and constant advice from senior people. When I think back on it, it was very, very nice.

Aspaturian: How large was the Purdue Physics Department altogether, in terms of its faculty? Did it strike you as a big department?

Benzer: Not very big, not by current standards. I don't think there were more than a dozen professors.

Aspaturian: Was most of the work, at that point, geared to war-related research?

Benzer: There were two war-related projects. One was the cyclotron guys downstairs. We knew nothing about what they were doing. And then, all of a sudden, they all disappeared and went to Los Alamos. But we didn't know anything about it. I didn't know anything about any atomic bomb until it dropped.

Aspaturian: So no word of that filtered back to you. And the other big project was the radar?

Benzer: Yes.

Aspaturian: Did you have any émigré scientists working with you on that?

Benzer: No, we were all Americans. But we had a constant stream of people coming in to visit the lab. Horovitz would bring them in to show them what we were doing. One was Linus Pauling [professor of chemistry, emeritus]; I still remember him—with a piercing eye. I was a graduate student, and he made a big impression on me, and also, you know, asked very piercing questions. Another one was Lise Meitner.

Aspaturian: What kind of impression did she make?

Benzer: Well, she seemed like a nice lady. She didn't make a strong personal impression. I still remember Horovitz explaining to her in German what I was doing. I had made a weird semiconductor device that had negative resistance, so that when you shined a light on it, it changed so that the current would jump—it was a gating device. So that was nice, having these people come.

Aspaturian: Anyone else that you remember?

Benzer: In the lab there was Bill Shockley, whom I encountered again in much later years when I was working in behavior. Also Frederick Seitz, who was an expert on solid-state physics. Harold Urey. But in the Physics Department, outside this project, Horovitz had all these connections. So he would invite a wonderful stream of famous people, like Heisenberg and Pauli and Weisskopf, with whom he was friends, and Teller.

Aspaturian: Wasn't Heisenberg in Germany during the war?

Benzer: Right. This was later on, because I stayed on in the Physics Department after the war. This is not only during the war but over the years. What I'm saying is I had a really good exposure to people while I was in this "hick" Indiana institution, just thanks to Horovitz. I got my Ph.D. I wrote my master's thesis, which Horovitz lost.

Aspaturian: You gave it to him and . . .

Benzer: He lost it, yes.

Aspaturian: Had it been typed with a carbon?

Benzer: No, no—handwritten. It's unthinkable now—you make five copies of everything.

Aspaturian: What was the subject of the thesis?

Benzer: Some of the people in the lab were trying to purify germanium—the semiconductor works on the basis of the impurities that are dissolved in it. So first of all, we wanted to get the germanium extremely pure. And the second thing was to dope it with this or that element to get the right properties. Some were so-called semiconductors and some were so-called conductors, depending on whether the current was carried by an electron or through the absence of electrons, called holes. My job was to characterize these according to their properties, in order to extend high voltage and burn-out. In the course of that, I ran across a number of bizarre phenomena and effects, including negative resistances and photoelectric effects. A lot of this was traced to the fact that in some of these crystals that were formed, there were P and N areas adjacent to each other, which formed a natural rectifying junction that was sensitive to light. So in the course of this, our research group was awarded six patents on various devices. There's about six in my name. I was still a graduate student. We got some royalties, which were shared by the entire group, but very minimal because most companies didn't pay off. Purdue did not have a very aggressive approach.

Also, the other thing that happened was that silicon turned out to be a more favorable material for many purposes because of its greater abundance. Germanium was quite scarce. There was another group working at the University of Pennsylvania that did the same things we were, using silicon. Of course, with its abundance and its higher temperature resistance, silicon largely took over as the element of choice.

I got my Ph.D. in 1947.

Aspaturian: Purdue hired you onto their faculty, I believe.

Benzer: Purdue hired me onto the faculty as soon as I got my Ph.D. I became an assistant professor, but continuing the same work, although now it was free of the secrecy. All through the war, we were under the wraps of secrecy, and we were astonished, as soon as secrecy was lifted, when an article appeared in *Electronics Magazine* by Sylvania Company, describing these detectors that we had developed. I don't remember them even giving us any credit. We certainly didn't know about it.

Aspaturian: How had they found all this out?

Benzer: I don't know. I think they were already manufacturing them. [Laughter] Well, I should say that one of the things that happened during that secrecy period was that the authorities decided this stuff was really hot. So it needs to be developed, it needs more resources than we have at Purdue, to properly develop it. So therefore, we ought to give it over to an outfit that's well equipped for this, like Bell Laboratories. And the Bell Labs people came, and we told them everything we knew, and they took on the project. After the war, that continued. And they just ran with it, and came out with a transistor.

Aspaturian: What happened to your research group after they took away your project?

Benzer: We continued, but I don't know what the funding was at that time. I never asked the questions; I just worked in the lab. I had my nose on the transistor. It's like Max Delbrück [professor of biology at Caltech; d. 1981] failed to discover fission, and he had it under his nose. [Laughter] I failed to discover the transistor, because I had three electrodes in there, and I was measuring things—using one to measure what the other one was doing—but I never had the idea of trying to use that arrangement as an amplifier. Instead, I had a different idea; I had the idea of making a crystal amplifier, but it was too sophisticated. It was based on putting a metal layer on top of a semiconductor and using a tunnel effect to control the current that's passing through, but I never got it to work. Instead, the Bell Labs guy did the most simpleminded thing, which was to have just these two wires next to each other and have one influence the other. It escaped me, and it was under my nose. Some time later, there was a big demonstration of it at Bell Labs. These

guys grabbed me and said, "You should have done this." [Laughter] And they were right. But, you know, maybe to some extent, because I was already into biology at that time, I wasn't really focused on that problem. Of course, being a graduate student and not being all that able or having big resources [played a role]. But by the time I got my Ph.D. in 1947, I was already interested in biology.

Aspaturian: What had happened?

Benzer: I was always interested in biology. But two things happened. One of the guys in the lab—his name was Lou [Louis L.] Boyarsky—told me about mapping genes on chromosomes, the work that had been done here at Caltech by [Alfred H.] Sturtevant and [Thomas Hunt] Morgan and their group. I thought that was very exciting. And then I read this book by [Erwin] Schrödinger, written around 1944, called *What Is Life?*, which inspired a number of other people as well—Francis Crick, for one. Max Delbrück was in the book—he had been at Caltech in the thirties, switching from physics to biology—and there's a chapter in there on Delbrück's model of mutation. Schrödinger talked about his model of a gene as an aperiodic crystal. And I was struck on the one hand by the possibility of similarities between solid-state physics and the crystal and gene structure and energy levels of electrons, and on the other hand by the idea that the interface between the metal cats whisker and the semiconductor, forming a special surface layer, might be treated as analogous to the membrane of the nerve-impulse conduction. So I got interested in these two angles. And I went up to the University of Chicago to visit Kenneth Cole, one of the well-known neurophysiologists to find out about that.

Begin Tape 1, Side 2

Benzer: Cole had an associate whose name was Marmont, who had done the electronics behind the invention of the voltage clamp technique, which was the hottest thing then in physiology. It was a way of keeping a voltage difference across the membrane constant, measuring action potentials so you could measure the current independently of the voltage. When the action potential's coming on, the voltage drops, so this machine fed in a lot more current to keep the voltage the same. And then you measure the amount of current. This is still very much used, a

key thing in neurophysiology.

But what happened was that a friend of mine, a former colleague from Brooklyn College who also worked in the same semiconductor lab at Purdue, and I both went to attend an American Physical Society meeting—by that time, I was into the American Physical Society; I'd given a number of presentations. The meeting was in Bloomington, Indiana. And my friend said he was going to visit a former Brooklyn College associate named Zella, whose husband teaches at Indiana University. He was invited to dinner; would I like to come along, and I said, "Sure!" This turned out to be Zella Luria, who was the wife of Salvador Luria. That's where I met them for the first time. But then I had become interested in viruses from reading Schrödinger's book. And I asked him if he knew anybody who worked on viruses. He said, "Well, yes, I work on viruses." So I said, "Tell me, did you ever hear of Delbrück?" So he pulled a picture of Delbrück out of the drawer. They had already by then gone quite far on developing a bacteriophage system. And Delbrück had set up a summer course at Cold Spring Harbor, a three-week course, for teaching the subject. Luria suggested I take this course, which I did; I signed up for the following year. Three weeks of that, and I was converted. That was the summer of '48.

Aspaturian: Who else was there at the course when you took it?

Benzer: At the bacteriophage course was Gunther Stent, who had gotten his degree in physical chemistry at the University of Illinois; Bernard Davis, from Harvard, the microbiologist—you may see his name now; he's testifying against the genome initiative, and gets into political issues quite a bit. Morris Schaeffer was there—he was an epidemiologist who knew bacteria but didn't know bacteriophage. Peggy Lieb, who is now a professor at USC in microbiology, was my lab partner at the course. She taught me how to hold a pipette. You have to hold a cotton plug in one hand and the pipette in the other, stick it in the flames so that you have sterile technique to transfer the bacteriophage. I've always been indebted to her for teaching me the basics. There were many other people there who I can't recall right now. But it was a mixed bag—biochemists, physicists, microbiologists.

Aspaturian: Delbrück taught the course?

Benzer: No, Delbrück had taught the course the first one or two years, and then, unfortunately, when I came, it was given by someone else. That was Mark Adams from NYU. And August Doermann was also involved at that time. But they were direct protégés of Delbrück.

Aspaturian: So this was your first encounter with bacteriophage research, viral research?

Benzer: Yes. I think I'd read about bacteriophage earlier on, in a book called *Arrowsmith* by Sinclair Lewis. It's a caricature of the Rockefeller Institute; it was famous for that, and there was apparently a lot of truth in it for those days. So I knew about the idea for this as a cure for a disease. But my interest was that it's the simplest kind of gene that reproduces itself and that we could study mutation and so on.

Aspaturian: So you were already interested in the very fundamental level of genetics.

Benzer: I was interested in how genes reproduce themselves. Immediately after, I went back to Purdue for a month or so. I told Horovitz I wanted to try biology. So he said, "Well, OK. Try it out for a year. Go on a year's leave of absence." He had a friend at Oak Ridge National Laboratory, Alexander Hollaender, who had built a pretty good biology division there, which was an outgrowth of what they needed during the war to study the effects of radiation on organisms. So some of that continued there. But Hollaender was a pretty enlightened person, and he was orienting this work toward basic biology.

Aspaturian: I'm struck by the fact that Karl Lark-Horovitz didn't object when one of his own protégés showed an interest in going outside the discipline and concentrating on something else.

Benzer: Yes, he had a terrific, incredible attitude. He'd become like a father figure at that time.

Aspaturian: And he'd invested a lot of years in you.

Benzer: Yes. Well, I may have been pretty strong-minded about it. In fact, I went to Oak Ridge for an interview, and when I came back, Lark-Horovitz said, "What did you say there?

Hollaender told me that you're such an arrogant young man. I had to do a lot of talking to convince him that he should take you."

Aspaturian: What had you said?

Benzer: I was probably a pretty snotty guy. He took me anyway. I went there on a salary, as a biophysicist for one year, doing bacteriophage. I went right in and did the work that I was interested in, which was the phenomenon of photoreactivation. It had been discovered that if you inactivate bacteriophage so that the phage no longer forms plaque colonies on plates of bacteria, and then treat them with invisible light, a large fraction of them will turn back on. So I studied that. [Renato] Dulbecco had been working on this also. But he was in Luria's laboratory in Bloomington at that time. [James D.] Watson was also there—a graduate student in Luria's laboratory.

Aspaturian: Did you know these men?

Benzer: Yes. I met them. There was a meeting on photoreactivation at Oak Ridge, which Delbrück attended. He may have been the main organizer, for all I know. Then, there was a guy, working I think with Dulbecco, named [Albert] Kelner, who, if I'm not mistaken, had originally discovered the effect of light on bacteria by the fact that he was using a water bath to incubate his bacterial culture. The heat in this water bath was maintained by lightbulbs that went on and off with a thermostat. And he discovered, after radiating the bacteria, that the ones that were near the lightbulb survived much better than the ones that were farther away. And he found the right thing. Subsequently, Dulbecco, working in Luria's lab, discovered he had several identical bacteriophage plates that had been radiated. And the ones on top had more plaque than the ones on the bottom. Off the record, Kelner had been there on a visit at some time and told about his work, but it hadn't particularly registered. So this rediscovery by Dulbecco may have been like Beethoven rediscovering one of Mozart's themes. That happens very often in science. Anyhow, the fact that it could work in bacteriophage was very exciting.

Aspaturian: Did Dulbecco or Watson make any impression on you the first time you met them?

Benzer: Oh, yes, I was very impressed with Dulbecco and thought Watson was rather strange. We had this meeting on photoreactivation at Oak Ridge—I guess toward the spring or so of my year there. And by then, I found out the places to go. So I approached Luria and Delbrück, and they both offered me to come as a postdoc.

I had to decide between these offers, and I asked Watson, "Where should I go?" And Watson said, "Well, if you come to Luria's lab, he won't leave you alone. He's very good, because every day he'll ask you what you've done. Whereas, if you go to Delbrück's lab, you may not see him for two weeks at a time, because he likes to go to the library and look up something and go his own way." So that, plus the fact that California had always been a major attraction to me, made me go to Delbrück's lab instead.

Aspaturian: Did you ask Watson because he was the only person you knew who worked with both of them?

Benzer: Well, yes, he knew them both. So I came here. I got a fellowship sponsored by the American Cancer Society, and I was here for two years.

Aspaturian: Did you keep your appointment at Purdue all this time?

Benzer: I was already on leave of absence from Purdue, at Oak Ridge. So I told Lark-Horovitz, "Look, I want to go to California, to Caltech." He said, "OK, I'll get you an extension." So he got me an extension. And when that was up, I said, "Well, I want to stay at Caltech another year." I got another extension. And at the end of that, André Lwoff invited me to come to Paris to the Pasteur Institute. So Lark-Horovitz allowed that. I mean, it's really amazing, because I know all my postdocs now, they're terrified they're not going to find a job. And here, just as I'd had the security in my youth from my parents' support, this guy was absolutely marvelous in his support.

At the end of my year in Paris they were having an important meeting, and I wanted to stay one more week before coming back to Purdue. And I asked for permission. And Lark-Horovitz gave me permission; but afterwards, when I came back, he told me that when he brought

that letter into the dean, the dean said, "Fire the bastard!" [Laughter] So I had absolutely stretched it to the limit.

But when I came back, they had acquired another so-called biophysicist, a neurophysiologist called Lorin Mullins. Lark-Horovitz had always been interested in biophysics, so he was happy to develop within the physics department a biophysics activity. So I actually joined up with Mullins, still as an integral part of the physics department, but a space had been set aside in the building for this biophysics activity. So I just walked into that.

Horovitz's interest in biology went all the way back to when he was still in Europe. He had been one of the first people to recognize the use of radioisotopes in biology. And he told a story that, when he was in Vienna, he gave a lecture on the use of radioisotopes. And a woman came up afterwards and said, "Dr. Horovitz, this is fantastic. To even give an enema to a cockroach is already a great achievement. But to use radioactive phosphorous is the height of sophistication." [Laughter]

SEYMOUR BENZER

Session 2

September 20, 1990

Begin Tape 2, Side 1

Aspaturian: What are your early impressions and recollections of Max Delbrück?

Benzer: Between the two of them, Manny [Mrs. Delbrück] and Max, they set a wonderful tone of camaraderie for the whole group. They were very adventurous people who did practical jokes, and anything bizarre would interest them. And particularly, they were very enthusiastic—she still is—about camping. So there were always people—graduate students—going with them on camping trips. They tended to go to a similar area, east of Indio, south of Joshua Tree, and explore it. It was always a challenge for them to find something new. They had numbers for the canyons; every time they found a new interesting canyon, they'd give it a number. So we'd always be hearing things like, "This weekend, we're going to Twenty-One, just found Twenty-Five." They took pride in this. And that was a wonderful way for everybody to get to know each other. These are some of the good things about Delbrück.

Aspaturian: How many of you were in his research group?

Benzer: I do have a photograph somewhere of the group at that time. The people I remember were Gunther Stent, Renato Dulbecco, Jean Weigle, Elie Wollman from Paris; graduate student Dale Kaiser, who is now a professor at Stanford. Another one—I think his name was George Bowen—was so brilliant everyone expected great things from him, but he just faded into nowhere and hasn't been heard from again. Those were the main people in the group, plus a couple of technicians. Dulbecco's wife was employed as dishwasher, washing the pipettes. What had happened was, there was a dishwasher who quit. And Max asked my wife, Dorothy, to take the job. She took the job; she lasted a few days or a week, and said it was kind of aggravating because everyone was making demands—"I want more pipettes; I want more plates." So she said, "To hell with this. I'm a registered nurse. I'd rather go work in a hospital." So she went to

Huntington Hospital. And she offered the job to Giuseppina Dulbecco. And Giuseppina jumped at the job because she had no other professional qualifications. And she loved it. I think she may have still been in it when I left, although I'm not sure of that.

Aspaturian: Besides you, and of course Delbrück, were any of the other people who had started in the physical sciences?

Benzer: Jean Weigle had been a physicist. He was professor of physics at Geneva, quite distinguished, and was still in physics when he came. He had had several heart attacks and wanted to have a warm climate. He had a Swiss friend near San Bernardino, and the guy told him about Caltech. Somebody introduced him to Delbrück, and they hit it off, and Weigle then became a research associate. He had independent means—I believe he had two sources. I think he had made a killing in the stock market by buying low and selling high. Later he married a widow, a woman whom I never met. I don't know if he got money from that or not. In any case, he had enough money to live as a bachelor. He lived with his wife in a single room in the Athenaeum. He died there, in fact, in '66 or '67 [Jean Weigle died in 1968—ed.], at home. As I said, he was originally a physicist.

Gunther Stent had trained in physical chemistry at the University of Illinois. Wollman was a microbiologist from the Pasteur Institute. Dulbecco had quite a solid background in physics from Italy. He knew a lot of physics and mathematics and had a good training in that, but he was actually an MD. He was one of the disciples of Rita Levi-Montalcini. She was also the mentor of Salvador Luria and Giuseppe Attardi [Grace C. Steele Professor of Molecular Biology]. She stimulated all three of them. She's in Rome at present.

So you had these very different backgrounds. Another person in the group was [Wolf] Weidel; he was trained in biochemistry. He was often at odds with the other people because he would sometimes say, when we had discussions, "Let the biochemists speak." Later, he was at the Max Planck Institute in Germany, but he died at quite a young age. So they weren't all physicists, by any means.

Aspaturian: Did Delbrück go out and actively recruit these people, or did most of them gravitate toward him?

Benzer: I think gravitation. Dulbecco obviously came from Luria; I came from reading the Schrödinger book; Weigle came to be warm; and Weidel probably had some German connection. And Dale and George were graduate students here.

Another person who was in the lab at that time was Margaret Lieb—we called her Peggy—who is now in the department of microbiology at USC Medical School. She is the one who I mentioned was my partner at the Cold Spring Harbor phage course and taught me how to hold a pipette. So I've always been indebted to her for that. She taught me a lot, because she knew microbiology already.

Aspaturian: What was the overall atmosphere like?

Benzer: It was very open. There was some social substructure in the group as in any group—some guys are buddies, some guys are not. I was very close to Jean Weigle, because we shared an office. He was the urbane continental bachelor and I was this boy from Brooklyn. We shared one room, which was office and laboratory—a room a little bit bigger than this, which was our joint workspace and office. Dulbecco's room was next door; he had a room to himself.

Weigle was much older and very continental, so I learned all kinds of stuff from him—French dirty songs and stuff like that, which I was able to use when I got to Paris. Dulbecco had two young children at that time. His wife and my wife, Dorothy, got along very well together, so we were very close. Stent and Wollman were sort of in a different clique. Weidel, I don't know if he was in any clique. Stent had come a year earlier than I had. We also overlapped a year in Paris, which we'll get to.

There were camping trips and there were parties. There were New Year's Eve parties, costume parties. Dulbecco and I went out to the Goodwill store and we each bought a dress for twenty-five cents, and we came dressed as women. I wouldn't dare to do it nowadays. And Manny Delbrück's mother said to my wife, "I know all the people here except that woman." "That's no woman; that's my husband." [Laughter]

Practical jokes. Delbrück would do things like, George Beadle was chairman of the Caltech Biology Division then. His secretary made his appointments. Max and Manny called him up one evening, 8:00 o'clock, and said, "Dr. Beadle, this is the American Cancer Society.

We're having a meeting at the Biltmore Hotel. You're scheduled to give a lecture to the Society tonight, and we're all waiting." He said, "Oh, my god!" and he jumped into a taxi and ran down to the hotel, and nobody was there. So Delbrück liked to do that. This was characteristic of Delbrück and his wife. They loved to have a story to tell. So that even if something bad happened—say, you broke your leg—there was a story to tell. Herman Kalckar, the biochemist from Denmark, went on one of these camping trips and Kalckar was insulting the mountains because, he said, they crumbled—they were made of crumbled granite. He said, "These are Hollywood Mountains." So he went off on a hike with Delbrück and came back with a broken leg. A story like that the Delbrücks just loved to tell all the time. Kalckar was the guy Jim Watson went to work in Copenhagen with, but couldn't stand it and left to go to Cambridge because Kalckar was taking up with a young woman and was completely distracted; and Watson almost lost his American Cancer Society fellowship at that time because he made this peremptory move. Paul Weiss was the guy who wanted him fired. Paul Weiss was also the guy who had been a senior man at Chicago when Roger Sperry [Board of Trustees Professor of Psychobiology, emeritus] was there, and Weiss had been, as I understand it, very skeptical about Sperry's work on neurospecificity, but then later took it over as his own. Sperry, if I remember correctly, was refused tenure at Chicago, and that might have to do with Paul Weiss for all I know; that's just speculation.

Aspaturian: Did Delbrück have any drawbacks as a research leader or an academic mentor?

Benzer: Well, he didn't really lead very much. I think everyone pretty much did his own thing. It was not a task force where he was director in any sense, and that was one of the advantages of coming here. Funds were easier then. Nowadays there's a tendency, partly because of the funding requirements organized around a project, for the leader to be the guy busy getting money for everybody. But in those days there was no money, so it was not that much of an issue. But in any case, Delbrück's personality was such that he wanted time to do his own thinking; he didn't want to have to be involved in everybody's project. But we'd have regular seminars of the group. One of the key things that Delbrück implemented was at a certain point he decided it was time for everybody to write up papers. He said we had to get out and get away from the lab. So there was a marine station at Corona del Mar that had some rooms where we could stay. He arranged

for us all to go out there, and Manny brought a typewriter. And people would write manuscripts, and he just locked us up for a few days and she would type them out. Then we'd all circulate the drafts and correct each other. And by the time we left, everyone had a good draft.

Aspaturian: Was this a semi-regular ritual among you people?

Benzer: Well, it only happened to me once in a two-year period, but I think it was something he regularly did. I tried it myself once with my group and didn't succeed. [Laughter] We didn't have Manny, for one thing. And I didn't have as strong-willed an approach as Delbrück did. We were all working on one manuscript, but we got just a whole pile of verbiage without ever—that manuscript has never seen the light of day. We were isolating behaviors of *Drosophila* mutants, and the manuscript was just a carload full of different types of behavioral mutants. So that paper would have been just a description of all of these, and it never was quite satisfying at that level.

Aspaturian: Among those of you working with Delbrück here in the late forties, was there a feeling of being at the dawn of a new day in biology?

Benzer: Oh, I don't know. We loved what we were doing, but I don't recall having any sense of history, that we were making history. Delbrück had a sense of history; his father was a famous historian. But my father had no history; I had no history; it wasn't part of my thinking. It was always exciting to be doing the experiments, but I don't remember feeling that this was breaking new ground, a new era in microbiology. I can't say I felt that.

Aspaturian: What exactly were you working on at that time?

Benzer: I was working on the continuation of the experiment I mentioned before—the bacteriophage experiment that I started in Oak Ridge. That was one of the manuscripts that got written in Corona del Mar. One of the nice things about working with Weigle was that he was a lark and I was an owl. So we were able to work together very well, because when you plated the bacteriophage, you had to put the plates in an incubator. It takes about five hours or so for the plaques to come out. So I could plate the things out at night; and he'd come in at 4:00 a.m. or so,

take them out, and incubate and count the plates; and then when I came in, around noon, he'd tell me the results and go home and go to sleep, and I would do the next step of the experiment. It really went extremely well.

Aspaturian: So you alternated really well.

Benzer: It wasn't alternating; it was successive, working together. He liked his privacy. He used to go typically every weekend up to the desert camping by himself, or with some lady friend, of which he had several. Of course, they always tell people, "Stay a postdoc as long as you possibly can; it's the best time in your life." So I just loved that period.

Aspaturian: You of course were already an assistant professor on Purdue's faculty.

Benzer: Yes, I already had a job, so that was never part of my worry. But I don't know if it was a worry for the other people either. I don't remember that being a particular part of the consciousness.

Aspaturian: Did anything major—in terms of your research or your development—come out of this period at Caltech?

Benzer: In development, yes, it was wonderful. This was my introduction to biology, and I drew a lot from all the seminars here, the other people, and also from a summer course I took while I was here at Pacific Grove. The course was given by Cornelius van Niel, who was in at the dawn of microbiology as such, when people first started studying bacteria in the early part of the century. He was stationed at the Stanford Marine Station in Pacific Grove, near Monterey. He gave a summer course; it was just like the phage course, but for bacteria. There was, again, the motley crew of students—many physicists, like Leo Szilard and Aaron Novick. But they were not there the same year that I was. So that was a wonderful indoctrination into microbiology.

What else did I get from here? I probably learned a lot from Delbrück in terms of attitude towards students. One of the unfortunate things at that time was a sort of prejudice against biochemistry. I think it was based mostly on ignorance, something I feel embarrassed about,

looking back. It was partly that Delbrück had scorned biochemistry as such and that carried over. I think probably there was a particular biochemist that he didn't like. So I didn't learn as much biochemistry as I should have.

Aspaturian: What were his particular reservations about biochemistry that you recall?

Benzer: I can't say. I think it probably came down to a few particular biochemists. I remember Dulbecco once saying, "I wash my hands of biochemistry." [Laughter] But it was completely off-base. Delbrück himself was very concerned about things like protein replication, so the attitude was just plain stupid.

Aspaturian: You went to the Pasteur Institute straight from Caltech?

Benzer: I went to the Pasteur Institute from here. How I got there was André Lwoff came to visit. He was an important research person at Pasteur, already quite famous at that time. At Pasteur he had been working with a bacteriophage called lambda, which had different properties from the ones we were working with. Delbrück and others—I think it was in particular Ugo Fano, a physicist who worked on phage at Cold Spring Harbor and he probably connected with Luria—went ahead and said, "Let's pick a set of bacteriophage that have similarities and differences, and we'll call them Type 1, 2, 3, 4, 5, 6, 7." So I started at T1—some were similar and some were different. These were all bacteriophages that infect the bacteria and twenty minutes later cause the bacteria to lyse—that is, the bacteria burst open. And there was something else, called lysogenic bacteria, where you have the culture of bacteria and every so often a phage particle comes out here and there. The bacteria will contain phage—they're basically permanently infected—and the phage seem somehow to be in residence in the cell, and they just occasionally come out. Delbrück's idea was that the infectious agent was just an ordinary bacteriophage, but it was inefficient—a weak phage—so it only caused lysing bacteria every so often.

Now André Lwoff from the Pasteur Institute had a different idea. His theory was that the bacteria themselves somehow carry the phage in them but it's not being expressed. So the difference in the views was between slow infection versus innate properties of bacteria. The

breakthrough came when Lwoff, who was working with individual bacteria, discovered that if you shined ultraviolet light on them, all of them very quickly released the phage. And that was extremely important, because it turned out that the genes of the phage were actually part of the genes of the bacteria, and activating them by various stimuli would cause that part of the gene in the bacterium to start replicating and would induce the production of phage. Those phage could come into another bacterium that didn't originally contain them, and those genes would then become installed in the bacterium. Delbrück was skeptical until that ultraviolet experiment. He had always tried to be uninterested in the lambda phage, which is now one of the backbones of molecular biology because it's one of the standard vectors for bioengineering. In the biotech company catalogues, you'll see twenty-five different forms of lambda. And then it's so simple it doesn't have any real genetics. The thought was, it was too simple.

Aspaturian: Was that Delbrück's thought, again?

Benzer: Everybody's thought. But then Jean Weigle was the first one to show you could make mutations in the lambda and that you could actually do recombination experiments with lambda, just as you do with other bacteriophages. So Weigle was the pioneer of the whole lambda genetics business, which is now a real industrial operation.

Aspaturian: Was he doing this while you were at Caltech, or did this demonstration come later?

Benzer: This came later. I think his big breakthrough probably didn't come until I was back at Caltech in '65. Because I remember clearly he gave me a paper to submit to the DNA Proceedings of the National Academy of Sciences [NAS], of which I had been a member since 1961. Members can submit papers for other people. Usually it's a tremendous headache, because you have to criticize them and send them back, and criticize them again, and three times around. Jean Weigle was unique; he, and only one other case in all my history of submitting papers for people, gave me a manuscript that required no editing whatsoever, which is perfect. And that had to do with the genetics of the lambda phage.

Delbrück could be extremely opinionated. He often had rather fixed ideas. The most extreme example I can think of is one in the later years when I was here. One of my students was

interested in the biological clock; and he had shown that you could make mutations that changed the biological clock in *Drosophila*. And he was telling this to Max, and Max said, "No, that's impossible." And then I said, "But Max, he's already done it." And Max said, "No, that's impossible." That was not a completely unusual kind of event.

It was often a very great source of stimulation that Delbrück would tell you something's impossible. You'd go ahead just to prove him wrong. The fact was, he had been wrong scientifically on many occasions. But as Jim Watson once said, "The difference between Max Delbrück and this other guy is that they both have been very often wrong. But when Max is wrong, it's usually for an interesting reason." [Laughter]

Aspaturian: I was interested in finding out how you got to the Pasteur Institute.

Benzer: What happened was Lwoff was here. I was dying to go to Paris, mainly because of Paris. So I approached Lwoff and said, "Could I come to Paris?" What happened was, we were on a camping trip to Mount San Jacinto—that's where most of the business was done, I guess, instead of the golf course—and we were climbing up from some campground about halfway up near Idyllwild. Some of us went to the top, but my wife and Lwoff wanted to come back. So they started back; they had one grapefruit between them. They got lost; they lost the trail. They were wandering around in the woods, and he was shouting and occasionally running into deer hunters, who became absolutely furious, because he was scaring the deer away. So finally they found their way back—probably from a deer hunter. She was begging for the grapefruit the whole time and he was holding on to it—it might save their lives. Anyhow, during that adventure, she somehow mentioned that Seymour would like to go to Paris. "Oh, he'd like to come to Paris? I'll invite him." And so he did.

Begin Tape 2, Side 2

Aspaturian: Did you go straight to Paris from Pasadena, or did you check in at Purdue for a day or two?

Benzer: What happened was my wife's father was living with us. In fact, we brought him with

us when we came to California. And that was a great help to us, because we had one young child, my older daughter, Barbie. So he was the babysitter, and that made it possible for my wife to work at the Huntington as a nurse, which she enjoyed very much. So we took him with us to Paris. But first we arranged for him and Barbie to go by train to New York. And Dotty and I drove across the country. Jean Weigle had loaned us his white Cadillac. Did I mention the white Cadillac?

Aspaturian: I don't recall the white Cadillac.

Benzer: Gunther Stent has a white convertible Cadillac. And that's because Jean Weigle had one. Jean had loaned us his Cadillac because he was going to be in Europe. What he would do was spend the winter here, three months or so, and the summer in Geneva. He had an apartment in Geneva, which he let people use when they visited there. My wife and I stayed there once. So we drove his Cadillac with the top down all the way east—it was probably Route 66, if I'm not mistaken—to New York. And then he picked up the car when he came back to New York. But we did stop at Purdue on the way, suntanned, in a white Cadillac convertible, and on our way to Paris. [Laughter] And they said, "He's never coming back." But they were wrong. I always intended to come back, and I did.

While I was a postdoc at Caltech, I was still being pursued by somebody in the semiconductor business. I'd known him during the wartime effort, but he joined a company out here—I think it was Hughes Aircraft. He tried to recruit me—at about ten times the salary I was getting as a postdoc.

Aspaturian: Were you tempted?

Benzer: No. But he came to visit once. He came up to the house while I was out and was waiting for me. I drove up in Jean's white convertible. He said, "Oh, you're doing so well as a postdoc; I'll never be able to persuade you." [Laughter]

SEYMOUR BENZER

Session 3

October 5, 1990

Begin Tape 3, Side 1

Aspaturian: So you went to Pasteur in 1950?

Benzer: It was in August 1951. After driving Jean Weigle's Cadillac to New York, we took a ship called *DeGrasse*. It was a small boat, which took nine days to get across. I don't cotton to ocean travel too well, and I hated it, except when they had a movie every day. One day a French movie, one day an English movie, and then I could forget that the boat was rocking.

We arrived in Paris on August 13th, not knowing that that was one of the biggest vacation days in all of France—it's Assumption Day; the day that I think Khrushchev decided to build the Berlin Wall because everybody would be away on vacation. We found a hotel; and it came out to be the hotel where Jean-Paul Sartre was staying, but we never got to see him.

We tried to find a place to live. It was extremely difficult. We went down to the Embassy. I was on a Fulbright Fellowship, so I went to the Fulbright office, but they didn't have anything. We hunted around and finally found an artist's studio occupied by an American couple, including a woman sculptor named Louise Bourgeois, who was using it for a studio. This place was like a one-room with a little bit of a loft, with an open-air bathtub and a potbellied stove; toilet outside—a communal toilet for this group of artists surrounding the area. It was a Turkish toilet, where there's just a place for your feet. There's a hole, of course; there's a place for your feet, and then you squat over it. And then to flush, you pull the chain, and you get the hell out of there as fast as you can; otherwise your feet get soiled. But they told us that in France everybody lives like this. They said, "You're spoiled Americans, so you have to lower your standards a little bit." Well, we were kind of desperate and that's all we could find, so we moved in.

It was extremely unpleasant. My daughter developed diarrhea, and that became a real problem with the toilets. We got a pot for her to do it in. She was eaten up by bedbugs. We went to try out the stove, and the whole place filled up with smoke. So we were pretty desperate. And about this time, François Jacob came by. He had been on vacation, and I had dropped a message

for him in the lab. Our address was 77 Rue de Guerre, but the French write a one like we do a seven, and the seven is crossed, so he was looking for "11," not "77." It finally dawned on him that we might have meant "77." He found us, and he said, "Why are you living like this?" And we said, "Well, we want to live like the French." [Laughter] And he said, "The French don't live like this."

In the end, we reneged on the commitment to stay there. Bourgeois and her husband, [Robert] Goldwater—I think he was an art critic, a professor of art at Queens College in New York—had already gone back to the States, so they were upset about this. But the Fulbright people said there was no obligation to stay at that kind of place.

All this time, of course, I was going to the lab during the day and getting started on my experiments, while my poor wife and child were suffering at home. We did have a car, and we finally found a place out in the country—a village south of Paris. We rented an apartment there; it was a two-story house where the landlady lived underneath and we lived upstairs. It was very charming, with roses. Across the street was a dairy where people would come and get fresh milk, cheese, and eggs. My daughter signed up for the local school—the kindergarten. She was by then four and a half, I guess. That was not so pleasant; she was frowned upon for being a foreigner; she used to come home and say they spit on her and taunted her.

The crunch came when it started to get cold. One reason why we'd taken this place was it had radiators. But they didn't seem to work, and when we said, "Where's the heat?" the landlady said, "Well, the radiators are not connected to the furnace. The workmen are going to come and connect them." Meanwhile, everyone was getting cold. We were burning wood in the fireplace—anything to keep our hands warm. The workmen came, banged around, connected the furnace to the radiator. And I said, "OK, now where's the heat?" "Oh, we have no coal." This was getting on to November, December. "Where's the coal?" "Well, all the coal is being sent to America." So I went down to the town to the coal merchant and asked him if he had coal. And he said, "Sure." "Well, where does your coal come from?" He said, "It comes from America." [Laughter]

It was getting worse and worse. And then finally, this angel, Sarah Rapkine, who lived in the center of Paris, about a mile from the institute, became aware of an apartment that was available in her apartment house. So we moved in there.

Aspaturian: Whose wife was she?

Benzer: Her husband's name was Louis Rapkine. They still have a lecture every year in his honor at the Pasteur Institute. This new place was so hot that we had to keep the windows open. There was a steampipe going through the room that we couldn't turn off. But it made life possible.

Aspaturian: But by then, you'd already been there about five months?

Benzer: I think it was more like four months.

Aspaturian: What about the Pasteur Institute? How did it differ from being in Delbrück's group at Caltech, in terms of overall approach?

Benzer: Well, the first shocking difference was Lwoff. Any time he visited Caltech, he was "anglais"—very charming, very bright, on first-name terms. And when we got to Pasteur, he was *le patron* and "Monsieur Lwoff"—he was the boss, and he then became much more formal. I remember my wife, who had been lost in the woods with him, saying sometimes she wished she could just poke him in the belly and say, "Hey, come off this." But Elie Wollman, who was in the picture, a dyed-in-the-wool Frenchman, said he thought Lwoff was perfectly right, and that when he became *patron*, he would be the same way. So we were in a strange position in the lab—the Americans would all *tu-toi* with the French, but the French were *vous-voi* with one another. They would *tu-toi* us—with children, and dogs, and foreigners, it's OK. Sometimes you wouldn't know which to use, and there would be a lot of circumlocution to avoid having to use either one. You could always tell in a French movie when they've slept together because they switch from *vous* to *tu*. So there was kind of a humorous twist. Jacob and Monod, I think, still *vous-voi*ed each other when they'd been colleagues for years. Unless you knew each other as close friends or family members, that's what you did. Elie Wollman was so formal I think he *vous-voi*ed with his wife.

The general atmosphere was more formal than with Delbrück, who was "Max" to

everybody. Lwoff's wife was a more formal person, too. She worked in the lab also. Lwoff had his own office and his own little laboratory, in which he had two or three technicians who did the experiments under his direction. But the others were essentially free to do what they wanted; he was not the boss in the sense of commanding a task force. So there was free interaction and cooperation among the other people in the lab. And the lab was always about half American. When I was there, there was also Gunther Stent; Mel Cohn, an American; and an Italian named Annamaria Torriani. There was a constant turnover. In the years I was there, it was like a college employing American biologists.

I was in a room with François Jacob, but most of the time we worked separately. He was working mostly with Elie Wollman at that time, and they did important, pioneering work. Lwoff was working out this business about proving that lysogenic bacteria carry the infectious phages in their genes. He was trying to figure out what would trigger all the bacteria to release phage, that is, change from the dormant to the active state. He knew that ultraviolet light triggered this response, and he was trying to figure out how that works. And every day he'd come in with a new announcement of, "*Messieurs, j'ai trouvé la solution*." ["Gentlemen, I have found the solution."] I don't even remember what it really turned out to be. [Laughter] That's what he was into at the time.

He'd had a distinguished career of working in protozoa before that; he was quite a famous scientist already. Jacques Monod was in the same lab. François Jacob was still in the early stages; he'd only been there a year or so when I came. You may know the story of how, when he first gave up being a surgeon, he tried everything from writing novels to painting. When our apartment was rather bare, I asked him to lend me some of his paintings for decoration, and he said he would do it on condition that I didn't tell who the artist was. So once we had him over for dinner at my house, and Sarah Rapkine was there and some other people. And at one point Sarah said, "Who made those paintings?" [Laughter] I said, "I can't tell you." And Jacob was getting red in the face. I said, "Do you like them?" She said, "No, they're terrible." Jacob gave me one; I still have one of his paintings of a still life. I thought he had some talent. He was living in a very elegant apartment. His wife had money, so they had an elegant apartment overlooking the Luxembourg Gardens, with paintings hanging. Mostly not his, but I think there was at least one that was his. And he had a Picasso. And I said, "Hey, that's a pretty good copy of a Picasso." And he just chuckled, but I found out afterwards it was a real one. [Laughter] He didn't tell me

until years later. Incidentally, Lwoff took up painting in the Impressionist style in his later years and was extremely successful. When he reached retirement age, he painted in his office. He has exhibitions in Paris and people buy the stuff. It's real accessible art; of course, the name probably helped.

Aspaturian: You were saying that after he gave up surgery, Jacob was floundering around for something to do.

Benzer: Yes. He had decided that he wanted to be a molecular biologist. He tried going to the Pasteur Institute to see Lwoff, kept going back over and over again. And then one day he came, and Lwoff was in a jubilant mood; he might have just made this big discovery about the bacteria lysing, and he was very affable, "Oh, sure, you can come work in my lab." And that's how it happened. So—persistence plus circumstance.

Aspaturian: Was Jacob one of your closest associates while you were there?

Benzer: We didn't get really personally close until toward the end of the year, when we had done a piece of work together and it came to writing up the paper. He invited my whole family out to his wife's family's country place. And there the wives got to be close; they hit it off together. And I think that more firmly established it at that point. We were always on good terms, but there was not much social life outside the lab.

The thing that was typical in France—probably still is—is that entertainment at the home was not casual, like it is in England, where you come over and have some tea and a couple of cookies. They make it easy. But in France, it was, and I would guess still is, taken very seriously. You'd be invited once in the year to a proper formal dinner, where the hostess would hire a maid for the day, if she didn't usually have one, and have a little bell to ring when the maid should come in, and serve a fantastic meal from soup to nuts. And that's it. Apparently in France, colleagues will visit in the bar, have a glass of wine together after work, although that's more of a lower-class thing. So I didn't have any interaction of that sort. And we missed it, because having come from Delbrück's group, which was so highly social, always going on trips together, that was kind of a shock. We felt kind of lonely.

Aspaturian: What about the other Americans there? Did you tend to kind of cluster together?

Benzer: Well, yes, a little bit, but not to a great degree. The Stents lived in the same apartment house; Sarah Rapkine found them another apartment upstairs. The only social interaction I would have outside the lab was when we would play music with Jacques Monod in his apartment. He had a very nice apartment which he disdained as being bourgeois, but he lived in it anyway. He had been important in the Communist Party during the Resistance, although he got pretty disillusioned later on. Inga Stent played the piano—she was trying to be a professional pianist—Monod played the cello, and I played a very lousy violin. But the three of us would sometimes play weekend trios in Monod's apartment, and that was always wonderful. He was a highly cultured, very cerebral person, really Cartesian. One of the stories that used to go around in the lab was about the difference between Lwoff and Monod. I heard this from Mel Cohn, who had already been at the Pasteur Institute several years: It had to do with a little "trick" cup, the kind that has a round bottom that you can spin, and after a while it spontaneously flips over and spins upside down. The question was, how does this work? Monod, not having touched the cup, would say, "Well, let's see; there must be a certain moment of inertia and a center of gravity, and the angle of momentum," and so on. Whereas Lwoff would pick it up and examine it, hold it up to the light and turn it upside down. [Laughter] And that typified the difference between them.

I worked, to a large extent, on my own for a good part of the year, trying to solve a problem that was set by Roger Stanier, who had said this experiment was almost impossible. So I took that as a challenge. And the question was: One of the mainstays in Monod's work at that time was called "enzymatic adaptation." You have bacteria in a solution that doesn't have a particular sugar—say, lactose—and instead has been growing on glucose. You take away the glucose and you give the bacteria lactose instead. Nothing happens for quite a while. Then they start growing on the lactose. During the interim, an enzyme has been induced in these bacteria so that they can hydrolyze the lactose and utilize the glucose that comes out of it. That's called enzymatic adaptation, and a lot of Monod's work had been on that kind of phenomenon. And Stanier had written an article on the subject, saying it would be nice to know if only a few of the original bacteria are adapting and then reproducing, or if all the bacteria are adapting simultaneously. The process was slow, followed by increasing growth, so it could have been

either alternative. He said, "But that's almost impossible to find out." But the experiments that I'd been doing with bacteriophage gave me a clue, a method by which I thought I could solve that problem. The idea was, take these bacteria, infect them with phage, put them on lactose, and see if they all adapt to the lactose, thereby allowing changes in the ultraviolet resistance of the inside bacteriophage simultaneously, in which case you would get a straight line while you plotted them. Or if some did, and others didn't, you'd get a broken line. I had a way to do this. I remember that when I came to the lab on the first day, I sat down with Lwoff and Monod, and they said, "What do you want to work on?" I described this experiment, and Monod said, "Oh, that's a very good idea." And Lwoff said, "I don't get it; what's the point?" [Laughter] So I went ahead and did it. I found a better way of doing it than the one I had originally thought of.

Aspaturian: Did Monod have a primary role in directing the lab, too?

Benzer: Well, he was a subgroup in the lab. And as I said, while Lwoff was working on lysogenic bacteria, Jacob was beginning to work with Wollman on genetic transfer, conjugation in bacteria. Bacteria have sex, and the male transmits its chromosome into the female. Joshua Lederberg and Edward Tatum had discovered this phenomenon. Lederberg and Jacob later had violent arguments over the years about exactly how it works. I think Lederberg turned out to be wrong. And Monod was working on this—by now it had become not enzymatic adaptation but induced enzyme synthesis, because he found out, by taking compounds similar to lactose, but which the bacteria could not attack, that these compounds were still able to induce the bacteria to make the enzyme that would attack lactose. So he changed from the idea of adaptation, which had sort of a teleological cast to it, to describing an induction. He was working on that phenomenon and how it's controlled.

Mel Cohn had been working with him quite a few years by that time; he'd been there for about four years or so. He got upset at one point that nobody in America offered him a job because they figured he's so happy in Paris that he would never want to leave. He was married to a woman, Ruby, who was studying literature at the Sorbonne. She did her PhD thesis on a French playwright, but she later became a Beckett expert. That was the year that Beckett's *Waiting for Godot* was playing in Paris, and people were very upset about it—either for it or against it. Most

people said it was a lot of nonsense, but Ruby said this is really hot stuff. And she became the foremost Beckett scholar and wrote a book about him. The last I remember, she was on the faculty of San Francisco State.

Aspaturian: Did you see the play?

Benzer: At that time, no. I went to see something by Ionesco—I think *The Bald Soprano*—but I did not go to see *Godot* at that time. We didn't go out an awful lot; we had the young child at home. Also, my wife was no owl; she'd get up very early, and she'd be tired at night. So my habit was to go back to the lab at night. And I ran into trouble almost the first day at Pasteur when I asked what the library hours were. Then I asked the librarian if I could have a key to get in at night, because I like to work at night. She was outraged; no one had ever had the nerve to ask anything like that. That was out of the question.

I did one other thing that upset Elie Wollman very much. When we still didn't have a place to live in town, he took us on a tour of Louis Pasteur's apartment, which was still maintained in a building across the street from the institute. And I said half jokingly, "Nobody's living here; why can't we stay here until we find something else?" Elie was absolutely outraged: how could we possibly say such a thing about a great national monument?

Aspaturian: Across the Channel that year, there was a lot of work going on on the structure of DNA.

Benzer: Well, during that year at Pasteur, Jim Watson came by. And he was carrying a book on phosphate chemistry. I think the general reaction was, What the hell is this? It seemed kind of far-out. He said he was really getting into it, and that it was very important. I think this was the year when he shifted from Copenhagen to Cambridge, because his senior colleague at Cambridge, Herman Kalckar, had become infatuated with this younger woman who had been at Pacific Grove. I met her when I took the course there. She was a bit of a vamp, and Kalckar fell for it, got divorced, and his life went completely out of whack. And Watson decided, "To hell with this, I'm going to Cambridge."

Aspaturian: Watson is described by contemporaries, some of them from that period, as this very odd, offbeat person.

Benzer: Watson? Oh, sure. I think he cultivated that persona. Purely to infuriate Lwoff, he would go around at the meetings wearing sneakers and have his shoelaces untied.

Aspaturian: In the photos in *The Double Helix*, I noticed he was wearing shorts.

Benzer: That, too. [Laughter] But I specifically remember the shoelaces. Yes, he made a point of being obnoxious. An arrogant young man, very bright. Now he goes around with a coat and tie, trying to get money for Cold Spring Harbor out of people—Long Island millionaire circles. And the kids at Cold Spring Harbor go around with their shoelaces untied.

Aspaturian: Was there much interest at the Pasteur in DNA?

Benzer: No, we were not really aware of it. We had to be hit over the head with it. I think the place it really came out was at a 1952 meeting at Oxford, when I think Watson may have brought the message about the Hershey and Chase experiment with the Waring blender.

Aspaturian: In fact, I found a quote about this meeting in *The Double Helix*, where he says, "Almost no one seemed interested, except Lwoff, Benzer and Stent, who were over from the Pasteur."

Benzer: Yes. We were into phage, and had some appreciation for it. So that was a real awakening. In retrospect it was tremendously stupid, because DNA had been on the boards since Oswald Avery's work, a very long time before that and very well documented, showing that you could transform pneumococci with it.

Aspaturian: Why didn't the Establishment pay attention?

Benzer: It happens all the time. [Laughter] When I was in Sperry's lab and said I wanted to work with mutant flies, they said I was crazy.

Aspaturian: I think you were in Paris when the State Department tried to lift Linus Pauling's passport. Do you recall what the reaction was?

Benzer: The same thing happened to Luria, and I remember the general reaction to that. Someone—a member of the group from England—wanted to refer a question from the audience to Luria, and somebody else from the audience said, "There is a rumor that Dr. Luria has been prevented from attending by being refused a passport. Are you in a position to scotch that rumor?" And whoever was the chairman said, "No sir, I am not." [Laughter] I always admired the style with which the British made that particular announcement.

Begin Tape 3, Side 2

Aspaturian: Was there a lot of politicking and jockeying for position at the Pasteur when you were there?

Benzer: Well, if there was, I wasn't aware of it. I was too busy, happy-go-lucky, doing research. But very likely there was. I mean, my students are not aware of what the faculty is up to here. But Lwoff and Monod were in an attic, a very crummy laboratory space, at the end of a corridor. You had to walk through other labs to get to it. And it was full. During the year I was there, the groups started to grow to the point that the attic could no longer hold both Monod and Lwoff. Now, what went on between them over that, I have no idea. I wouldn't be surprised if there was conflict, but I was protected from it. I was probably naive, too. Jacob and I shared a large room with a large table in the center, and at a certain point it was decided that that was the lunch room. Every day, at one o'clock, lunchtime, you quit your experiment. It cramped our style sometimes, but we planned around it. Everybody would come in and sit around the table, with a coffee pot. Unfailingly it would be put on and forgotten, so that when it boiled over there would be a big eruption and commotion. The coffee came from a special coffee shop around corner on the

Boulevard Pasteur, a special blend that was very good. Lwoff sort of pontificated at the table, and Madame Lwoff was the subpontificator. We'd talk about the theater or politics. Other people talked too; the Lwoffs didn't monopolize it, but they clearly directed the conversation, so we'd all be carefully watching Lwoff's table manners. How he'd peel a peach would be a whole elaborate work of art. Or he'd take out the cheese—Camembert—and scrape it in a delicate way. I tried to imitate all these motions, sometimes without knowing exactly what they were. After the coffee dripped through the pot, you had to stir it—sometimes there was a knife we used for this. But once, the knife had been used for cheese, so I went to stir the coffee with the wooden handle. Lwoff was absolutely horrified. And I said, "Why, what's wrong?" He said, "It would be hard to explain to you if you don't know." [Laughter] It was great—it was a whole education.

My French was good enough that I could understand what they were talking about, especially in politics, but I couldn't be sure what side they were on. [Laughter] There was always something a little bit missing when the French talked. And, of course, the language in the lab was a sort of mixture of French and English. It was not at all uncommon for sentences to consist of half French and half English words, choosing the best words for the purpose. For instance, there's a French expression, *se débroullier*, which means, "to blow away the fog," to work your way out of the fog. So I remember that somebody kept saying, "Well, you do this, and you do that, and you *débroullier* yourself." [Laughter] Jacob taught me some French children's songs that I still remember and taught to my children. So it was fun; it was just a tremendous experience.

At some point, the group just got too big to all fit in one room for lunch. So Monod developed his own separate lunch group, within the same total space but in a separate room. I wouldn't be surprised, now, in retrospect, if a lot of politics went into that. That might have been the real falling out, for all I know. But if so, it didn't come down to me.

Aspaturian: So Lwoff stayed at your table and Monod presided over another table in another room?

Benzer: Yes. And the work I was doing was more related to the Monod group. So I would go some days to one table and some days to the other. And Madame Lwoff, when I came to the

Lwoff table, said, "*Tiens!* Seymour—*avec nous aujourd'hui*." ["Well! Seymour has joined us today."] She was that kind of, you know, Nancy Reagan type. Basically not a bad person, but she was not a warm person. We had dinner at their house 1.0 times and it was a very formal affair. There's a funny story about that. The Lwoffs lived in an apartment house. Gunther Stent decided to bring flowers, but he got off at the wrong floor. He rang the bell, and a nice old lady opened the door. He thought, Well, this must be Madame Lwoff's mother. He sat down, gave her the flowers, they chatted for a while; and it finally dawned on him it's the wrong place. [Laughter] He asked, "Isn't this the apartment of the Lwoffs?" "Oh, no, no; that's the next floor." He said, "Oh," and he grabbed the flowers and took off. [Laughter]

There are a lot of Stent stories. He liked to tell these stories on himself actually. Did I tell you the Toscanini one? This was in Pasadena. Toscanini came through with the NBC Symphony Orchestra on his final concert tour—the last chance to hear Toscanini play. He was at the Pasadena Civic Auditorium two nights. I went down to buy tickets; they were completely sold out. So I said to my wife, "Well, we'll just sneak in at intermission." So we did. We were sure somebody would be sick and not show up, two people, out of the whole auditorium. But every single seat was occupied. The ushers said, "May we see your ticket stubs, please?" and then they threw us out. We were terribly embarrassed. When I told Max Delbrück about it at lunch the next day, he said, "Oh, what a great idea. Let's all go tonight." [Laughter] So, the Delbrücks went, and the Benzers, and Gunther Stent, and maybe Stent's wife. About six of us sneaked in at intermission, no problem at all. Then, the same story, and we all got thrown out except Stent. And we're outside the auditorium cursing, "How did Gunther get away with it, that son of a gun?" And then a few minutes later, the doors open wide, and Stent's escorted out by an usher and the doors are closed again. [Laughter] The ushers by then took pity on us; so when it came to the encores at the end, they let us go in and stand in the back to hear the encores, because this was the last chance in the world to hear Toscanini.

Regarding Paris, I'm famous there for bringing exotic things into lunch, like South African caterpillars. Unfortunately, they came dried. [Laughter] I used to bring in a crab or a sea urchin or whatever things I found at the market. Lwoff used to tease me and said, "Did you ever try *tetine de vache?*"—that's a cow's tit. So I went to the butchers who specialize in it. I got a slice of the cow's udder and cooked it, and it was actually quite delicious—very rich, you know,

200-percent cholesterol, but actually quite tasty, a spongy texture. And then I told him I'd had that, and he said, "Ah, that's not the right thing—you're supposed to have the nipple of the cow, not the udder." So that was the next challenge. He gave up at that point.

Scientifically, it was wonderful in the sense that as soon as anyone made an exciting observation, there would immediately be a group of people in the hall discussing it—what's wrong with it, what should we do next. If you're in rather confined quarters, every discovery's an event. So it was absolutely wonderful.

Aspaturian: Were there any drawbacks, anything that you think you missed out on, or where the institute missed the boat at that time?

Benzer: Well, DNA. [Laughter] Other things were going on. But everyone was so busy and satisfied that I don't think there were many feelings of that nature. Later on, they got into severe competition with other people, but they did very well. The drawbacks were in terms of not having the amenities we were accustomed to in America—you know, paper towels and a box of Kleenex and more space. The scientific creature comforts, so to speak, were less, so that took a little bit of getting used to initially, but certainly didn't inhibit getting great work done.

Aspaturian: Was it hard to go back to Purdue?

Benzer: No, because I'd always loved it there—I came as a graduate student, and it was a place I'd always loved being at. Still do. When I go back there, I feel very much at home. It was time for my daughter to start school—time to go back to America. Purdue provided an apartment for us. I had a nice lab to move into. So that was fine. I certainly missed a lot of the things in Paris, but I knew I could go back there. So I don't remember that as being in any way traumatic or sad.

I remember getting on the boat and the Americans saying, "What's for dinner?" And they said, "Hot dogs." And they said, "Yay! Good old American hot dogs!" That was a bit depressing.

Back at Purdue, I was very much on my own initially. I went into a biophysics department, but there were just two people. I had, I guess, three rooms at my disposal—a kitchen, my own office/laboratory, and a larger room that I used as a classroom but also for

research when not teaching. That was infinite space compared to what I had in Paris, which was one bench interrupted by lunchtime, which was much more than I had in Cambridge later on. At Cambridge, I asked for two feet of bench space where I could put a dessicator and the specimen, to know that it would be there the next day. And I was told, no, I can't have that. The story was that in Cambridge a telephone booth became unoccupied one day, and there was a tremendous fight among three departments over who would get it. [Laughter] That may be apocryphal, but it's believable. It was true at that time, but later on they got bigger quarters. So no, it was nice coming back to Purdue. I had a supportive chairman, and I got the lab in which to continue the work I wanted to do. The experiment I started out to do was supposed to take off from the Hershey-Chase Waring blender experiment. I wanted to put bacteriophage-injected DNA into the blender with the idea that by interrupting the injection process at various times, one might be able to show the sequence of the genes on the chromosome. That's the experiment I was trying to do; but in the course of it, I had to have a mutant marker so I'd know when the new gene would come through. So that's when I started working on so-called *r* mutants of bacteriophage.

SEYMOUR BENZER

Session 4

October 12, 1990

Begin Tape 4, Side 1

Benzer: At the time I came back to Purdue, there was already another biophysicist there—a guy named Lorin Mullins. He worked on nerve junctions and on the problems of the sodium and potassium channels opening up when a nerve impulse traveled along.

Aspaturian: I didn't realize research on that was conducted that many years ago.

Benzer: That it was known? Well, the biggies in that were [A. L.] Hodgkin and [A. F.] Huxley, who had worked out the mechanism. I wasn't terribly interested in that at that time. Little did I know that years later, in my lab here, people would be working on trying to clone a gene for the potassium channel.

I was trying to do this experiment I had mentioned about using Waring blenders to interrupt the transfer of DNA from a phage into bacteria by shearing the phage off at different times. What happened was, to do that experiment I needed some kind of genetic marker so I would know when the gene entered the cell. So I started working with *r* mutants. [Pointing to a picture on wall] See the picture up there with plaques? The little fuzzy one is the normal bacteriophage. To study it you spread bacteria all over the petri dish and then the phage attacks bacteria and that releases more phage, which spread out until they clear an area on the plate. But the shape of the plaque that's formed depends on the characteristics of the dynamics of the infection. The normal-type phage produce little plaques, and certain mutations would cause them to make big ones. They're called *r* mutants because the difference is traced to an atypical phenomenon called rapid lysis. Typically if bacteria are in rather high concentration, and if one bacterium gets infected with the phage, and then a short time later with another one, it produces a phenomenon called lysis inhibition. The lysis was delayed and you got a much larger burst of phage at the end. But the result of this lysis inhibition causes the plaque to be awfully small and

fuzzy. Whereas with a mutation causing a defect in that process, there is no lysis inhibition, so even if the cell is really infected after the first infection, it had no effect, and these produced really big plaques. So these are the *r* mutants, for rapid lysis. They've been studied by Al [Alfred D.] Hershey and August Doermann, who published papers on them. Hershey had actually discovered that a lot of different *r* mutations could be recombined with one another and seem to be in a sort of cluster—an area for a genetic map of the phage. You have a chromosome in *Drosophila*, a gene on the chromosome, and then there's a part called the centrum, which is used by the cell before the chromosome during mytosis when the cell divides. And near the center, typically there's a lot of sort of condensed DNA, both hetero- and [word muffled], which doesn't do very much. It's part of the chromosome, but it contains most of the DNA that is not very active—junk DNA. So if you take a gene and transplant it from the place on the normal chromosome where it's active, and you put it in there, it often becomes inactive.

The interpretation of this was that all these *r* mutants were the same mutation, but at different places in the heterochromosome. The idea that it was one gene that was being split into different parts didn't seem to be part of the thinking, because people thought of a gene as a unitary thing, which could not be split by a new combination.

I was setting up some of these experiments on lysis inhibition for a course I was teaching on bacteriophage that was modeled after the Cold Spring Harbor course that I had taken years before. So I had to make some stocks of these phages. And I found out the problem with the rapid-lysis mutants is that they rapidly wipe out all the bacteria and you get a very low [word muffled].

Then I heard a talk by George Streisinger, who was working down in Luria's laboratory in Urbana. Luria had moved from Bloomington to Urbana, Illinois. I remember once saying to him, "Why move from Bloomington to Urbana; that's like moving from pillar to post." And he said, "Oh, but it's a much more gilded post." [Laughter]

But he was there; and [Sol] Spiegelman was there at Urbana, and a guy named [Irwin C.] Gunsalus and a guy named [Harlyn O.] Halvorson. There was a whole cluster of microbiologists there—it became sort of an intellectual center that was quite active. George Streisinger was still a graduate student there at the time. He told me he had some strain of bacteria on which he could grow the *r* mutants and they gave some to me. So I started playing with that strain.

Along about the same period, I was asked to give a seminar in the Biochemistry Department. The department was in the agriculture school—still is, actually—which was good, because they could draw on all the state agriculture money. It's probably a good place to be now. [Laughter] Those people had sort of automatic budgets. The dean of the agriculture school was Earl Butz, the guy who became secretary of agriculture until he made some unfortunate joke on an airplane. [Laughter] They asked me to give a seminar, and I thought I'd give a seminar on the size of the gene. People had been trying to estimate just what the size of a gene was by bombarding it with X rays.

Aspaturian: You bombard the chromosome?

Benzer: You bombard the chromosome and try to make mutations. And you see the frequency of mutations, and you know something about the number of ions per centimeter that the radiation is producing. And from that, you can calculate the target size of the gene and make some estimate. There were various estimates based on that.

At that time, I read an article by Guido Pontecorvo, who was professor of genetics in Glasgow. He was the brother of Pontecorvo the physicist, who defected to Russia—and there's a third Pontecorvo who's a movie director. Anyway, Guido Pontecorvo was interested in this problem of a lot of mutations being in almost the same place, and wondered what was going on. He enunciated the idea that maybe the gene is not just one indivisible particle, like a bead on a string, and that the only reason we think so is that to observe recombination within this very small structure is a very rare event. Because recombination between chromosomes depends on the fact that you're trying to see recombination between two genes on the chromosome. The farther apart they are, the more likely a recombination event is to occur between them. Recombination involving two genes that are very close would be extremely rare. You'd have a limited number of offspring to examine, and the chance of seeing it becomes vanishingly small. And he's saying, "If only we had a system of doing this."

So my mind was alerted by this idea. And when I was plating out these bacteriophages in preparation for the course, I plated some of these *r* mutants on two different strains of *E. coli* bacteria. And I had two different strains of K-12 phage, one that was lysogenic and had Lwoff's

lambda phage in it, and one that didn't. What happened first was that when I plated these *r* mutants on the plain K-12 strain, instead of making the big plaques they made the little plaques. So they were showing lysis inhibition on that strain. Then, when I plated them on the strain that had the lambda, I got zero plaques. And having been alerted by reading Pontecorvo's article, I immediately, really instantly, realized…. Well, at first I thought I made a mistake. I thought I had forgot to put the phage on there. *Dummkopf*, do it again! I did it again and saw the same phenomenon. So I immediately realized—a eureka moment, and they're all too rare—that this was a system in which I could do very fine genetic mapping. I could take two *r* mutants, cross them with each other, and take the progeny and put them on this K-12 lambda strain. The *r* mutants themselves would produce no plaque, but if in any of the progeny there was a crossing-over between these two different mutations, such as to produce a wild-type recombinant that had neither mutation, that would produce a plaque. And that you could put 100 million plaques on one plate. So a quick calculation told me that that was enough, knowing the number of nucleotides in the DNA of the bacteriophage. This was about 1954 or '55—after the Watson-Crick discovery. So, based on the number of nucleotides in the DNA and the phage, I would have enough resolving power to separate the *rII* mutations, even if they were just one nucleotide apart.

Aspaturian: Let me see if I understand this correctly. By putting *x* number of bacteria with the phage on a plate, and seeing how many . . .

Benzer: No, the bacteria are all on the plate. I could put 100 million *rI* mutants on the phage. The question has to do with two independently rising *r* mutants. They're in the same gene, so to speak, but are they located in the same place on the gene? If you put either one on the plate, you get zero plaques, but if you infect bacteria with both simultaneously, sometimes a crossing-over of DNA happens while they're replicating DNA. And I put all of that on the plate and . . .

Aspaturian: But there must have been some formula or algorithm used to work backward from that finding to localize where the gene . . .

Benzer: Well, you see, the number of plaques you get is a measure of how far apart these

nucleotide mutant sites are on the gene. The point is, even if they were only one nucleotide apart, I could still detect it. If the distance was more than that, I would get more than one plaque—the number being proportionate to the distance.

So I was very excited by this finding. I remember telling one of my associates, a biophysicist there. He said, "Oh, yeah," or something like that. It meant nothing to him. Or maybe he said, "That's nice." But he had no idea about genetics, and I had not much idea about neurophysiology. We didn't really have much communication; we were two separate guys.

So that became my business for the coming years.

Aspaturian: How quickly did you communicate this to your colleagues?

Benzer: I wrote it up. Of course, what I did was isolate a whole bunch of these mutants and map them all against each other. I wrote up a manuscript. About this time, I was in Amsterdam for a meeting; I think it was the Congress for Photobiology. And Delbrück was there, I think—not attending the congress, but he just happened to be in town. I was already well out of his lab. And I hit him with this manuscript. He was quite annoyed, because he was on vacation in Amsterdam, having a good time; he didn't want to read any manuscript. I certainly appreciate that sentiment now when people hit me with a manuscript, and I tell them, "I'm not interested, I'm away from home." Nevertheless, he did read it, and he marked on it, "You must have drunk a triple highball before writing this. This is going to be offensive to a lot of people that I like." [Laughter] This was because it was attacking the idea of the people who believed that the gene was indivisible. It was rather badly written, I'm sure. So I think it took the whole year before I came up with a more acceptable version. And I think Delbrück had communicated the feeling at that point. That was around 1957, I think. He also presented this work at a meeting at Johns Hopkins University, at a symposium at which Arthur Kornberg did part of his synthesis of DNA. Erwin Chargaff was also there, I remember. And Chargaff was quite irritated by all these people telling their exciting results in molecular biology, saying, "I feel like I'm at a convention of Druids where not one person has failed to turn lead into gold." He was bitter then; he's bitter now.

Aspaturian: Why?

Benzer: He had the structure of DNA under his nose. He had discovered the base-ratio composition of DNA, but he just didn't have the flash of insight to understand what it meant. I think he always just resented that Watson and Crick should have come up with this model and gotten so much notoriety out of it, when he had done the basic biochemistry. Just plain envious bitterness. I don't think he's ever come out of it.

Aspaturian: While you were working on this, I guess the word of the double-helix structure came out?

Benzer: Yes. Just a little further back, 1953, there was a summer meeting at Cold Spring Harbor that I attended at which Watson presented the DNA structure. If I remember correctly, it hadn't even been on the program, but it was made a special lecture.

Aspaturian: Had you heard in advance that he and Crick had done this? Or did it come as a complete surprise?

Benzer: I think I had heard some things about it, but this was the first time I saw an actual presentation of it. Some people were saying, "So, big deal, double helix—so what?" [Laughter] And other people were jumping up and down. It was the awareness of that structure that first made me want to study the gene structure, trying to relate it to DNA.

Then a postdoc came. One of the interesting things that was happening, as they accumulated all these different *r* mutations, was that I found that they were not happening randomly within the structure. Well, I should back up a second to the whole question of the definition of the gene. People used to simplify the idea by saying that a gene is something on a chromosome. If you look at [Thomas Hunt] Morgan's book about the gene, I don't think there was any mention of the possibility that it may have a structure that could be split. But my work with the *rII* region showed that the whole process involved a unit of recombination, a unit of mutation, and a unit of function. And the gene had all these properties. So, when I began to realize that the gene could be divided into hundreds of parts, it called for a reevaluation of the notion of what is a gene. I found that within this *rII* region there are actually two different

functional regions that could be identified by a functional test, in that if you had two *rII* mutants affecting a cell, and those mutations are located within one-half of this region, they could not help each other. The cell acted as if it was just infected with *r* mutants. But if you take an *r* mutant for one-half of the region, and another one for the other half of the region, and put those two in, they somehow complement each other, so the cell would go ahead and lyse. These are two separate units of function, each of which can be subdivided by mutation and recombination. So I made up three names, being a physicist. I called them *cistron*, *recon*, and *muton—cistron* for the functional unit, *recon* for the recombination unit, and *muton* for the mutation unit.

At this meeting at Johns Hopkins, I was attacked by Elie Wollman, who said these are very unfortunate names because they don't translate well into French—*cistron* sounds like a lemon, and *muton* sounds like a sheep, *recon* is a dirty word. [Laughter] But I had already announced these names, so I stuck with them. [Laughter] Wollman was kind of upset about that.

This created quite a bit of interest among geneticists. There was a symposium on genetics in the summer of '57, '58 maybe. Dr. [Edward B.] Lewis [Thomas Hunt Morgan Professor of Biology, emeritus] was there. I met him in the men's room after my talk. And the only thing he had to say was that he was angry about my insistence on using the term "wild type" to distinguish between normal and mutated specimens. He said, "'Wild type' means the type you go out and catch." But I had run into a problem because another scientist had what he called a T-phage T4 wild type, and I had a different phage T4 wild type I'd gotten from another lab. And at one point, I'd crossed them with each other. So there should have been only wild type coming out. But I got a whole kaleidoscope of mutants segregating out between the two. So I thought "wild type" didn't make any sense. Call it normal or standard type, the one you start with. So Lewis was irritated by that. I was pretty ignorant about *Drosophila* genetics, so in my work on phage I was sort of making it up as I went along. I didn't know the history. But the whole point of the *rII* business was to run it into the ground with regard to the resolution.

Aspaturian: What was the impact on the molecular biology or genetics community of this particular discovery? Did people go out and start looking for systems of their own?

Benzer: Yes. Other people started doing the same thing. George Streisinger, in particular. I

remember I came here to give a seminar and I was dismayed to find out he was doing the same thing on it, following my footsteps on a similar but different gene. But then things very quickly become a matter of course in science, just a short moment of revelation and then everybody's doing it and taking it for granted.

Dick Feynman [Richard Chace Tolman Professor of Theoretical Physics, d. 1988] took a year off on a sabbatical and worked in Max Delbrück's lab.

Aspaturian: When?

Benzer: I wasn't here at the time. Taking a rough guess, I would guess '59 or '60. And he worked with the *rII* mutants. He fussed with them for about a year and then gave it up. But he had discovered something without realizing it. Sorry, I don't remember what it was, but I think it was related to the later discovery by Crick and [Sydney] Brenner, using the *rII* mutants. This had to do with the nature of the genetic code. I'm talking much later now; this is after I was in Cambridge, I think, in the 1960s. But it was something under his nose, and its significance was just not apparent at that time.

I was busy mapping these *rII* mutants to death when I discovered that some mutants had just a piece missing. And that was very useful for mapping, as is explained in the *Scientific American* article, because the way these missing pieces overlap made it possible to map these instantly to the right segment. It's a system also used in *Drosophila* genetics, and it made that thing very simple and straightforward. Given a new *rII* mutation, I could very rapidly locate where it was on the map. One of the funny things was that the pattern of mutation was not at random. When you have adenine, thymine, cytosine, and guanine repeated over and over again, you might a priori expect the chance of mutation would be pretty much uniform. But it was not. There were hot spots.

Aspaturian: It turned out that some base combinations were more unstable than others?

Benzer: Yes. I only theorized that at the time, but it was later confirmed that certain combinations, such as A and T, don't bind to each other as strongly as C and G do. So if you

have a lot of ATs in a row, you have a higher chance of having a hot spot in that region.

The next thing was to try to create mutations with chemical agents. I had a postdoc named Ernst Freese, who had been at Caltech as a physicist. Max Delbrück tried to talk him out of going into biology, which only stimulated him further. Then he came to my lab. He started working with growing bromine uracil, which is a slight variation on thymine. Like thymine, it goes into the DNA, but the DNA is not too happy with it, and you have a high chance of getting a mutation at these places. So he made the mutants and I mapped them out and found hot spots in completely different places. So this was exciting, because it could be a key to the sequence of the DNA if you could get enough information that way. Quite a bit of work in my lab for the next few years was on this. By this time, I was beginning to expand and get bigger grants and have technicians.

I was still in the physics building, but then Purdue decided to invest a lot of money in the life sciences. They built a new building for it. And the president thought Mullins and I should go into that department and become biologists. We didn't want to, because it was such a crummy Biology Department, and we had an excellent Physics Department. So the president called us to come to his office, along with the physics chairman and the biology chairman. He said, "What do you want?" We said, "Well, we don't want to go in there." And he said, "Do you want me to make a separate department of biophysics?" We said, "Yes, that's a good idea." And the president said, "Well, I'll do it, provided Benzer will be the chairman." That was the last thing in the world I wanted. Mullins was very anxious to be chairman. I wouldn't be caught dead being chairman. I said, "I'll go to biology." So Mullins never really forgave me for that, I don't think. So we moved to the Biology Department. So I had bigger quarters and I was beginning to get better grants.

So I had two or three technicians isolating *r* mutants. I had it all worked out. It was all done with shreds of paper, streaking things on the plates with the papers. So you didn't have to use pipettes. It was all very cheap. That was all possible because of very high sensitivity. So, in the end, I'd say I had something like 20,000 *rII* mutants, and doing it with different mutagens. Each mutagen would produce its own spectrum of mutations. And then we tried to relate these changes to [word muffled], because not only could you make mutations from normal to mutant but you could also use chemicals to try to make them revert. And each one had different

sensitivity for reversion. And Freese in particular was trying to relate these changes to changes of the base structure of the DNA.

I, at one point, was doing other things, like using fluorouracil, which would not go into the DNA but into the RNA and cause mistakes in the translation of the RNA into the appropriate amino acid. So, I was working with a student named Sol [S. P.] Champe. The idea was to infect the bacterium with an *rII* mutant that wasn't able to multiply. And then put in fluorouracil, which would get into the RNA and cause mistakes in translating the protein, so that instead of mutant protein, you'd get back normal protein. This would be a sort of phenotypic reversion that would make the phage be able to go ahead and lyse the cell. So this was successful and it worked at a different point for every one of the mutants. We tried to use this to identify the specific bases that were involved each time. But, you know, it was nowhere near being able to give us a nucleotide sequence, because each of the particular spots were separated by numbers of nucleotides.

Another important finding was when, testing different *rII* mutants on different strains of bacteria, I found that on some strains of bacteria they didn't actually do this at all and on others they did. This depended on individual mutations—one mutation would work on this strain and the other mutation would work on that strain. By this time, people were into the RNA translation machinery, going through DNA to RNA to protein.

I had the notion, which turned out was independently thought of by Charles Yanofsky at Stanford, that you can have suppressor actions happening in the cell. If you change parts of the translation machinery, you can have an indirect translation of an indirect message to give a normal result.

Begin Tape 4, Side 2

Benzer: So that got me interested in this translation machinery. Translation machinery is supposed to work by way of transfer RNA. It was called soluble RNA at that time. The notion was that amino acids do not make proteins by fitting directly onto the messenger RNA—some kind of adaptor is needed. And that was what the transfer RNA was. There's a special one for each amino acid. The amino acids were supposed to be on one side, and the other side would have so-called anticodon, a series of three bases, which would fit onto the corresponding bases in

the messenger RNA. So this one would fit here, and then the next one would fit here, and then the amino acid would get strung together.

My idea was that there must be differences in the transfer RNA in these different strains, giving different changes, different effects with the different *rII* mutations. So my students and I were making RNA and testing it. The idea was, if there are changes like this from one strain of standard bacteria to another, there should be changes from one organism to another. So you take out transfer RNA from yeast, say, and transfer RNA from *E. coli* bacteria, and the other part of the equation is a so-called activating enzyme that connected the amino acid to the transfer RNA, which is supposed to be specific for each. So we took the transfer RNA from one organism, and the activating enzyme from another, and found that they often did not cross-react. That meant there had to be changes going on in both the enzymes and in the transfer RNA. I speculated from this that the genetic code would not be universal. With all these changes going on, the code did not work through direct interaction between amino acids and the RNA, but through the transfer RNA and the activating enzyme, which are subject to change. So it doesn't take much stretch of the imagination to think that this would drift and that the code would not be universal. But in case after case, in one organism after another, people kept finding the code was pretty much the same, except for variations in the third base of a triplet. The first two bases would be fixed, but the third one could often shift a little bit. But that was considered minor; by and large, the code seemed to be universal. There was a meeting in India at that time, and one of the things they had in the street markets was a man with a bird. You ask a question, and they give it to the bird, and the bird goes in the cage and brings out an answer. So my question was, Is the genetic code universal? And the bird in the cage gave the answer, "The news from home is good." [Laughter] It wasn't clear what that meant.

Quite a few years later, it came out the code is not universal—there's mitochondrial DNA. We really don't know where mitochondria came from. It might have derived from some independent organisms, which joined forces in a symbiotic relationship, and that would give you two genetic codes. So I feel vindicated now a little bit. But as far as the main organisms are concerned, probably there's such a close interaction between them that they're kept in line against drifting too much from one universal code.

Another problem I got into at that point was the question of the transfer RNA. Crick had

enunciated this idea that the amino acids cannot interact appropriately with the messenger RNA. And that transfer RNA must be a mediator. Nobody could figure out how to test this process, but I had an idea in the work we were doing that you attached one amino acid to its appropriate activating enzyme—attached it to its proper transfer RNA. And by then, we were able to make the protein synthesis grow *in vitro* in a test tube. And then to change from one amino acid to a different amino acid without removing that attachment, synthesize some protein, and see if that amino acid goes into the correct position, corresponding to transfer RNA or the amino acid. And we did this. We found a guy in the basement who knew a chemist, Bill Ray, who happened to know a good reaction for transferring. Nickel was the catalyst he used to make a cystine change to an alanine. We did this experiment and it worked. The amino acid went into the wrong place. So that was nice. Competition developed, though. The word got out about doing this experiment to a man named [François] Chapeville, who was working at Fritz Lipmann's laboratory at Rockefeller, and he went ahead and actually got the experiment to work before we did. So this is one of those things where we met in a hotel room in Atlantic City and made peace by putting all the names on the paper together, including Lipmann and me. And although I never worked with Lipmann, we have our names on the paper together. But that was an elegant experiment, whether or not it was Chapeville's idea. We said, "Ideas are cheap. What counts is actually to do it." Not exactly a unique point of view—getting less and less unique all the time. [Laughter]

One more thought in this same period was the question of degeneracy in the code. From experiments using artificial RNAs, it seemed you could have more than one triplet for the same amino acid.

Aspaturian: So two different triplets could code for the same amino acid?

Benzer: That's right, particularly in the third base. And by then, of course, we'll get these artificial RNAs. We had to set up a testing list, because Robert Holley at Cornell at that time had used the countercurrent distribution technique, which is a sort of trainer fractionation that enables you to separate molecules by their partition coefficients, even if they are very similar. He had taken transfer RNA and separated it in all these different fractions. So we collaborated with him and he gave us his set of tools. And what we did was use a given amino acid and an activating enzyme. We would be able to assay for each of these fractions of transfer RNA which amino

acids it would respond to. The question was, Which amino acid would they accept? And we found more than one that would accept the same amino acid. So you'd go along, and sometimes you'd have only one, sometimes two, sometimes three peaks of the same amino acid. I think that came before the adaptor stuff. But it provided a demonstration of what we call the physical basis for degeneracy codes in amino acid—degeneracy meaning more than one triplet for the same amino acid.

So, by this time, I was getting "fairly famous" in molecular biology. This was about the time that I decided I was really interested in behavior.

Now, what's been left out of this narrative is the year I spent in Cambridge with Crick and Brenner, the year '57 to '58.

SEYMOUR BENZER

Session 5

October 19, 1990

Begin Tape 5, Side 1

Benzer: I went to Cambridge for 1957-1958 because of a problem I wanted to work on with Sydney Brenner. It had to do with the question of how DNA's one-dimensional structure of bases relates to protein's one-dimensional sequence of amino acids. We didn't know what the genetic code was, but we thought it might be nice to prove that there's colinearity between the bases in the DNA, the amino acids in the proteins.

Aspaturian: Clarify one thing for me. The genetic code would be the mechanism whereby the instructions in the DNA are translated via RNA into the makeup of the proteins.

Benzer: That's right. More specifically, what bases—the four letters—in the sequence of DNA would be translated into a sequence of amino acid and protein. Brenner and I were both interested in solving this problem, and my going to Cambridge—besides wanting to see England—had to do with finding a system by which we could do this. We needed a system where we could study the genetics in fine detail, like in the *rII* region, and at the same time study the protein product of the gene in more detail.

We had already spent some time on this. Alan Garen, who had worked in my lab at Purdue, had tried to find the protein that's made by the *rII* gene without success. So the question still was, What gene could be used for the gene-protein combination? While I was in Cambridge, I was also joined by Sol Champe, who was still my graduate student at Purdue; I brought him along. The idea was to pick some protein in the bacteriophage, which by then was known to consist of many different proteins put together into a complicated structure. The question was which bacteriophage protein to use to get mutants and at the same time do fine-structure mapping.

Cambridge at that time was a good center for protein biochemistry, particularly because Vernon Ingram, who was on the staff of the MRC—the Medical Research Council lab—had

developed a technique called fingerprinting, in which you take a purified protein and treat it with an enzyme, like trypsin, which cuts it in specific pieces. These short pieces could then be run on a chromatograph sheet of paper. Then you stained that with a reagent and then hydrin, which would detect the peptide fragments on the paper. Ingram adapted that technique to sickle-cell hemoglobin and showed that you could find a change in one of these spots which corresponds to a change in an amino acid.

At the time I came to Cambridge, the Medical Research Council unit was housed in the Cavendish Laboratory—it's a famous physics laboratory that Rutherford headed at one time. It was not inappropriate, because one of the main activities there was using X-ray diffraction to study DNA. This was the department of which Sir Lawrence Bragg had been head. Bragg had been Crick's mentor for his PhD. As you know, the two of them had a big run-in, because Bragg felt that Crick shouldn't fuss around with this DNA nonsense and should get back to the protein-structure research that he was supposed to be doing for his PhD thesis. Bragg later agreed to write the foreword to the Watson book, *The Double Helix*. At first, he was very irritated by the idea, but his wife said, "Oh, don't be so stuffy, Louie." So he did it. So from the Bragg heritage at the Cavendish, there were Max Perutz and John Kendrew, who were doing X-ray structures on myoglobin and hemoglobin, and Crick and Sydney Brenner.

I should tell one story about Sydney that happened while I was still back at Purdue, and he was still in South Africa. I said, "Why don't you come to Purdue?" And he said, "Good idea!" So, when I applied for a grant, I put Sydney Brenner down as one of the prospective personnel in the grant. And he promptly received job offers from five people who were on the review panel. The information on the grant was supposed to be kept confidential, but once they heard that he was a free agent, they were all after him. So he never did come to Purdue; he went back to England, where he had studied. He had gotten his PhD in physical chemistry at Oxford, I believe. Sydney was actually an MD by training, but he never went into medicine.

Seven of us shared one room in the Cavendish Lab: Crick and Brenner, Streisinger and me and my student, Champe. There was also a crystallographer, a German whose name I don't remember, and Mahlon Hoagland, an expert on biochemistry, who came on sabbatical that year. He knew a lot about transfer RNA. I think that was the year that Crick got turned on to transfer RNA and actually worked in the laboratory. I have a picture of him with a lab coat on, which is a real collector's item. It was a room about this size, with seven people in it.

Aspaturian: So it was what—about 12 by 25 feet?

Benzer: Just about that size. It was great, because Crick and Brenner were arguing all the time. We would all read Crick's mail that would be sitting on his desk. It was a tremendously stimulating environment.

Aspaturian: In *The Double Helix*, Watson describes Crick as an ebullient nonstop talker. Is that true?

Benzer: Yes, that's true. We could always tell when he was in the building; you could hear his "Ha, ha, ha, ha" down the hall. He was tremendously brilliant and stimulating—his mind was working all the time. My wife was very impressed with him. She said, "Closest thing to pure intellect." But that didn't preclude other things. He was into all kinds of adventures on the personal level. He was very urbane, well educated. He reminded me most of Henry Higgins in *My Fair Lady*. There was quite a resemblance. That kind of style. No shrinking violet, that's for sure. I think Watson opened his book by saying, "I've never seen Francis Crick in a modest mood." And Crick always threatened to write his memoirs and open with the sentence, "Jim was always very clumsy with his hands." [Laughter]

I guess I did several things during that year. One was working with Ingram to learn his fingerprinting technique; get familiar with the protein chemistry, which we would need. After I learned the technique, Ingram said, "Why don't you do a mutant hemoglobin, a sickle-cell hemoglobin sample," and I think one or two others. He gave me this hemoglobin D, which was collected from a Bantu in Africa by some guy named Lehman who went around the world collecting blood samples. It showed some abnormality, so I ran the sample through the technique. Sure enough, we found a difference and published a small paper on that. Lehman was the third author, because he had supplied the sample. It was the first time I'd published a paper with somebody I never met. I still haven't met him. So I learned a little bit about protein chemistry.

The other main experiment, which Champe, Streisinger, Brenner, and I did, was to try to

take apart the bacteriophage by various means, separate the different proteins, and then try to do fingerprints on them. I think we published a paper on that.

Another thing I did was work with Crick on the structure of poly-A, the molecule that had a lot of adenine strung together. The two strands pair with each other and form a special structure. We did that in the tower of the Cavendish Lab, which is where Watson and Crick had put together their model to get the double helix. The same model-building pieces were still there, so I had the nice privilege of working with those same historic pieces to try to put together the poly-A structure.

The other main project had to do with studying the weak spots in the *rII* gene where different mutagens produced different spectra of mutation. Leslie Orgel, who was there, and I worked on mutations induced by proflavine. And we found, much to our surprise, that the mutations it produced were almost uniformly spread throughout the gene instead of having all of these hotspots that we had found before. We didn't realize it at the time, but this turned out to be historically very important, because these mutations were working by a different method from the others. The other mutagens were causing changes in the pairing of the bases, so that instead of adenine-thymine at one site, it changed to guanine-cytosine, or vice versa. The way proflavine turned out to be working was that its molecule was fitting into the DNA structure while it was being replicated. The proflavine molecule is very similar to one of the bases of the DNA, so they were sort of squeezing into the place of one of the bases, so that the replica would then be missing a tooth in DNA.

Aspaturian: In other words, you had the absence of the matching base when the strand was copied.

Benzer: Yes. There were many places with fairly equal likelihood of that happening. This finding was used later on when Crick and Brenner tried to prove the triplet nature of the genetic code. We didn't know—nobody knew—how many bases you needed to code for one amino acid. We knew that two were not enough, because they would only give you sixteen combinations, and there are twenty amino acids. Three would be more than enough, but you still had to prove that this was the right number. They did this clever experiment—this was later on; I was already back

at Purdue—using my *rII* mutants, in which they took three proflavine mutations and combined them so that all three were in the same gene. Assuming the code was based on triplets, what that did was snap everything back in frame and restore the ability of the protein sequence to function, because these three mutations together would cancel each other out.

While we were in England, we suffered from lack of central heating. We had an apartment near the university, which was very conveniently located, but we froze to death, because all we had was a small kerosene burner. Being warm was a constant preoccupation. I bought a sweater of the type used by the fishermen on the Faroe Islands, an about-one-inch thick wool sweater, which I've never been able to put on again, because everywhere I am it's too hot. But that saved my life.

But Cambridge was absolutely delightful. It was a complete contrast to Paris socially, because from the day we arrived we were being constantly invited to tea. The English make entertaining very easy; they give you tea and a few cookies, and that's a vehicle for social interaction. It was wonderful.

Life in the lab drove me a bit wild. You'd come in in the morning, about 10:30 or so, and there would be coffee time. Then there was a little time to work; then it was lunchtime. Then you'd come back after lunch and before you knew it, it was tea time. And then you were home. Almost nobody would come back in the evening, except the crazy Americans, who were driven types. So, to get back into the Cavendish Lab in the evening, I would have to ring the bell for the concierge to allow me through the gate. At Easter time, they would shut off all the gas and electricity, which was insanity for the Americans. The English always seemed to be drinking coffee and tea and taking it easy, playing cricket. And they got all these Nobel Prizes. [Laughter] So there's some secret that I still haven't figured out—some kind of self-discipline where they use their time and their brains very economically. But socially, it was very nice.

I was expecting awful food in England. English cooking is terrible. But the food is not; I mean, they have wonderful ingredients. So we had a wonderful time with the food, doing our own cooking. In fact, we formed a little gourmet club—the Dulbeccos, the Benzers, and the Streisingers—three couples, in which the men did the cooking and the women did the washing up. The challenge was to go through the whole gamut of English game; so we went through grouse, partridge, hare, fish, guinea hen, stuff like that. George Streisinger was very much interested in food, and Dulbecco as well.

Speaking of the food, when I arrived in England, I read this book about life in Cambridge, which included a list of all the local restaurants. They sounded fantastic. So the first thing I said to Crick was, "Let's go to lunch at a different place each day." And he said, "Oh, no, no." He liked to go to the Eagle Pub and get a sandwich and a beer. So I went along on one of those. He asked me, "Have you ever tried Merrydown Cider?" I said, "I'll try anything." Well, first you get merry, and then you fall down. It seemed almost like apple cider but it had a very high alcohol content. And I don't take alcohol very well, so it knocked me out. After that, he went along with my idea to try different places, and it wasn't long before I got the idea that each one was worse than the last. They were all pretty bad. The worst was one called the Firehouse, where I almost choked to death on a bit of Brillo pad that was in with the hash. That was a pretty close call. But that was an exception. Mostly it was just mediocre food. Streisinger came about a month after I did. And he came in one day and said, "Seymour, I just found out about all these wonderful restaurants in Cambridge. Let's go to a different one for lunch every day." [Laughter] So maybe that's one reason why we started our gourmet club.

Aspaturian: This is a little off the beaten track, but I'm raising it now since we're talking about your year at Cambridge. When Watson published *The Double Helix*, a lot of people in the scientific community were outraged because they thought he painted not only an unfair picture of science but also an inaccurate picture of what was going on at Cambridge. How did you feel about it?

Benzer: I read it in manuscript before it was published. He brought it around while we were at Woods Hole. He wanted my wife to read it. He said, "These books are bought by housewives, so I want to try it out on a housewife." [Laughter] Of course, I read it, too. I just couldn't put it down. But there were a lot of arguments at the parties there, and some people were absolutely outraged, as you say. They were quite polarized about it. I think it's a very honest book and very self-revealing, too. He's not kind to himself in his book. I thought it was great. He toned down some of the parts in it—some nasty parts about Rosalind Franklin, I think, that he was prevailed upon to moderate a bit. But I thought it was delightful. Now, some people objected that the young generation shouldn't read that stuff. But they all know what goes on, and they don't need the Watson book to find out. I doubt if it ever turned anybody off science. Maybe just the

reverse. I thought it was an historic book. Crick was upset. I was living in Pasadena by that time, and I remember Watson calling on the phone; and he was obviously drunk and very upset, saying that Crick was trying to prevent the publication of his book by the Harvard University Press. And I think Crick actually succeeded; I think he scared them off. I don't remember who published it in the end, but I think Harvard University Press did in fact bow out [Atheneum (NY) published *The Double Helix* in 1968—ed.]. So Crick tried to interfere on that. I don't remember hearing any more details about it. I don't know if Crick still has any hard feelings about it at this point. It may have had to do with royalties back then. [Laughter]

Aspaturian: Now, he's written his own book, of course,

Benzer: He's written his own book [*What Mad Pursuit: A Personal View of Scientific Discovery* (New York: Basic Books, 1988; Penguin, 1990)], which is not unsuccessful, but it's not a runaway bestseller; it's not in the same league with Watson's, nor is it as exciting.

Aspaturian: I've always thought *The Double Helix* stood up pretty well as a work of literature. It's in that class.

Benzer: Yes, it's a very important book. Gunther Stent assembled all the reviews, and he wrote a review of the reviews. I think he published a paperback edition of *The Double Helix* with a very long foreword, putting in his own two cents.

I'm trying to think of other Cambridge stories. There's one where Crick asked me to explain to Fritz [Frederick] Sanger what was happening with the *rII* gene and the overlapping-region mapping. And I had a hard time getting through, because he was a biochemist, and he dealt with real molecules, and this was rather abstract. I remember that incident particularly.

Another incident was something that happened at the Kapitsa Club, which was a physicists' club that had been started when Pyotr Kapitsa was at Cambridge, before he went back to Russia. Crick asked me to give a talk at this club once, and one of the people there was [P. A. M.] Dirac, the famous physicist. I began with sort of the historical background, talking about how there was a big time lag between [John] Dalton's idea of the atom and Bohr's theory of the

structure of the atom. And similarly, I put the dates on the board for Mendel's concept of the gene and then Watson and Crick's structure of the gene. And Dirac looked at it and said, "Biology is catching up." [Laughter] There was a smaller interval in biology than there had been in physics. So that was a memorable event.

There are great stories about Dirac. One is that he gave a lecture; there were equations all over the board. And then when he asked if there were any questions, somebody said, "Professor Dirac, on the fourth line there on the left, I didn't understand how you got from one equation to the next." And Dirac just stood there and didn't answer. The guy said, "Aren't you going to answer my question?" And Dirac said, "That was not a question; that was a statement." [Laughter]

Another thing that happened in Cambridge was that the Cricks had no car, and they borrowed ours. We had a British car that we owned. Crick's wife, Odile, used to borrow it frequently, to the extent that once at a party I met a visitor who, when I was introduced, said, "Oh, you're the owner of the Cricks' car." [Laughter] Crick himself did not drive. He preferred to be driven, I guess. They had a place out in the country—a little shack that they would go to on weekends. They used to have a lot of parties. One I remember particularly was not at their house but in a village nearby, at a house in which Byron had lived. It was a New Year's party, which was billed as a fancy headdress party. I came as a geisha girl [laughter], with all the things sticking in the hair. It was a contest for the best headdress. Dulbecco won the contest—I was runner-up, I gather—because he just took a coal scuttle, put it over his head, and looked like a Roman centurion. I had to hand it to him, that was very imaginative.

My two children went to the Byron school, which they rather liked. It was a nicer school experience than my daughter had had in France, where she got spit on. I think the kids had a good experience that year. The English were just generally much more hospitable in every way. They still disdained Americans, but they were friendly. They thought it was funny, the way we talk. My wife's name was Dotty, and I remember Crick kept trying to say her name the way we say it. Sometimes he'd get me to demonstrate how I say it and try to get other English people to say the soft 't.' I think the kids had a good experience that year.

One of the Cricks' daughters—he had two—was the same age as my younger daughter, Martha. They were close friends and spent a lot of time at each other's houses. Odile Crick is half French. She was, and still is, an artist, quite a lot of talent. The house they lived in was kind

of a double helix—two separate helices, which they owned and then rented out one side. So essentially each helix had one room on each of four floors. Odile would do things like painting a woman on the bathroom wall, with her legs draped over into the bathtub. The Cricks are in La Jolla now, and she has exhibitions of her work sometimes. She's also a marvelous cook.

SEYMOUR BENZER

Session 6

November 2, 1990

Begin Tape 6, Side 1

Benzer: While we were in Cambridge, we had rented our house to someone in Purdue's math department who had children. That was OK. But they never told us they had a dog, and the house was a shambles when we got back. The furniture was all ripped up. My wife sat down and cried. [Laughter] But she got over it.

Aspaturian: By this time you were in the Biology Department, is that right?

Benzer: Yes, I was in biology, and I guess Sol Champe was still my graduate student. He had come with me to Cambridge and then came back and continued to work at Purdue. I acquired another graduate student, Ruben Levinson, an Israeli; and Bernard Weissblum, who was a postdoc who'd finished medical school. I knew him from Brooklyn, because he lived in the same apartment house my sister did. My sister and his mother were friends, so that's how we were brought together.

Another person who came around that time was Masayasu Nomura, who is now a very famous biochemist. His main work has been to take the ribosome apart and show all the different proteins that fit together to make its structure.

Aspaturian: Did he come over from Japan, or was he native-born?

Benzer: From Japan. I met him in 1956, the year I went to Japan to the International Genetics Congress. I was hot with my stuff about splitting the gene. The congress was in Tokyo, and I traveled around Japan before that. It was just absolutely lovely staying in Japanese inns at that time. And at that time it was not astronomically expensive. The comedown was the congress at the end of the trip in Tokyo, with these big buildings and meeting halls. That was the other aspect of Japan, which is not very attractive.

The experience of traveling in Japan was that I was greeted at the airport on arrival and taken by the hand; they tracked me every step of the way. Each place I went, there was a local host who would be busy on the phone arranging the next stop. It got to the point where to get one day of freedom, I finally claimed I was sick and wanted to stay in my room. So they left me alone, and I was able to wander around. That was in a town called Wakayama on the seashore east of Osaka. That was the nicest day. Otherwise, there was constant wining and dining, which was really very nice. They were all knocking themselves out.

Aspaturian: Was Japan still under the occupation then?

Benzer: I don't know if it was formally occupied or not. I remember making a terrible *faux pas* at one of these dinners. They pulled out all the stops, a banquet hall with the geisha girls entertaining, filling your cup with saki all the time, saying "*dozo*" constantly. It was really charming, because once everybody got a little liquored up they started performing folk songs from their own native districts. I still remember hearing the songs, and there's one I can actually sing in Japanese. [Laughter] But at one point, one of the guys offered a toast, and said, "No more atomic bomb." And I had a reflex reaction—I said, "No more Pearl Harbors." [Laughter] All the faces fell. [Laughter] Fortunately, it wasn't in Hiroshima or Nagasaki; I think I was in Kyoto. But it certainly wasn't the right thing to say.

Also when I was in Tokyo, Gunther Stent and I ended up in the same hotel room. This was still the real old style—the girls would come and undress you to take the hot bath at night, and sleeping on the tatami mats. They were crazy about Gunther, because he has a very hairy chest and that's unusual for Japanese males. So he made a big hit. It was just this magical, Wonderland life.

Aspaturian: Was it the biologists who were feting you every step of the way?

Benzer: It was the biologists, yes. I remember one connection was a guy named Watanabe in Tokyo.

The other adventure Gunther and I had together was to climb Mount Fuji with Watanabe.

Ordinarily, there's a bus that takes you about halfway up. We missed the bus, so we had to walk all the way—about 10,000 feet altogether, I think. We got halfway up the first night, and there was a small Buddhist temple there, with a little old lady who took care of it all by herself. She took care of us; it was my first experience of Mandarin oranges. I remember distinctly sitting around conversing with her, with Watanabe as interpreter. She asked what we do. And we said genetics. And she said, "Ah, Mendel." And we were absolutely astonished—here's this old lady completely away from civilization, and she knew about Mendel. That experience was repeated almost everywhere I went. Obviously Mendel must have been in the syllabus in Japanese schools. Every student in the same grade throughout the whole country—at least at that time, maybe now, too—was reading the same page of the same book on the same day.

In contrast was my flight back to the States. I sat next to an American businessman who asked me what do I do. I said, "Genetics." He said, "What's that?" So those two experiences made a deep impression. Another impression was that the Japanese labs were very poor, with extremely little or no funding. I remember I was in one bacteriophage lab in Nagoya where they had one pipette and you'd wash it out between usings. They told me this expression, *boro, boro*, which means "dirt poor."

Aspaturian: So this was when you met this young man who became your student?

Benzer: Yes. Nomura—he's now at UC Irvine—was just finishing his studies. I met him through Francis Ryan, a microbiologist from Columbia. He and his wife were in Tokyo for a year on his sabbatical. He brought over this student who he thought was very bright, so he could make contact with someplace to go in America. Now, Nomura didn't ask me whether he could come to my lab. What he asked was whether it was a good idea for him to go to Spiegelman's lab in Urbana. I said, well, he'd learn a lot, and actually, while Nomura was at Spiegelman's lab, they made the important finding that there's a form of RNA in the cells that is rapidly degraded and resynthesized. That turned out to be messenger RNA, but they didn't have it quite pinned down. Afterward, when it was really clearly pinned down by others, Spiegelman said, "I had it first." They did have the observation right under their nose, but without, as I recall, fully appreciating what exactly it was doing. Nomura was involved in that, to my recollection. Then he went for a while to Harvard, to Watson's lab. Then he came to Purdue to work with me.

I was still working on the *rII* gene, which had these special selective properties that I could analyze in great detail. But the problem was, what sort of protein is it making? What's the function of that protein? So I prevailed upon Nomura to work on trying to isolate it, which he didn't succeed in doing. I think it's only in the last year or two that somebody has succeeded. [Laughter] So I've always felt regretful for having wasted his time on that. Actually, Alan Garen, who had already been in my lab just before going to Cambridge, also worked on trying to resolve that problem.

I have a few other memories of Japan and the Genetics Congress. One of the people there was George Beadle, who was a very distinguished and outstanding geneticist. I told him I was having trouble getting people to pay attention to this question of the structure of the gene, and the difference between cistron and muton and recon. I asked him, Could he use his influence there? And he said no, that it was up to me. He said he was not in the position to do anything like that.

Another experience was eating yellow watermelon and seedless watermelon for the first time. It was the Genetics Congress, so they'd created all kinds of mutant plants to try.

Another person I met there was the biochemical geneticist J. B. S. Haldane, a very interesting character, who was dressed in his Indian and white robes. I also met his wife, Helen Spurway, one of the most raucous women you could hope to know. She was very aggressive. While they were in India, she made a point of assaulting a policeman so she could be put in jail. She wanted to find out what it felt like, in sympathy with the poor Indians who were being locked up. She was also on a crusade to prove that the Immaculate Conception couldn't be true, because if it were, then Jesus would have been a woman, homozygous from the X chromosome. I still remember her. She was just incredibly raucous, with a grating edge in her voice.

Haldane was quite famous. He was already pretty old by that time. But I remember distinctly his saying, "Cistron, recon, and muton—what nice sounding words!" [Laughter]

Another event at that meeting was I met an Israeli named Leo Sachs, who is a good seven feet tall. I've got a lot of pictures of him standing, with the Japanese coming up to his kneecap. I think it was Ray Owen [professor of biology, emeritus] who had to meet his wife at a certain time. The question was where should they meet, and he said, "I'll meet you by Leo Sachs." [Laughter] So that's become a common joke.

There was also a famous geneticist there called [Hitoshi] Kihara. One of his colleagues took me to his lab in Tokyo, opened the door of the lab, went in, and there was his lab assistant

prostrate on the laboratory bench, fast asleep. That was pretty traumatic, and we woke the guy up, and he jumped off and clicked his heels and bowed several times.

The general picture at that time was anything but one of prosperity. Things were pretty primitive. One unusual thing was I actually got to stay in a Japanese home in Mishima, which was, and still is, the home of the National Institute of Genetics. The guy's name was Tsujita. He invited me to sleep in his home. It was very primitive; his wife cooked, and, much to my regret, made a point of cooking steak [laughter], because I was really in love with the Japanese food. They had probably spent a month's income to buy the steak. The kitchen was just a corner of the room, where they had a chunk of charcoal. And I remember sleeping with the mosquito net, which was absolutely necessary, on a small couch. That was a very nice experience. He's dead now. His laboratory has grown quite a bit, and the town as well, though I haven't been back again.

They took me out for sukiyaki in a restaurant—spent another month's salary on that, probably. But that was quite exceptional, to be taken into a home, because most people's homes were so modest that they didn't want anybody to see them.

I also recall an experience at the hotel in Tokyo. I wanted to stay one day longer than the original reservation, but they said, "Sorry, this room is booked." Instead, they put me in the Western wing of the hotel, which was very depressing—overstuffed furniture with slipcovers, a Victorian kind of atmosphere. It was the absolute antithesis of the beautiful Japanese economy of line. On the way to the bath, I passed by my former room and looked in. And in that same room, there were twelve people spread out—one mat per person. It was a twelve-mat room. So it really brought home to me the disparity between the way we lived and they lived. This was already a high-class hotel.

Scientifically, there wasn't any really great excitement visiting these labs. And the scientists were a scaffold for the tourists. I got to see Tokyo, Mishima, Nagoya, Kyoto, Osaka, Nokijama; I made a point of making a detour to the pearl-diving activity.

Aspaturian: How long were you there?

Benzer: I think between two and three weeks. It was September; it was hot, but I didn't mind it. Osaka was depressing; it was just like Chicago, with its traffic and noise. I met a number of

people who still crop up every so often.

One of the experiences was being taken, at my request, to a soy sauce factory. There were these vast elevated vats, but the upper surface of the vat was continuous. There was a level, and the vats consisted of depression wells—you walk around on top. Very slippery; you could fall in and get fermented. So that was impressive. At the end of the tour, they said they would send me some soy sauce, and when it arrived, it was a five-gallon can of soy sauce, which took a very long time to use up. When I travel—if I'm alone—I cover a lot of ground.

Aspaturian: After you got back from Cambridge, you went to an embryology workshop at Woods Hole, about a year later—in 1959. I was wondering what prompted you to do that?

Benzer: Well, I was deep into this genetics business, analyzing and splitting the gene, studying mutations and how they work. I thought I should look further afield at what the genes were doing. Woods Hole is a lovely place; I'd been there briefly with my wife, just passing through for a day. So I went back and took this embryology course, and it was a wonderful experience. We got to work with various kinds of embryos. In one of the experiments, we'd get a male fish and a female fish and we'd scoop the eggs out and fertilize them with male sperm and just stare and watch it. It was absolutely incredible to see the cleavage and the division and the differentiation. You get so involved in it that when a fish actually hatches and swims out, you feel like you're God, you created it. There were also experiments with sea urchins and several other organisms. And lectures. It was wonderful. My family was with me, two kids. We had a small hut on the eel pond; the whole house might have been no bigger than this room.

The course was absolutely delightful. But it was very old-style embryology. All embryology courses given now are molecular genetics. I remember some of the characters who taught the course. One of them was Maurice Sussman, a very amusing guy; he worked with slime molds. And he taught me Sussman's Third Law of Embryology, which is "For every observation there's an equal and opposite observation." That still holds true to this day.

In some ways, though, this embryology course could have been given thirty years earlier. One of the shocking events was in an evening lecture when the professor happened to mention the word "gene" for the first time—I hadn't heard the word "gene" all summer—and "gene mutation". One of the students asked, "Yes, but what is a mutation?" And the professor

answered, "Oh, that's a very deep problem; we don't know anything about that." And I thought, "My god, what am I doing here? [Laughter] I'll go back to my genes and my mutations." Nevertheless, the whole exposure was very impressive. In my work on development now, I have a feeling for it that I would not have had if I hadn't been through those experiments.

I went back to Woods Hole for a second course in 1965. By that time, it had gotten so crowded that it was a bit unpleasant. Also, I was no longer anonymous. You didn't walk down the street without people grabbing you and trying to shove a manuscript in your face or tell you about their latest discoveries. Also, at the beach, you couldn't get off the beach into the water without somebody nagging you. So that became rather repressive. Nevertheless, the second summer was, in many ways, extremely pleasant, too. We had a house on the water, just an abundance of mussels on the beach. We could pick out our mussels and steam them in wine. We had welks to make welkburgers—grinding them up. I had this book by Euell Gibbons—*Stalking the Blue-eyed Scallop*, talking about all these creatures, which ones you can eat, and how to cook them. So that was my Bible that summer—we made this paella thing . . . .

Aspaturian: I notice food looms large in your recollections.

Benzer: Yes, I love food. One of the greatest things in the Japan trip was the discovery of sushi. I had many food experiences there that left an indelible impression on me.

Aspaturian: By this time, you had a fairly substantial reputation in biology. Were you happy about this? Was the renown becoming a nuisance?

Benzer: No, it was no big deal. Well, sometimes it was a little bit of a nuisance. I have a cousin Sidney Benzer; he's a dentist, and works in New York, the White Plains area. So he sometimes spent the summer at Woods Hole. And he complained to me that when he had the name "S. Benzer" on the mailbox outside Woods Hole, around Cape Cod somewhere, someone was always coming to the door, asking, "Are you . . .?" And he said, "No. That's my cousin Seymour," and slammed the door. [Laughter] Woods Hole was full of neurobiologists, especially electrophysiologists. It's always been a stronghold for them—probably dates back to the early

days when some physiologists sort of got the place going.

By my second summer there, ’66—I had already been at Caltech for one year on a sabbatical—there was very much the feeling that the neurophysiology establishment there was resentful of the molecular biologists.

Aspaturian: Why was that?

Benzer: Molecular biology had become so successful. Also, they were resentful about the microbiologists going into neurobiology.

Aspaturian: Had that started happening in a big way by that time?

Benzer: Sydney Brenner didn’t help by projecting a very arrogant attitude when he gave a lecture there. I wasn’t there, but I heard about his saying in essence, “You shmucks don’t know what to do about neurobiology. We’re going to come in and clean it all up, and within two weeks we’re going to solve all the problems.” This didn’t go down very well. From time to time, I found this had rubbed off on me, because people are constantly confusing me with Sydney Brenner; and if not, they also identify me as having the same attitude. I don’t know whether I told you, but on two occasions I had to vote for candidates for foreign members of the American Philosophical Society and the National Academy of Sciences. In both cases I received a ballot in which Seymour Benzer was listed as a candidate for foreign member. [Laughter] In both cases, they meant Sydney Brenner.

Aspaturian: What did you do?

Benzer: I wrote a note, saying, “I’d love to have dual membership, but I really think you mean Sydney.” And they said, “Oh, my god!” [Laughter] And it goes so far that once Sidney Altman, another biologist, gave a seminar here and Giuseppe Attardi gave the introduction. And just before sitting down, he said, “I now give you Seymour Benzer.” [Laughter] A carryover from the “Sidney.” And everybody roared, and he looked around: “What, did I say something wrong?”

Aspaturian: So this has been sort of a leitmotif of your career?

Benzer: Oh, yes. Sydney and I exchange badges if we're at the same meeting. Once I arrived at a meeting we were both attending, where he hadn't arrived yet. When I wanted to check in, they said, "We don't have any room reservation for you." So I said, "Well, do you have Sydney Brenner?" And he said yes. [Laughter] So I said, "Well, that's me." I took his room.

Begin Tape 6, Side 2

Benzer: When we were moved into the life science building on the Purdue campus, we chose a lovely laboratory in the building's subbasement, which was kind of depressing because in the physics building we had nice rooms on the third floor, with windows. Now this other guy, Mullins, whom I mentioned in an earlier interview, tried but couldn't negotiate himself a job as chairman of biophysics. To get us out of the subbasement, he put up the argument that he was working on olfaction, the neurophysiology of smell receptors. He said that since all odors are heavier than air, they would all sink down to the subbasement, and he wouldn't be able to do the research. So they gave us some rooms up on the third floor in addition to the subbasement—six small rooms, a nice little suite. He took half the rooms and I took half. We also still retained some space in the basement. There was a problem, though. We were both dependent on the elevator, going from the third floor to the subbasement. It was a real pain in the neck when the elevator broke down. And that became an issue. When I was threatening to leave to go to the Salk Institute [for Biological Studies] at one point, the dean came around and asked me, "What can we do to keep you here?" I said, "Well, build another elevator." He said, "OK, we'll build another elevator." [Laughter] It even became an issue in connection with the Salk Institute. The institute was built by Louis Kahn, a famous architect from Philadelphia—a Yale product, I think. He came around interviewing the institute's prospective fellows to find out what they would like in the building. So I said, "Elevators. Make sure you have elevators." [Laughter] He built fourteen elevators into that building, twice as many as really necessary. I always felt responsible for that.

While I was still at Purdue, in 1959, Harvard offered me a full professorship in biology. So I made a visit to Harvard that winter. The dean was McGeorge Bundy; he was personally very

impressive. Immediately he offered me more than he had originally offered, because I was getting more than that at Purdue. It was mid-January. He walked me across the Quad at what seemed like minus twenty degrees centigrade. I liked to be warm, but still—Harvard. I accepted the job with some trepidation, because I was really very happy at Purdue; I'd been very well treated. I remember my chairman in physics once saying—this was when I was already into biology—"Go tell the president of the university about your work and cheer him up. He has such a boring job." [Laughter] So I did.

One reason for my trepidation was the weather. Another was that teaching is taken seriously at Harvard, whereas by then I think I was already a Distinguished Professor at Purdue and had no requirement for teaching. The other was, people kept saying, "You know, these Harvard types. Once your colleagues go to Harvard, you can't talk to them anymore. But that won't happen to you, Seymour." These things weighed on me a little bit. But nevertheless, I was going to go. Then I began to develop chest pains, which I talked myself into being a cardiac condition, possibly psychosomatic. The pain was not psychosomatic but the interpretation was. I was finding that every time I exerted myself, carrying books or something, I had this nagging pain. I thought, "I'll have to go to Boston in this cold weather; that doesn't make a lot of sense." I actually went to the hospital for an examination; they did all kinds of tests, couldn't find anything. I think I was thirty-five. The doctor said, "You're not too young for heart trouble," and I remember that I was quite taken aback by that. He couldn't find anything. It later dawned on me that it had nothing to do with exertion but with a particular movement that I was able to trace to a muscle. If I moved this arm the right way, it would prompt that pain. But in the course of it all, I got so insecure about the effort of moving and living in a cold climate that I turned Harvard down. So I have two diplomas from Harvard; one big one, signed by the corporation appointing me, then a smaller one rescinding the appointment. Harvard insisted on having the last word for everything.

While we're on the subject, I've had five offers from Harvard. The first one was earlier on; it may have been about '57 or so, shortly after I had really gotten into this *rII* gene business. There was a guy I knew named Bernard Davis, who had just achieved his lifetime ambition of being appointed to a professorship at Harvard. So he invited me to Boston to recruit me. I was then an associate professor at Purdue, which meant that I had tenure. It was a recruitment like none other. He took me out to Howard Johnson's, then to a New England boiled dinner. Finally,

he took me to the campus to show me what my lab would be—two rooms. He said, "This is currently the leprosy laboratory. However, we'll get it cleaned out for you." [Laughter] Then he asked me what my work habits were. And I said, "Well, I tend to work at night best." "Oh, that won't do, because you won't be able to interact with the other people." When, finally, he offered me an assistant professorship, I said, "Wait a minute, I'm already an associate professor with tenure at Purdue." "Well, anyone who wouldn't rather be an assistant professor at Harvard than an associate professor at Purdue . . ." So this was my first Harvard offer. The real offer, the full professorship, came in 1959. I took that one more seriously. The next one was 1965 or '66.

Aspaturian: You had been at Caltech that year on sabbatical, working with Sperry, right?

Benzer: I had been in Sperry's lab, not working with him, unfortunately—it would have been a good experience. But I was spending the summer at Woods Hole. While I was there, the head of neurobiology at Harvard tried to recruit me to his department—took me off to see the dean. I told him what salary I was getting at Purdue, and he said, "Oh, my god, that's more than the dean is getting." [Laughter] "But nevertheless, we're willing to concede." But then Kingman Brewster, who was president of Yale, came over from Martha's Vineyard on the boat and handed me a letter, offering me a full professorship at Yale. I was very impressed that he went to the trouble of coming to deliver this in person. I was very inclined to accept the Harvard job, because I loved the guys I'd been working with that summer. I am still very fond of them, the neurobiology group. But then I came back to Woods Hole, and it happened that Albert Tyler from Caltech was there. He was a professor of embryology here—died of a heart attack a few hours after a baseball game at the biology picnic [1968]. Anyhow, before he died, I told him about this. "I may not go back to Caltech; I may just stay here and take this job at Harvard." But Tyler said, "Now wait a minute, don't do that. You have to give Caltech a chance." Of course, I had been at Caltech a whole year, and nobody ever said anything. And he said, "Well, wait. We have to tie it up in a package with the right kind of ribbon on it. " So I put Harvard on hold and came back to Caltech. At the same time I had a second offer from the Salk Institute, and I said, "Look, you don't want to monkey with me. I just reneged on a job I accepted at Harvard." He said, "That's OK."

When I went in and told the president of Purdue, "Look, I'm having chest pains and decided not to go to Harvard—will you take me back?" He said, "Absolutely. You've made my

day." [Laughter] And I said, "Yes, but I might be a sick man." He said, "I'll take my chance." In a way it's nice to relive all this history of courtship, seduction . . . and betrayal.

SEYMOUR BENZER

Session 7

November [exact date unknown] 1990

Begin Tape 7, Side 1

Aspaturian: What brought you to Caltech, the first time you came?

Benzer: During the sixties, I was getting more and more interested in behavior. One reason was my two children. I have two daughters with very different personalities. If you have one daughter, you don't notice anything, but if you have a second one, you begin to wonder, "Are we doing things differently, or is it genetic?" So I got interested in this general problem of personality and behavior—how much is genetics and how much is environment? And how do you study such a problem? I had actually begun to be interested even before that time. There was a meeting about '63, I think, at Cold Spring Harbor, where I remember having a conversation with Marshall Nirenberg. We had this feeling that all the molecular biology problems were on the verge of being solved. It was a little bit like the physicists at the end of the nineteenth century saying, "All we have left to do is one more decimal place." Little did we anticipate all the recombinant DNA technology. So that was another part of it, the fact that molecular biology was going so well, becoming rather crowded. When things get to that stage, you wonder why you should be doing something somebody else is already doing. It's just redundant.

But it was also combined with this new interest in the roots of behavior—I was mostly attracted by that. One book that had an important influence on me was one by [Dean E.] Wooldridge. I think it was called *The Machinery of the Brain*. Wooldridge, I think, was connected with Ramo-Wooldridge. His book certainly focused my interest quite a bit at that time, similar to the way Schrödinger's book had influenced me earlier. It was a book by an engineer about the brain, and for me—especially with my background in genetics—it raised the general problem of how you get from a set of genes and chromosomes to a brain that thinks and behaves. So I thought that would be an interesting subject to tackle: How do you get from a gene to a behavior? And the timing was right for coming to Caltech. I was able to move easily at that time because my older daughter was graduating from high school and my younger daughter was

graduating from elementary school—they were six years apart. And all my students and postdocs were getting their degrees or fellowships. Even my secretary got married to a minister, who was transferred to some other town. So it was like a clean sweep. I was certainly eligible for a sabbatical, and no better place to come than Caltech, of which I had such fond memories from my postdoc years with Delbrück.

And who at Caltech would be a good excuse for all this? Well, that would be Roger Sperry. I remember asking Delbrück whether it was a good idea to come to Sperry's lab. I don't remember exactly what he said, but I ended by saying, "I could do worse, couldn't I?" And he said, "Yes." We had that conversation when I visited here in connection with my negotiations with the Salk Institute. We were on our way back from a camping trip, stalled in traffic on Freeway 10. And there was all the smog, and I thought, "What am I doing wanting to come back here into the smog? But, what the hell, it's worth it."

So I wrote to Sperry, and he wrote a very warm, enthusiastic letter back, which gave me a completely wrong impression of his personality. Because when I came, I found a relatively inaccessible person; you always felt he wanted to be somewhere else. I think part of that was due to the fact that he's very susceptible to infection. He actually has a daughter with cystic fibrosis, who's now in her mid-twenties I think, and doing OK. He met his second wife—I think she was a nurse—when he was laid up with tuberculosis that he caught from monkeys. Later on, he was doing some experiments with a dolphin, and he caught pneumonia from a dolphin. So he's generally always worried about picking up infections. He's not a hypochondriac—he's just extremely vulnerable to infection.

One experience I remember specifically: I was in a room here on the third floor; I had no telephone. But as a visiting associate, I had been given a master key. So I went in once and used Sperry's office phone. I told him about it the next day, and the day after that, I had a phone installed in my room. [Laughter] I always suspected that was to avoid contamination. But that's only speculation.

That first year was really wonderful, because there I was, learning a new field, every day, something new.

Aspaturian: What exactly were you doing?

Benzer: Initially I was reading and going through the things that were going on in Sperry's lab. That was a zoo, because Sperry had quite a large group of people doing their own thing. His main interest at that time was with the human split-brain patients. I think that research had been started by an earlier student—Ron Myers. And when it began to really flourish, then Roger pitched into it very strongly. The main person in the lab working on that was Michael Gazzaniga. Joe Bogen was the neurosurgeon they worked with—he's at USC. He had been treating epileptics by splitting the corpus callosum to prevent the spread of seizures from one side of the brain to the other. He was also giving the patients anti-epileptic drugs. I don't know whether it was ever proven that the cutting was really doing the job. But anyhow, that was a source of patients for Sperry. So they had human subjects. They also had people working on fish, training fish to come and discriminate between colors. If they pushed the red control they got fed; if they pushed the green control, they didn't get fed. And pretty soon the fish learned to push the red control. They had frogs, and they had cats, which I stayed away from, because I was allergic. The cat experiments were interesting because they showed that if you scoop out half the brain in a very young cat, when the cat grows up its functions are essentially normal. One hemisphere could take over everything, if you start when it's still plastic enough. But in an old cat it doesn't work at all.

Aspaturian: Of course, you know, Sperry's no longer involved in any of this. He's gone off on a totally different tangent.

Benzer: He was already doing that then, which was a little disappointing to me. Already in 1965, when we'd have group meetings every week and talk about science, he seemed only to be interested in consciousness. So it was a little difficult. The thing that attracted me to him initially was his work on chemospecificity. These were experiments in which you have a fish nerve going to one side of the brain, and if you cut the nerve, a new one will regenerate from the eye. So they did things like rotate the eyeball to see whether the nerves came to the right place. And generally speaking, they did. So he enunciated the idea that there were chemospecific tags on the end of the neurons and their targets that made them able to connect up in the right place. This is still a controversial issue after all these years. But that's what interested me, because it was a question of how the genes control that chemospecific tag. That's still one of the most important problems

in neurobiology. And progress is being made, but in terms of identifying molecules. Otherwise, there's still a lot of contradictory results. But by the time I arrived, nobody was doing those experiments in Sperry's lab anymore.

Aspaturian: Were you doing actual lab work, or was a lot of your initial stuff just research and observation?

Benzer: Initially, part of it was just seeing what other people were doing. Some people were working on learning in chicks, particularly Arthur Cherkin, who became a good friend. And Evelyn Lee Teng, who is now at USC, was also studying them. They were studying the dynamics of the phenomenon of memory-consolidation. So there was exposure to this field for me.

One thing that nobody was doing was anything having to do with genetics. In Sperry's lab, not one person had any particular interest in that. And I came in with this genetic imprinting. Even before coming, I had felt that if you're doing genetics, it's important to work with an organism where you can work on populations, because if you run a rat through a maze over and over again, it takes weeks to get any significant amount of data that would be statistically significant. But if you have a bunch of flies, they all have the same genotype, and when you run them through a maze, you immediately get to do hundreds of flies at once.

Aspaturian: So had you already thought of fruit flies as a model system before you came?

Benzer: Yes.

Aspaturian: I understand that fruit flies had sort of fallen into disrepute among molecular biologists since Morgan's day and were not considered a real good animal to work with anymore.

Benzer: Well, molecular genetics, and particularly bacterial genetics, had boomed so much because of the speed with which you can get results with simpler organisms. I contributed to this with the phage genetics. So *Drosophila* genetics was looked on as sort of, well, it was nice while it lasted. [Laughter] But for me, I already had the idea of using *Drosophila* to study the effect of

mutations within large populations.

Aspaturian: So by the time you came here, you'd already considered that *Drosophila* might be the way to go?

Benzer: Yes. But I was also interested in all these other possibilities. I did some other experiments with one of the postdocs in Sperry's lab—Emerson Hibbard. He knew about frog anatomy and tracing the nerve pathways of the frog. He had done some of what are called rotation experiments. Normally the optic nerves cross over so that the nerve enervating the right eye goes to the left side of the brain, and vice versa. So my idea was that at an early stage in the frog's development, we'd cut out one eye before the nerves were wired up, using anesthetics, so that there would be just one bundle hooking up in the brain. And then, if any of them made a mistake, you'd be able to see them easily. So my idea was to give these frogs phylouracil while they developed, to create similar analogs of the normal DNA and RNA components, particularly the RNA component, so that these chemospecific tags on the optic nerves would be messed up, and some of the nerves would go to the wrong side of the brain. The eye is there, but one eye has been removed; so some of the nerves might go the wrong way. This is what Ray Guillery found in the Siamese cat. Siamese cats squint, and the reason for that is a genetic defect that causes the optic nerves to make mistakes in connecting up in the brain. But it has nothing to do with the chemospecific tags; instead it correlates with pigment cell defects. White tigers have it also.

The experiment didn't work, because the doses of the chemicals we were using interfered with the development so strongly that the whole animal went to pot. I still think that kind of experiment, properly done, might be a very good one.

Aspaturian: The chemicals were too toxic, in other words, to use as labelers.

Benzer: Well, the obvious thing to do then would have been to put them in just briefly at a particular stage of development and then take them out again, so they're not screwing up everything. But we never got around to doing more detailed experiments, partly because by that time I was getting involved in the *Drosophila* work.

The question was, what is the simplest kind of behavior you can think of for which you could make mutations and changes, and work out the relationship between the gene and the behavior.

I've found out since then, that between gene and behavior, there's a tremendously long series of events. But the simpleminded idea was to work with one of the strong behavioral reactions of a fly: phototaxis—that is, going toward light. If you just put flies in a tube and shake them all down to one end and lay the other end down in front of a light, they generally go to the light. I couldn't find a test tube anywhere in Sperry's lab. [Laughter] And no chemicals. The lab was famous for chemospecificity, but there was no chemo anywhere to be seen in the whole lab, except the anesthetics they used for surgery. So we went around to Ed [Edward B.] Lewis's lab for test tubes.

Aspaturian: Did you know Ed Lewis by this time?

Benzer: I had known Ed Lewis way before, when I had been here as a postdoc. I remember that at the time I thought he was working on an old-fashioned organism—writing all those symbols on the board. It was too complicated, not to the taste of a phage biologist. But he kept on going. It was with the advent of molecular biology that the significance of all his work became clear, and then of course the homeobox thing just hit the fan.

Aspaturian: Were people like Lewis held in contempt by the phage mavens at that time?

Benzer: No. He was a nice guy. He was very good with flies. And it's good to have somebody like that around. But at the time it seemed sort of like having a Greek mythology scholar; it's nice to have one around for the university at large. He taught the genetics class, and kids counted the flies. Of course I'm giving you the jaundiced point of view. He was the true inheritor of the Morgan-Sturtevant tradition, and that was just fine.

So I went around and got some test tubes from him, and I got some flies. And I started doing these experiments.

Aspaturian: What did you do, zap the flies to see if any came out that were nonphototactic?

Benzer: No, what I did was to measure the phototaxis, and then I found that that was a very consistent response and I worked out the conditions. One aspect was population. The other aspect of behavior is, it's really statistical. When you put a single fruit fly through the same test two times, one time it may go to light, the next time not. That's a statistical decision that's made. The fly may go predictably ninety-five percent of the time, but not always. So I felt that I needed a method for multiple tests on population. And for that I devised—again borrowing from molecular biology—the countercurrent distribution procedure that Holley had used to fractionate transfer RNA while he was working out the degeneracy in the genetic code. I was familiar with that fractionation technique. Countercurrent distribution is used to separate two substances, to purify one substance away from others on the basis of partition coefficients. Say you have two liquids like water and ether. You put down your material and you shake it up. Each substance has a certain ratio of partition between the two solvents. One substance may go sixty percent into ether, another one may go fifty-five percent into ether. So after mixing them up the first time, you transfer the top layer to a new tube and the bottom layer to another tube, and you shake them up again. And if you do this enough times, you find that ultimately the two substances become separated into different tubes.

The question with phototaxis was whether the flies were just running to get away from the starting point, or were they really running to the light? So you weigh down the test tube so the flies are at one end, with their backs to the light. The phototactic ones should stay where they are. Blind flies would distribute themselves in the tube—they would show no reaction. So the idea was to make a countercurrent distribution out of this. Some of the flies are moving; some are not. You separate these into two tubes and then add another tube to each one and do it with two more tubes. And then when you get up to, say, tube number five, you will have only those flies that have responded five times.

Aspaturian: So at the very end, you have a small subset of flies that don't exhibit phototaxis.

Benzer: That's right. To build such a machine, I wanted to have a whole series of tubes and be able to bang them down in one direction, and then lay the machine in front of the light, and then be able to rotate the bottles around the light. I went over to central engineering, to the people

who had built the Mount Palomar telescope. They built me a machine with glass tubes that weighed about thirty pounds, such that you could hardly lift it. Also, it would smash all the tubes when it rotated. But in the process, all this mental process, it dawned on me that when you're tapping this apparatus down, you're emptying all these tubes. So you just shift them back again. It's very simple and quick—just fifteen seconds, for each trial. So in two minutes I had as much statistical information as it would have taken one several months to get with rats. [Laughter] And then, I would do the opposite—this would be distribution going to the light; then the opposite experiment, going from light. When I started exposing the flies to mutagens and then picking mutants, I found some that just didn't go to the light at all.

So the first thing was, this gave rise to a lot of nonphototactic mutants. The other thing was that it gave me a lot of mutants that were unexpected. Just banging the tubes would cause some flies to have kind of an epileptic fit. They'd go into a faint and be there for minutes, then they'd recover and be normal again—the so-called "easily shocked" mutants. Others were just plain sluggish; they could hardly move in either direction.

Aspaturian: So you found a lot of deviations, just with this simple experiment.

Benzer: Yes, I found a whole spectrum of weird aspects of behavior that could be changed by changing genes from this very simple experiment. Each of those has become a whole study in itself.

I'm fooling around with this stuff in Sperry's lab, and I could see all the possibilities of how you could use these gene mutations of phototaxis to dissect the whole pathway between the light and the response. But the first question was whether the mutagens affected the receptors in the eye responding to the light. Then there was the question of whether they're making signals that go down to the brain, and the question of whether the brain is perceiving this correctly. And then the question of the brain sending signals to the legs—they don't fly in here; it's walking—to go in the right direction. There were all these possibilities. We were doing this kind of genetic dissection with the idea of creating mutants that correspond to interference along every step of the pathway, as a way of getting the connection between the gene and the behavior. I gave a seminar on this in Sperry's group.

Begin Tape 7, Side 2

Benzer: I don't know whether I told you what my mother said when I said I was going to start working on the fly brain. Her first reaction was, "From this you can make a living?" And the second thing was, she took my wife aside: "Tell me, Dotty, if Seymour's going to examine the brain of a fly, don't you think we should have his brain examined?" [Laughter]

Anyhow, this became relevant when it came my turn to give the seminar. I laid out this whole plan. The whole lab was in a sort of uproar for about a week after that, people arguing with each other. They were pretty much split down the middle between those who thought that this was great stuff and others who thought this was pure crap, that I'll never solve any problems that are important. They were really screaming at each other.

Aspaturian: Where did Sperry come down on this?

Benzer: I don't remember if he was even there. I don't remember his making any comment on this at all. He was probably thinking about consciousness. Sperry was already very much antireductionist. The main impression I have is that he thought, "All right, but this is not going to answer the really deep problems. You're just going to find lower- and lower-level mechanisms. But that's not going to tell you anything because the mechanisms are emergent as you go from a low level to a higher level, and new things emerge that cannot be predicted by the lower level." My attitude to that is, it may be true in the limit but there's an awful lot of stuff to be filled in in the meantime, enough to keep you busy for a long time. So there's no point in arguing with that on that level.

Aspaturian: After you gave the seminar and you had these supporters and detractors, did you have a flood of visitors trooping in and out of your lab to see for themselves what was going on?

Benzer: No. Around the corner was Felix Strumwasser, a neurophysiologist. He was pretty skeptical about the whole thing.

Aspaturian: Why were people so skeptical?

Benzer: Why? A lack of imagination.

Aspaturian: Well, I mean, was there some sort of mindset in neurophysiology that inhibited people from . . .?

Benzer: I think part of it is just ignorance, just as my ignorance of biochemistry made me scorn it incorrectly, regrettably. I think that many people were ignorant of genetics then. They certainly didn't know anything about molecular genetics—phage stuff was all this mumbo-jumbo—and these complicated things that a *Drosophila* geneticist did. All those symbols to study the genes were just complicated and unnecessary, because, you know, to figure out how a nerve membrane potential is propagated, what do you need genetics for? Obviously, that attitude was completely wrong, because genes are what make all the parts of a nerve. It was obvious to me. One of the big days in my life was at a neurolunch, where somebody was giving a talk, and during the questions, Strumwasser asked, "Can you find a mutation that changes this property?" And that was a really big event for him, to discover the idea of genetics after all these years. Actually, he and I had problems. Later on, in 1967, when I was on the faculty and Caltech decided to build up neuroscience, we were on the search committee together. Sperry had earlier tried to get this independent department of psychobiology, on the grounds that people in this field just wouldn't come unless they had their own department. Caltech traditionally is against splitting departments. Physics, math, and astronomy in one department. Strumwasser was approached on that, and it was pretty much of a stalemate about making any appointments, until he went on sabbatical for a year, in '68 or '69. That year we made five appointments in neurobiology just because he wasn't there. That really got us off the ground. So, we often had opposite perceptions of everything, to the point where when we agreed on something, I really began to doubt my judgment on it. [Laughter]

But getting back to 1966, I'm still in Sperry's lab. That summer I decided to go to Woods Hole to take a neurophysiology course. When I came back to Caltech, there was this flurry of deciding between Caltech and the Salk Institute offer and the Harvard offer.

I had signed up with the Salk Institute, but I was thinking of backing out. I didn't like the way it was going. It was October, and I set a deadline for giving Salk a decision. The imposition

of that deadline made Caltech hurry. And Delbrück was the one who carried the ball for Caltech to hurry up and expedite its normally slow procedures to make me an offer here, which I accepted. [Lee] DuBridge called me and asked if I could come to his office now, and I said, "Well, I'm not dressed for seeing presidents." I was in some sloppy outfit. He said that didn't matter, and when I came in, he gave me the glad hand, and we were all very cheery. So I took the job.

Aspaturian: You'd backed out of Harvard; you'd backed out of Salk. What prevented you from backing out of Caltech?

Benzer: This was where I always wanted to be. [Laughter] Ever since the Delbrück postdoc period, smog notwithstanding. Ray Owen was the chairman [of the Biology Division] at that time, and I said to him, "You know, the smog." He said, "Well, I can't help it; can't do anything about it." I thought that was a good approach to the problem—not to defend it, just a fact of life. So that was the only minus. I think I was also a little intimidated about whether I'd be able to hold my own as a professor here, what with all these great professors. But after I'd been here on sabbatical and heard some of the lectures, I decided I could compete with these jerks without too much trouble. [Laughter]

It was also the question of taking on teaching responsibilities, which I was not used to and I wouldn't have had at the Salk. But the real problem with Salk was all the infighting and struggles among the colleagues. It was turning out to be anything but the ideal platonic institute that we had originally imagined. It had become clear by then that they would just have to reinvent all the academic structure in a very painful way. Whereas here, Delbrück's argument was always, "Don't go somewhere where you have to start from scratch. Caltech is a going concern with a history." At that time, I thought it was just sour grapes, because he wasn't being asked to join the Salk. But I know now that he was perfectly right. There's still a struggle there. Although it's a beautiful place. [Laughter] Every time I go there, the view of the ocean is wonderful. Twenty years later, it's finally shaping up. But even so, it's a struggle.

The one technical problem was that I was on sabbatical from Purdue. I had decided I wanted to stay at Caltech a second year before the job offer came through. But I was obligated to go back to Purdue, because they didn't want to pay me for a second year on sabbatical. However,

I had an NSF [National Science Foundation] grant from my phage work, with several years left on it. NSF very graciously allowed me to switch to *Drosophila*, with no questions asked, for which I've always been grateful. I guess they had enough faith in me by that time. So I started taking salary from the grant for the second year at Caltech.

Aspaturian: That must have been one reason Caltech decided they wanted you. Historically, they've always been high on people who can pay their own salaries out of their grants.

Benzer: Sure, I can understand why. My postdocs have to get their own fellowships. [Laughter]

Aspaturian: Have you been here ever since, in this particular suite of offices?

Benzer: Yes. I have not taken a sabbatical again. What I did do—this was part of the initial understanding when I accepted the job—was to spend the summers at the Salk Institute. I did that for five or six summers, which was good—like having it both ways.

SEYMOUR BENZER

Session 8

November 30, 1990

Begin Tape 8, Side 1

Aspaturian: We were going to talk about your experience with the Salk Institute this session.

Benzer: I think it was the fall of 1959, shortly before or after I had reneged on going to Harvard, that Jonas Salk came to talk to me. He had this plan to start this wonderful institute for scientists that would be perfect, just like Plato's. He didn't say they would go around in togas, but the idea was they could have free thought and work and do science without any restrictions that one has in a typical university with committees and teaching and students. What he had in mind was a kind of institute of advanced study like the one in Princeton. He probably didn't know too much about what goes on there. [Laughter] Have you ever read that book, *Who Got Einstein's Office?* [Laughter] Anyhow, I didn't know all of that at the time. It sounded like an absolutely great idea, and it was going to be in California, which solved my problem about being too cold at Harvard. So I was extremely interested. But I told him, "You don't want to deal with me. I accepted a job at Harvard and I backed out. You can't trust me." He said, "Never mind, I'll take my chances." As it turned out, I backed out of the Salk Institute, too.

Aspaturian: Was this after he had become so famous for discovering the treatment for polio?

Benzer: Oh, yes, he was super famous from the invention of the vaccine—a mixture of famous and infamous, because he certainly was a great hero in the public eye. It was a terrific accomplishment. But in the scientific profession, there was a certain amount of resentment against him for not being a great scientist. I think it was just the fact that he'd gotten so much publicity out of the vaccine, whereas a lot of other people who were involved did not. His main contribution had really been sort of to organize the effort based on other people's work. And, in fact, when they gave the Nobel Prize for the vaccine, they gave it to two other guys, the people who had first been able to grow the virus in tissue cultures, way before Salk. After they did that,

Salk had this great idea to save all these kids, and he organized the effort with the backing of Basil O'Connor, who was head of the March of Dimes Foundation. O'Connor had been Roosevelt's lawyer, and, of course, FDR had polio. So O'Connor was on a crusade to combat the disease, and he backed Salk financially in this very big project, which was controversial. It's still not ended really—the controversy between Salk and Sabin about whether the polio vaccine should be an inactivated virus or an attenuated virus that could multiply. In fact, there was a real disaster—the so-called Cutter incident, where a batch of polio vaccine that had not been inactivated went out and a number of kids came down with polio. But it was a tremendous accomplishment. I still remember as a kid, as a teenager, what summertime was like. Jim Watson calls Salk the "hero of the summer," because as children we couldn't go to swimming pools. That was supposed to be a place to get infected. And after the vaccine, we could go to swimming pools.

Anyhow, Salk's idea for the institute was pretty much irresistible. It turned out this thing came about by the coexistence of Leo Szilard and Jonas Salk. Szilard had had the same kind of idea. I don't know which one heard about the other or how they came together, but Szilard said, "This is wonderful. With my brains and Salk's money, we can make a real good institute."

Aspaturian: Was Salk planning to endow it from his private funds?

Benzer: Well, Salk had prospects of getting money from the March of Dimes, because Basil O'Connor wanted to do something in recognition of Salk's great accomplishment. So that's where the initial money would be coming from.

Then came the question of who would be at the Institute. Szilard made a lot of recommendations about who should be offered jobs at Salk, and these people recommended other people. They developed an initial group that consisted of Renato Dulbecco, who was working on animal viruses; Ted Puck, who also developed tissue-culture techniques for growing human cells; Matt Meselson, who was a Caltech person; Jim Watson; me; and two other people. One was a person I recommended—Edwin Lennox, a former physicist who became a molecular biologist. He was a good friend of mine at the University of Illinois, near Purdue, when I was there. And he recommended an immunologist, Melvin Cohn.

Then we had this meeting in New York, at O'Connor's expense, although he was not

there. For us humble boys, what a living. I think we may have stayed at the Waldorf. Room service, and the sky's the limit. We just ate it up. But what I specifically remember was the discussion about where the institute should be. Salk said it had to be in a beautiful place, with a good climate, so it had to be California. His two obvious choices were Santa Barbara and La Jolla. And Leo Szilard said, "Make it La Jolla, because there's a good Chinese restaurant there." So everyone said, "Great, we'll make it La Jolla." The Chinese restaurant—I later checked it out—was called George Chou's Chinese Village. It was quite mediocre, and I think still is. It moved to another location and expanded, but the last I checked—probably ten years ago—it was still mediocre. Anyhow, that's how history is made.

Salk had to battle with the city of La Jolla over the exact site of the institute. The city offered to give him some parkland, a piece out of Torrey Pines Park, south of the golf course, absolutely prime. Salk referred to it as the most beautiful place on earth, and it certainly would rank quite high on that scale—a 300-foot cliff overlooking Black's Beach, the ocean, and La Jolla. So this location went along with the grand concept.

Aspaturian: Was UC San Diego down there at that time?

Benzer: UC San Diego was already there, and the school fairly embryonic. Scripps Clinic was still in downtown La Jolla. There was a Scripps Hospital, which was a separate institution.

So, Salk decided he had to engage an architect, and he engaged Louis Kahn, who I think was a Yale-connected person, certainly an East Coast type. And Kahn went around to the putative fellows of the institute asking them what they would like. I had a hang-up about elevators, because at Purdue I had had to depend on an elevator that was always breaking down. So I had elevators at the top of my list. Kahn ended up putting fourteen elevators in the institute, far more than necessary.

In addition, Kahn had the illusion that the climate is just perfect in California at all times, and he designed the building in such a way that you had to go outdoors to get from one lab to another. And that, I think, was a terrible mistake, because it led to a feeling of isolation among the individuals working there. Not to mention that sometimes it rains. He had the parking area some distance from the institute, not really very far. I remember Dulbecco saying he liked that because it's good to walk. I said, "Yes, but what about when it rains?" He said, well, he had

noticed that when it rains it usually comes from one side, so you can walk along the other side. Dulbecco was always a great rationalizer. He's now the president of Salk Institute, by the way.

So what happened was, Louis Kahn asked Salk, "How much money have you got to put into the building?" And Salk said, "Ten million for endowment"—this was all from the commitment from the March of Dimes—"and a million dollars a year for operating expenses in perpetuity." So Kahn went home and designed a building for $20 million. In fact, he bragged about this at some dinner he had in La Jolla. He talked about other buildings he had designed, and he said it was always his policy to make the building for twice as much as the amount of money available, because you could always count on the fact that people scurry around to find the extra money.

Salk went for that idea on the argument that later on it would cost much more to build it. That was absolutely true. But at the time it had the effect of eliminating the endowment. And everything suffered from then on. The institute, which was supposed to be completely free of any worries about money, instead was always worrying about where the next buck was coming from.

Aspaturian: Is that still true today?

Benzer: Still today. They're in much better shape now, but they're essentially running on soft money, and it's constantly a concern. For at least the first ten or fifteen years, it was always touch and go.

Aspaturian: So they liquidated their entire endowment to construct a more expensive building.

Benzer: Yes. And this led to problems, because all these great things that had been promised were not for real. There were also some pre-existing wooden structures there. They may have been constructed for the purpose of temporary quarters. We'd all come and have meetings there. I would come from Purdue, because I wouldn't move until the building was ready. And the same for the others. Dulbecco was here at Caltech. Cohn and Lennox were at the Pasteur Institute.

Aspaturian: You said Salk had a list of people he wanted to recruit. You, Watson, Meselson, some others. Did he get a commitment from all of them to come?

Benzer: No, no, I'm sorry. Watson withdrew early in the game, on the argument—referring to Salk and O'Connor—that "these are not our kind of people." That's a little ironic now when I think about it, because they're exactly the kind of people Watson deals with now, in getting money for Cold Spring Harbor. He has to think about money all the time, and he's been a tremendous success at it. There was an article I just saw the other day, probably in *Science*, about the history of Cold Spring Harbor, in which Watson said, "I think about money all the time."

Meselson's decision not to come I think had to do with the fact that there might not be enough women around. He suffered from a lack of women at Caltech. So I think he preferred to be in a place like Harvard. Maybe I'm reading too much into that, but that's the way I remember it.

Puck was pretty cozy at Denver and I think he had qualms about getting into an enterprise that had that degree of uncertainty.

I was keen to come because it was such a beautiful place—and warm. Dulbecco had become rather restive at Caltech, for reasons I don't know, and was interested in leaving. Well, one very important reason was that he got divorced and married his lab technician. So he had a reason to want to get out of town.

Lennox and Cohn were very interested because they didn't really have other jobs in the States. They had been at Pasteur for quite a while.

Another person who was recruited slightly later in the game was Leslie Orgel, who was recommended by Francis Crick. He was basically a physical chemist. So, the ones who went were Dulbecco, Cohn, Lennox, Orgel, and Salk. And I was supposed to go. Salk also ran into C. P. Snow and got the notion that the institute should be a place where you can do the joining of the two cultures—Snow had been expounding about that. So he asked Snow who we should get to bridge the two cultures, and Snow recommended Jacob Bronowski. So Bronowski became one of the fellows also. Bronowski was quite famous then for inventing what they called "Bronowski's nuts," which were a form of coal made by compacting coal dust into little briquettes. They became quite popular in England, and I think were relatively smokeless fuel. He was also famous for being a member of the "Brain Trust" on television, these smart guys who answer many questions.

Aspaturian: I thought he was primarily an anthropologist.

Benzer: He was everything. [Laughter] He was a poet, he wrote books about Blake, he was a mathematician, and he was a physicist. He was everything—the real Renaissance man. It shows in his TV series, *The Ascent of Man.* It was very good. He died of a heart attack [1974], which was exacerbated by all this intensive travel he did, including going off to Peru at these tremendously high altitudes; people had to help him to walk.

So Bronowski represented the humanities. Jonas Salk was the director. And we decided Bronowski could be deputy director. There was also a president, brought in from outside, with the idea that he would be getting money. Of course, I remember the first president was a guy who is now, or at least until recently was, president of the Aspen Institute. I can't think of his name at the moment. He brought in an associate named John Hunt. They were not very successful in raising money. In fact, I remember once I joined one of the tours that was given for people who wanted to visit the institute—to hear what was being said. The tour guide pointed to where the new building was going to go up, and then she pointed to the executive office, and said, "That's where the fund-raisers are. But they're no good; they're going to be fired and we're going to get new ones." [Laughter] I was amazed by that. It turned out to be true. She knew more about what was going on than I did. It was the kind of place where if you wanted to find out something, you asked the dishwasher, because of his network. So it was a small beehive. This was later on, after the building was in place. But in the early days, some of the people actually came and set up labs in these wooden buildings. Lennox and Cohn, I think, and Dulbecco. Actually it was a wonderful atmosphere in the shacks. It was just delightful; everyone crowded together in a small space. Lennox invited Rod Porter, an English biochemist who later got the Nobel Prize [1972] for his work on antibody structure.

I would come down for meetings at which they would invite people from various fields to sort of explore what things should be done at the institute. There were the inside fellows and the outside fellows. Outside fellows included Jacques Monod and Francis Crick.

Aspaturian: Sort of like a scientific advisory board?

Benzer: Yes. But they also got a stipend and were expected to show up at the meetings. The

institute still has that. Mark [Masakazu] Konishi [Bing Professor of Behavioral Biology] has just become an outside fellow. They'd show up for the meetings and get good meals and walk on the beach, and they'd give advice, which may or may not have been paid attention to. Salvador Luria, I believe, was also an outside fellow.

Aspaturian: How about Delbrück? Was he involved in this in any way?

Benzer: Delbrück was not involved. Dulbecco and I talked about going there when I was visiting Caltech. I remember Delbrück shaking his head and saying, "No, it's not a good place to go," because Caltech was a going concern with a history, and the Salk Institute didn't have a history, any sort of tradition that you could depend upon. My interpretation at the time was that Delbrück was just jealous that he hadn't been asked. But I think now that he was absolutely right.

They were trying to get a younger group of people—in their thirties or so—at that time. Delbrück was significantly older. He could have done well as an outside fellow.

I decided to spend a whole summer there and actually work in the place, see what it was like. And, as I said, it was delightful. At this point—I think it was about 1963—the building was going up. You could see the concrete molds rising.

Aspaturian: I'm curious. You had accepted an invitation to become part of Salk, and yet for all that time you were still at Purdue. Why didn't you just pack up and go?

Benzer: Well, there was no building yet. There was a meeting in New York at which we were given letters of appointment to accept or not. And I remember being sort of astounded by the letter, which said, "This appointment is for life," without any statement about retirement. That was certainly a hard thing to turn down. So I accepted on that basis at that time. But the actual date of going was another question. The guys who actually moved there immediately had reasons they wanted to go. Lennox and Cohn would approximately triple their salary and Dulbecco wanted to leave Caltech. But I had no strong motivation to go. My kids were in the middle of high school and elementary school; it was not a convenient time to move.

But when I went and spent a whole summer there, I was definitely planning to go. But then, toward the end of summer, arguments about authority and commitments began to develop,

and it definitely was very unpleasant. It became a matter of the Fellows against Jonas Salk. I don't remember exactly what the issues were, but it became clear to me that this was an unpleasant thing to be getting into, that the Fellows were beginning to argue among themselves. It partly had to do with the fact that the money had become a serious issue.

There was also the question of who would have the authority in making decisions. The Fellows wanted to run the institute, and Salk wanted to run the institute. He said, "I'm the president; I'm the founder." And they said, "Well, we're the Fellows."

Aspaturian: Do you remember how your colleague Dulbecco reacted to all this?

Benzer: Well, the Fellows were pretty much unified. Although, among us, we had different ideas about rules and regulations. I just can't remember what the specific issue was.

I think the Fellows did not respect Salk as a scientist, so they certainly were not prepared for him to make the decisions on what research should be done. That was certainly part of it. But as far as Salk was concerned, he had built the institute, he should have authority over it.

Aspaturian: Do you recall what it was Salk wanted them to do, that they didn't want?

Benzer: I'm trying to search my brain. The memory of the fight remains, but I don't remember exactly what the issues were. The basic defect was that the two groups were using each other. The Fellows were using Salk to get the institute; Salk was using the Fellows to give it respectability. It was flawed at the outset, I think. Salk is a very sweet guy, if you ever meet him. He's a very charming, warm person with a great sense of humor and has a lot of remarkable characteristics. He certainly fought very hard to accomplish what he did with the vaccine. He was a man with real determination—sort of a large visionary.

It came close to the end of my summer there. The Fellows all were taken around by real estate agents and they all bought houses, except me. I think that the day after I left town to go back to Purdue they all went out and bought houses, and I didn't. That was also an expression of my ambivalence. The houses, they paid something like $50,000 then; they're all worth in the millions now, overlooking the cliffs. So that was certainly one of my dumb steps. Although at the time the prices were horrendous, and the institute had to help out with interest-free mortgages.

I went back to Purdue, and I thought it over and decided, "I'm getting into a mess; why should I do this? It's not worth it." So I resigned from the Salk Institute. But a couple of years later I was approached again. They sat me down and said, "Things are much better now; the place is working. Would you reconsider?" And I said, "Well, yes, maybe." I think I came again. By this time the building existed. There were 8,000 square feet per person, absolutely vast. And they asked me to draw up the floor plans for my laboratory, which is a hell of a lot of work. I think that's when I decided I didn't need this, the elevators notwithstanding. It was very hard to give up the idea of being associated with such a beautiful place, a beautiful location, potentially a beautiful environment, and a lifetime job and retirement.

Aspaturian: You were at Caltech on sabbatical [from Purdue] when the second opportunity came up?

Benzer: Yes. I was at Caltech on sabbatical; that was 1965. At that point, there was a three-way decision between Harvard, Salk, and Caltech. I'd already pulled out of Harvard, although Meselson had gone there. While I was here on sabbatical, he came to visit and said, "Look, I've been delegated to ask you if you want to reconsider going to Harvard." I said, "How can I? I thought my name was mud at Harvard." And he said, "Well, half the people have forgotten. And the other half have died." [Laughter] And I said no.

Even after all this, once I decided to take the job at Caltech, the Salk people still harbored the idea of developing neurobiology. They provided houses and gave us laboratory space, which was ample. Actually, it was in Lennox's space; he couldn't fill his full 8,000 feet, so there was plenty of room for us to move in during the summer. We came and we did this for five or six summers through the early seventies, and it was absolutely delightful. So I had it both ways. I had Caltech during the year; I had Salk Institute in the summer, with the perfect climate and no smog, and just a fond association with the Harvard neurobiology group that I had not gone to. [Laughter] Plus the thought that maybe, if the Salk Institute really got on its feet, to the point where it was more desirable than Harvard or Caltech, I was very well established there. But it didn't get much better.

Aspaturian: How significant a research center has the Salk Institute become?

Benzer: It's now become quite a significant place. Dulbecco got the Nobel Prize while he was there [1975], but it was based on work he had done at Caltech. Crick got the Nobel Prize [1962], again for work done long before. Then they hired Roger Guillemin, who worked on somatostatin, for which he got the Nobel Prize [1977]—but again, it was for work done before he came. I'm trying to think of any big bang that's come out of there—not too obvious. It's still relatively small. There is fine work going on in a number of fields, and they've recently built up neurobiology in a serious way. They've got Charles Stevens from Yale. They had Floyd Bloom, who was an outstanding brain physiologist but left to go to Scripps, I think partly because of friction with other people. Guillemin has left. Dulbecco left, to get the hell out of there; he went to England, partly because his wife is English. They didn't want their daughter to have an American education, so they went to England for a year or two, during which time he got the Nobel Prize. By then Fred De Hoffman was the president. He had previously been vice president in charge of research at General Dynamics, and he recently died of AIDS contracted from a blood transfusion. He was reasonably successful in bringing in money. But because he had a lot of jet-set friends and a lot of travel to and from Europe, there was some question along the lines of, "What are you doing with it?" When Dulbecco got the Nobel Prize, De Hoffman flew back and forth between La Jolla and England to seduce him to come back, which he succeeded in doing. This may have had something to do with the fact that Dulbecco was approaching British retirement age, which is pretty strict in England, plus Salk was offering him more blandishments. So Dulbecco did go back.

Lennox left; he couldn't take the infighting there anymore. He went to England and stayed there.

Besides the issue of money, a lot of the infighting had to do with organizational structure. They had to construct that from scratch, to the point where they now have assistant professors and full professors just like any academic structure, except for having the students. It's a big struggle, to reinvent a structure, and they fought over every aspect of it. Having achieved the power to make these decisions, the Fellows were burdened with all kinds of crap. Lennox once showed me the agenda for a Fellows' meeting, about thirty items, the last one of which was dogs. This had to do with the problem of dogs wandering around the institute.

Well, that's the Salk Institute. But we had these wonderful summers, for five or six years,

which were really terrific. And then I'm not sure exactly why it petered out. There may have been a question of whether money continued to be available for this. I had some problem in choosing one or two people from Caltech to come with me; there would be jealousy on the part of the others. There was also the problem of, we went to La Jolla every summer; we never went to Europe or anywhere else. So things sort of wore off.

SEYMOUR BENZER

Session 9

January 18, 1991

Begin Tape 9, Side 1

Benzer: I started at Caltech in the fall of '67. At the time, this particular room was one big room—a conference room. I had it carved up into three spaces. It had to be built into a lab pretty much from scratch. Some of that may have started while I was still in Sperry's space upstairs, although I'm not exactly sure of the chronology. But the only negotiation, to my recollection, is that Caltech just did everything the way I wanted, including start-up money. There were two hang-ups. One was about telephones. George Beadle, when he was chairman, had hired an executive assistant named Jerry Fling. Jerry Fling would set down the rules all over, and one of them was not too many telephones. They'd have a phone out in the hall for each group, but nobody would answer it, because the chance of it being for you was one in ten. And if you wanted to make calls, you'd stand out in the hall. I'd experienced that in Sperry's group, and I didn't like it at all. I'd been spoiled at Purdue. So one thing I insisted on was telephones. So we got a telephone in every room of my lab. Jerry Fling left at a certain point, went up to Santa Cruz. But his ghost was hanging over this place for a long time.

Lody Kempees carried on the tradition after he left—other things kept being done just because that's the way Jerry Fling used to do it. Including telephones. Each year, when the telephone situation was reviewed, Lody would come and ask me, "Can I please take out a few phones?" She finally managed to take out quite a few of the phones, which I found weren't needed quite that much.

The other thing was secretaries. Jerry Fling had organized the secretarial pool, and I was used to having my own full-time secretary. Ray Owen was the chairman when I was appointed. He said, "You know, it's our tradition not to have individual secretaries." I said, "Well, I'm used to having my own full-time secretary." In the end, he said, "Well, if that's going to make a difference between your accepting the job or not, then let's do it this way. You try out the secretarial pool. If that works, OK. But if you need your own secretary, then you can have it." So I said, "Put it in writing." And he did. The secretarial pool turned out to work quite well.

I've not, in fact, needed a full-time secretary.

Aspaturian: Who did you work with most closely when you first came here?

Benzer: You mean other faculty members?

Aspaturian: Yes.

Benzer: The one who was most important to me was Ed Lewis, because he was the *Drosophila* guru, and he was tremendously helpful. It wasn't only the fact that he had the whole *Drosophila* kitchen and dishwashing setup going, which he still manages. He actually found Evelyn Eichenberger, who was rescued from a job in a factory, I think, packing valves into boxes. She was a friend of one of his technicians. Ed Lewis took her into his place and had his technician train her to do *Drosophila* genetics manipulations. And that was a tremendous boost. She's still with me; this has been twenty-five years, because she started with me even before I officially started on the Caltech payroll. I don't know what I would do without her if she retired. When people come back to the lab, after having left years ago, Evelyn is now the only one they knew who's been a mainstay and a tremendous help through all these years. Very reliable, sweet lady. So she was the one I worked with. [Laughter] She did a lot of the manipulation of stocks, and I did experiments by myself. But Ed Lewis was the main resource. Other people who were often helpful resources were Herschel Mitchell [professor of biology, emeritus], who was in the lab just next door in Alles [Gordon A. Alles Laboratory for Molecular Biology]. He was a *Drosophila* geneticist but more biochemical. He was often very helpful on that level.

Beyond that, I was able to draw advice and equipment from various people, but I didn't have any strong collaborations with other faculty members, nor do I now, actually. It's hard enough keeping up with my own people. There was an exception a few years ago with [professor of biology] Elliot Meyerowitz and two postdocs in my lab and two in his lab. We did a big project together. But mostly I've not had any real collaborative interactions with the faculty.

Aspaturian: Were you brought in as a professor of neuroscience?

Benzer: No, I was brought in as a professor of biology. That changed some years later, when Robert Sinsheimer was the chairman [professor of biophysics and chairman of the Biology Division 1968-1977]. He came in and said, "I'd like you to be the James G. Boswell Professor"—I guess they got the money for some chair, and they picked me. And they called it a neuroscience chair. I found that a little awkward at the time, because I didn't quite think of myself as a neuroscientist. But I went along with it, and I guess I grew into the job. James Boswell is the nephew of the original James Boswell for whom the chair is named. I don't know if I told you the story about James Boswell when I was a postdoc with Delbrück. Someone in Development hooked up with James Boswell, who had shingles, which is a virus that affects the nerves. He came around and said he would give money for someone to work on animal viruses to understand them better. And we were working on bacteriophage, which of course attack the viruses that cause diseases in bacteria. Delbrück called Renato Dulbecco and me into his office—we were both postdocs—and told us about this. And I said, "Forget it; I'm not interested." And Dulbecco said, "Yes, I could get interested." So Dulbecco picked up the animal viruses, and as you know, he was quite successful at it. This current Boswell is the nephew of the one with the shingles, if I'm not mistaken. I think he's a big landowner in California. Every few years or so, the Development Office tries to set up a luncheon appointment between him and me. And it never works. Maybe we're too radical or Communist or something. I'm told he hates Caltech for some reason. There's some problem in the relationship. It's a curious history.

Aspaturian: What was the division like when you first came here permanently?

Benzer: It was smaller; it was friendlier. Some of the people were old timers, even dating back to when the department was first formed in the thirties by Morgan. Sturtevant was still alive. He was fun to go and talk to. He was emeritus, but he was still working up in the space which is now Ed Lewis's. I remember going to him with my first discovery. I had decided to study phototaxis and simple behavior, and I had discovered that flies that had only vestigial wings did not run to the light. When I told this to Sturtevant, he said, "Oh, yes, that sounds familiar." He had all of his and Morgan's reprint files out in the hallway upstairs, which were a great resource. He went to these files and took out a paper from 1917, when he was in Morgan's fly room at Columbia.

Another geneticist had been studying phototaxis on flies. And Morgan said, "Why don't you pull the wings off and see what happens?" So this guy had found that without the wings, the flies don't run to the light. If you take off one wing or half of each wing, they go with half the enthusiasm. But that paper also mentioned another mutant that had normal wings but did not show phototaxis. That mutant was called "Tan" because of a light body color.

James Bonner [professor of biology, emeritus], who is still here, was here practically from the start of the department. At that time, Jan [Cornelis A. G.] Wiersma was still here. He was the first faculty member that Morgan recruited. I think he hunted all over the world, including Europe, to find out who was the best neurophysiologist—I don't think neurobiology was a word yet. He ended up with Wiersma from Holland. And Wiersma brought along [Anthonie] Van Harreveld, who was also still here. They seemed to be infinitely old—I think they were fifty or something like that—at the time when I was a postdoc. But by the time I became a professor, they were approaching retirement age.

Another person who was helpful at that time, hired as a technician, was Maria-Paz García-Bellido. She's the wife of one of our current Fairchild Fellows, who's quite famous and was then already well-known as a *Drosophila* geneticist. His wife worked in the lab as a technician. She was doing experiments on transplantation—if you take a piece of brain out of one fly and put it in the abdomen of another fly, would it make nerves and would it connect up? The results were never terribly clear, partly because we didn't have very good grasp of the histological techniques at that point to see what was really happening inside. And then she left, and became a PhD, a professional *Drosophila* geneticist. She's now working in Dr. Lewis's lab. [Antonio] García-Bellido is working with Eric Davidson [Norman Chandler Professor of Cell Biology] on the sea urchin embryos; that's a new adventure for him.

The first postdoctoral fellow I had was an absolute disaster. He was a Vietnamese who got his PhD from Purdue and came here. He kept very much to himself. He claimed to make some findings, but when I asked to see his research notebook, he said, "It's all up here." This finally came to a head, and he had to leave. The next I heard—this was during the Vietnam War—he had gone back to Vietnam. The next time I heard about him was when Ed Lewis came to me with a manuscript that this guy had written and sent to Linus Pauling, asking him to put it in the *Proceedings of the National Academy of Sciences* with a Caltech address on it, based on

work he was supposed to have done in my lab. It was a completely idiotic manuscript, and much less than I could sign off on. [Laughter] Linus Pauling had sent it to Ed Lewis, saying, "It's about flies; why don't you give me your opinion on it." And Ed Lewis came to me. So that never got published. I have no idea where this guy is now. But it was an absolute disaster.

I've had better luck since then. My first graduate student was Ronald Konopka, who had come from Dayton, Ohio. Initially he was interested in plants and the fact that they have a circadian rhythm in response to the amount of light they get. The flowering depends on the light and dark periods. He worked the first year with James Bonner, but he switched from plants to *Drosophila*, because *Drosophila* have a circadian rhythm also. His project was to isolate mutants that affect the circadian rhythm. The whole idea of my enterprise was this—you have behavior, and a lot of it is innate, especially in *Drosophila*. And if you want to understand behavior in relationship to genes, you make a mutation that knocks out one gene at a time and see what that does to behavior. Just as in biochemical pathways in bacteria, for instance. You isolate mutants that don't make the end product, and various mutations can block one enzyme or another along the steps of the path. So the idea was to use that for behavior, and it worked. I first started working with phototaxis. At the beginning, I had to relearn a lot of things that are obvious to people who study learned behavior—like the same stimulus doesn't always give the same response. As I told you earlier, the way I studied phototaxis initially was just to take two test tubes and put them end to end and bang the flies down to one end. We mutated the flies according to a method that Lewis had worked out, by feeding them nasty chemicals that attack the DNA and cause mutations with a high frequency. And then we isolated the mutants by putting the flies in this infractionating apparatus and doing the type of successive fractionation I mentioned before.

The problem was how to move one set of tubes against another, be able to shake the flies down to one end, and then shift the tubes. So I went over to central engineering, to the people who had built the Mount Palomar telescope. They made a machine—two metal drums with holes for test tubes, two rays of tubes that would rotate with respect to each other. But gradually, this evolved into a much simpler apparatus, and we found many different types of mutants. They weren't only nonphototactic mutants—we also found flies that were naturally sluggish and didn't care about moving to light or away from light. We got a whole set of mutants like that. And

there were other ones where just the act of banging the test tubes made them go into a kind of epileptic fit and then into a coma. We even found ones that were photonegative—they'd go away from the light instead of to the light. We found a whole spectrum of mutants.

Then the question is, What's wrong with them? This was when Yoshiki Hotta came to work with me. He came from Japan and was trained in electrophysiology. He'd been working on guinea-pig-intestine physiology. He was just here and gave a seminar this week. It took a certain amount of courage and imagination on his part to come and work with me. [Laughter] I'm not sure; I should ask him exactly how that happened, why he latched on to me. But it was a very lucky event, because he's an extremely intelligent man, imaginative and intrepid and a joy of a personality—a complete contrast with that first postdoc. He's quite prominent in Japan now, and made a good career. The project he did is something that came from Sturtevant originally, the idea of using mosaics to map out—to relate—body parts. There are ways of making mosaic flies that are partially mutant and probably partially normal. And Sturtevant had had the idea of how to make maps out of this, based on the pattern of how *Drosophila* develop. Initially the nuclei in the egg multiply, and then they migrate to the surface of the egg, where they set up just a single layer of blastoderms. Already at that stage, apparently, each part of the egg is destined to become a certain part of the fly. Sturtevant had the idea of using that for making maps that relate the blastoderm to the different parts of the body. Sturtevant was the guy who had the idea for mapping the genes on the chromosome and their order in the first place. He actually had in the drawer some data that he had drawn up on 400 or so flies. I think they were the yellow body marker for the mutant parts. So we had drawings of which parts were yellow and which parts were brown for each fly. And there were different combinations.

The problem was how to make maps out of those. Sturtevant had had the idea for the maps, but he never really worked it out. So a postdoc in Lewis's lab and García-Bellido took Sturtevant's data and showed that you could make maps of the body parts of the fly that could then be related back to the positions of the primordial cells in the blastoderm. What Yoshiki Hotta and I did was to extend that to behavior. If you have a fly with mutant behavior, the question is, what part of the fly has to be mutant in order to produce the behavior? We made mosaics in all different combinations of parts. We wanted to see which genes give mutant behavior, which give normal behavior, and how that relates to the body parts on the map. And that way, we would be able to put on the map the focus for that mutant behavior, which often was

not any of the visible body parts but the nervous system—the internal parts. So that worked out rather nicely. Also, some of the mutants were interesting. One of the mutants is one called "drop dead". When the flies hatch, they seem quite normal but after a couple of days, they start staggering around and they drop dead. We just picked that mutant up again now, because of my interest in brain degeneration in humans. We want to see if we clone that gene, what the possible correspondence is to the human gene having to do with brain degeneration. Most analysis with mosaics shows something: if you make mosaic flies where, on the average, half the body tissue is drop-dead mutant and half is normal, a great majority of flies—like ninety percent—don't drop dead in the mosaic. And that suggested that if half the brain is normal and half the brain is mutant, the normal half can supply some factor that keeps the other half from degenerating.

We know from the mosaics how to map to the brain. And for further analysis, you could show that in the drop-dead mutant, there must be two foci that had to be mutant in order for the mutant behavior to happen. The counterexample was a mutant where the broad wings stay put. When we looked at the muscles that control the wings, we found they were degenerated—a kind of muscular dystrophy, if you will. When we made mosaics of that mutant, the great majority of flies had the condition. So that's a domineering focus, as opposed to the submissive focus you see in drop-dead. We made up the words "submissive" and "domineering" in analogy with recessive and dominant mutations.

When we made these maps for behavior, we had to make a name for the units of distance on a map. Although Sturtevant had worked out the idea of mapping the genes on the chromosome, somehow the unit of distance got named after Morgan. One-percent morgan means one-percent chance of crossing-over among the progeny. We decided to make up for that by naming our unit after Sturtevant—we called them sturts. If a behavioral focus is ten sturts away from, say, the determinants of the leg, then that would correspond to a ten-percent chance among mosaics that the two would have different [word unclear]. But, you know, that was a sentimental thing with me, naming it after Sturtevant, who was very much liked and admired.

Aspaturian: Was that rare in the division when you came?

Benzer: [Laughter] No. Well—no more so than for any other area. Well, Wiersma was not the most magnetic personality. He did have bad teeth. In fact, Delbrück used to say, "Whenever

Wiersma talks, you have the feeling of teeth sputtering out on the floor." [Laughter] He was a decent person but not a charmer. But Van Harreveld was very much a solitary man, a very quiet, nice man. We lived in the same apartment house for years, but I had virtually no contact.

Aspaturian: You were living in an apartment all this time?

Benzer: We had had a house in Indiana that was a lemon. We were so glad to get rid of it when we came here in '65 that we didn't want to have anything to do with a house. And that was one of the great mistakes of my life, because we could have bought a house on Lombardy Road for $50,000. It was very stupid. It wasn't completely stupid because instead of worrying about the fuse box or the furnace, I was able to concentrate completely on my work. Van Harreveld had the same attitude, just lived all his life in an apartment.

Bonner was always a gung-ho individual—still is very much the same. He had quite a large group of people working with him. Van Harreveld was largely solitary; he had maybe one postdoc. Wiersma didn't have a very large group. These guys worked with their hands in the lab.

I remember one adventure that was very nice. Wiersma worked with crayfish, electrophysiology, sticking electrodes in the muscles and in the optic lobes. I asked him once where he got the crayfish from. He said he went out and caught them. I said, "Take me along." So he took me. It was out along Rosemead. If you go way south on Rosemead, there are a lot of transmission lines, sort of a desolate area; it's like getting near the Whittier Narrows area, maybe. He had a creek there where he used to catch crayfish. I always admired his skill and his courage. There was always the danger of getting bitten, and he knew how not to. That was nice. As I recall, that was about the only social interaction I had with him. He was also in Cambridge in '57-'58, when I was there on leave from Purdue. And we had no interaction there to speak of. But that was more than I had with Van Harreveld. So I was not getting much from the neurobiology community.

The one I did have a little interaction with was Felix Strumwasser.

Begin Tape 9, Side 2

Benzer: He was a card-carrying neurophysiologist and was rather antipathetic to the genetic

approach. When I gave this presentation on *Drosophila* and behavior to Sperry's group, he was one of the naysayers. He had a physiology setup. And I had a bright idea about an experiment involving *E. coli*. Normally it's a rod-shaped bacteria, but if you irradiate it with ultraviolet light, that prevents cell division, so you end up with a long snake. And I thought, Great, we'll stick an electrode at one end and try to pick up a propagated action-potential at the other end. So I went to Strumwasser and said, "I'd like to try this out." He took an electrode and he showed me a setup, all this electronic equipment. Took an electrode and stuck it in, and checked on the oscilloscope and nothing happened. He said, "There it is, go ahead. Feel free; choose the equipment, and go ahead and do it." And he left. I didn't know what knob to turn or whatever, so nothing ever came of that.

I did reprise that same kind of experiment years later. This would be in the early seventies, during one of my summers at Salk Institute. Yoshiki Hotta was with me then. He came in '69. And we invited Julius Adler, who works on bacterial chemotaxis at the University of Wisconsin. We spent the summer with the idea of trying to get electrical signals out of bacteria. There was a mutant bacteria that didn't have a cell wall. So instead of making rods when you irradiated it, it would just grow up into big blobs. We spent most of the summer trying to measure action-potential in normal bacteria, all packed together, trying to measure bulk electrical properties. But then we finally got these big ones, and Yoshiki put the electrode in, and it just went *poof!* The other day, someone mentioned that we could have discovered the patch-clamp electrode at that time, which created a big bang about ten years ago in physiology. We just had a little piece of membrane on the end of the electrode and you measured the action-potential out of that. But we didn't have that frame of mind and the technology was not there. But we had a fun summer, trying to do that. Since then, people have succeeded in doing that experiment, so maybe we were too far ahead of our time. But the amusing thing was that at the end of summer, when everything was a complete bust, I said, "Let's just take the afternoon off." We went out on the cliff at the Salk Institute. What we did was run around, catch butterflies and other bugs. And in the course of the afternoon, we had confession about what would we work on if we really could. Adler, who was working on bacteria, said he would really like to study insects and butterflies. Hotta said he would like to study dogs and cats and animal behavior—he was an MD, I think, but the idea of working with regular patients didn't appeal to him. And I said, "Well, I'd

like to work on human behavior." So all of us had compromised on what we wished we could work on, because we had had to choose systems where you could really do something. But that was very revealing. It was a wonderful afternoon. [Laughter] More fun than we'd had all summer.

Back here, Delbrück was around, but I saw him mostly socially because there wasn't too much communion. He was working on *Phycomyces* by that time, and I wasn't terribly interested in that. Still here also was Jean Weigle, who had been my roommate and a close friend when I was a postdoc here in Delbrück's lab. But he died [in 1968] of a heart attack. His wife had died sometime before, and he was living alone in the Athenaeum when he died.

Dulbecco had left; he went to the Salk Institute. Besides the attraction of the Salk Institute, I think he did a certain amount of grumbling about the Jerry Fling methods by which our division operated here. I don't know any details, but at one point, I had a glimmering that he felt rather constrained and annoyed about some of the things that he couldn't do here. Plus, he got a divorce, so he had a very strong reason to want to get out of town. But I think he was unhappy about Jerry Fling. Which was a good thing, and very timely now when funding has forced us to be a little more thrifty.

Pretty soon I'm branching out into a different kind of mutants. Ron Konopka found the circadian rhythm. We had the drop-dead mutant, we had all these nonphototactic mutants, we had mutants in which the poor phototaxis was due to the eye receptors degenerating, like in retinitis pigmentosa. Now that the genes that cause retinitis pigmentosa have been cloned in humans, this particular *Drosophila* defect turns out to be very analogous to some of the human forms. The structural change in the rhodopsin gene in both organisms leads to degeneration of the photo cell. More and more, that's why I'm so interested in this proposal; more and more of these homologies are coming out. In fact, the NIH's [National Institutes of Health's] National Eye Institute has organized a meeting on the subject of *Drosophila* as a model system for studying human eye diseases. They're going to have the vertebrate eye people and the *Drosophila* eye people both present their cases. I'm especially interested in just that problem.

So people are coming around; it's taking a while. But this was actually initiated by the director of the National Eye Institute.

In that respect, one of the things that happened here very early in my stay was that

Wiersma had done all this beautiful work on neurophysiology in the crayfish. There was a meeting here with NIH people to try to convince them that the invertebrates were worth working on at all. And Wiersma and Don Kennedy, who's now president of Stanford, talked about their studies of crayfish behavior. So did J. Z. Young, the man who developed the squid giant axon preparation. These guys from the NIH needed to be convinced. I don't think there was any immediate conversion on that occasion, but now, if anything, they seem to have an inferiority complex if they're not working on *Drosophila* or on nematodes, where you can do the molecular stuff. Because they overcompensate by saying that these are not real organisms. So that's gone full circle, I think.

Aspaturian: Would you say that *Drosophila* is about the most complex organism with which you can get really rigorous results in this kind of research?

Benzer: Well, I don't know. It depends on what you want to study. You can get rigorous results with humans now. Modern technology makes it almost as easy to work with humans as with flies, and that's why I have the courage to get into the human business now.

Aspaturian: But there are so many more behaviors to look at in humans.

Benzer: Humans are wonderful. There's a book on viewing disorders of man, containing 4,000 hereditary disorders in humans, one or two thousand of which have been actually mapped on the chromosome. Many of these have behavioral components, and hundreds affect the eye. There's a similar book on *Drosophila*. And we're finding that more and more of the genes correspond to one another.

Aspaturian: But surely the *Drosophila* book is more comprehensive as it applies to *Drosophila* than the human book is as it applies to humans.

Benzer: The beauty with humans is that the mutants are self-selecting. They come into the clinic, out of a population of three billion or more people. I would not make a statement like the

one that you made.

It's true that we have to be very careful, because very often when you focus in on analyzing some part of a complex organism, it's because you assume that it may be more amenable to analysis than an overall simpler, smaller organism would be. For instance, neurophysiologists quite commonly work on vertebrate muscle, whose individual fibers tend to be something like two or three microns in diameter. And getting an electrode in is very difficult. But when some of my students—Bill Harris, Lily Jan, and Yuh-Nung Jan—took a look at the body wall muscles in *Drosophila*, they found that each one of those is a big, single-celled cylinder. It contains many nuclei, but electrically it's just one membrane around—about 80 microns in diameter and 100 microns long. Any idiot on the first try can stick an electrode into one of those. And it's tremendously advantageous compared with vertebrate muscle fibers. A lot of physiologists still have the idea that *Drosophila* is too small to work with electrodes. If you look at a particular part of it, it's in effect much bigger than anything else.

Aspaturian: I wasn't thinking at all of sizes of complexity. I would just think in human studies you'd get so swamped by the range of complexity that it would be very hard.

Benzer: Well, again, it depends on what you study. I'm trying to give you an example of how smallness is one of the criteria. Largeness is another criterion. If you try to do an electroretinagram of the human eye, you get about 50 microvolts; if you do it on a fly, you get 15,000 microvolts. [Laughter] The fly is small; physiologists say, "Oh, too small; why bother?" And you get just the opposite result.

In humans, of course, you have the possibility of communication when studying behavior, and more interesting kinds of behavior. There often can be big surprises in what is amenable to analysis. And after all, the whole molecular biology area derives from humans. The whole idea of one gene/one enzyme harks back to the inborn [inaudible] of metabolism—the discovery of phenylacetyl—being a specific gene. And molecular biology in the more recent age was largely catalyzed by Linus Pauling's discovery that sickle-cell anemia involved just one amino acid chain. So humans mustn't be underrated.

SEYMOUR BENZER

Session 10

February 1, 1991

Begin Tape 10, Side 1

Aspaturian: I was wondering what your opinion was of the Caltech students you taught, undergraduates and graduates. What has it been like to teach here?

Benzer: Well, the classes were usually rather small. I've been teaching a course in behavioral biology, which is mostly taken by middle-level undergraduates every year. And then every other year I teach a graduate course on a chosen topic. Professor Mark Konishi and I have been sharing courses, and we alternate. So they're quite different. The graduate course is usually organized around some fairly defined subject in which we choose a set of readings—a survey on several papers in the field—and the graduate students take turns and present them. Those often are very rewarding, for the kids really delve into the subjects with great gusto. We learn a hell of a lot from it, so that's very nice.

Aspaturian: Do you have mostly biology students, life science students?

Benzer: Mostly biology students, but occasionally someone will stray in from mathematics or economics, engineering. There's always one or two every year who are just interested.

Aspaturian: Have you worked with SURF [Summer Undergraduate Research Fellowship] students at all?

Benzer: Yes, we've had two SURF kids. Early on, before SURF, I had a senior who was going for a dual degree and stayed on for a fifth year. He worked in the lab, and he was terrific. We had our first SURF student a few years ago—a real go-getter who seemed to be into everything. He did a bang-up job in the lab here, and then we found out he was also teaching genetics in a high school. He also organized the International Students' Day that we had here about two years

ago. He's a Syrian kid—Bassam Mora. And then he worked in [David] Van Essen's lab. He was just all over the place. Partly I think gathering credentials and recommendations for going on to medical school. He was one of those superwhiz types—very skillful, ambitious, and did the job. I was very impressed with him—you know, "the most likely to succeed." [Laughter] He was it.

Last year we had another SURF student who was not quite up to the same level, but nevertheless did a nice job. And we've had occasional students who come in to work as part of a biology course in which they can get credit for doing research ten hours a week. Those students have been quite variable and not terribly rewarding, because all of a sudden they disappear for three weeks; they're studying for exams. They're cheap, because they don't have to be paid, except in credits, but I don't think that has been tremendously successful. It's more useful for the kids than for us; we don't get much out of it.

Aspaturian: Do you enjoy teaching?

Benzer: Not particularly. Given a choice, I would not, because I find it very disruptive. If I know I have to give a lecture, I'm spending days before that thinking about it. And that's very hard to reconcile with doing research. On the other hand, I can't deny that it has its rewards in terms of turning on an occasional student. There was a cynic who summed up teaching as casting false pearls before real swine; it's not that bad. [Laughter] Caltech students are so bright that it's the ultimate pleasure to deal with them.

I had taught earlier on at Purdue. As a graduate assistant I taught physics, and later on I taught biology. But when I was made a Distinguished Professor there, they said, "Well, you don't really have to teach if you don't want to." That was one reason why I was attracted to jobs at places like Salk Institute, which wouldn't require any teaching. When I came here, I was told, "We don't have any such thing as research professors. Everybody teaches." But there was no pressure put on me. Ray Owen, the chairman when I was hired, said nothing about it; then toward the end of the first year I said, "Well, I think I'd like to teach a course." [Laughter] And he said, "Oh, well, that's very nice."

Aspaturian: Was there peer pressure?

Benzer: No, no one ever said anything. I thought that was remarkable. But I knew it was expected, sooner or later. There's usually a year's grace period where you're not required to teach in any new job at a good university. So I developed this course in behavioral biology.

Aspaturian: Are you and Mark Konishi still teaching it together?

Benzer: Yes. It works very well, because he teaches the ethology part and I teach the behavioral genetics part. So his emphasis is purely how the behavioral systems work, and mine has to do with how they develop and how you can use genetics to analyze them. We've gotten reasonably good ratings and feedback. We never got the turkey award, like some of my colleagues. [Laughter] I don't know if they still give turkey awards. Two of my distinguished colleagues got them. [Laughter] I won't mention any names. But I remember one particular professor who's in astronomy, and the students said, "Please, President Brown, find something else for this guy to do rather than teach. He's absolutely terrible." [Laughter] Those reviews are distorted, because it's often one or two students who write the report. If you're lucky, you'll get an evaluation from someone who enjoyed the course.

Aspaturian: Speaking of your distinguished colleagues, you've been through several division chairmen here: Owen, Sinsheimer, Lee [Leroy E.] Hood.

Benzer: When I came, Lee DuBridge was president and Ray Owen was chairman. After him was Sinsheimer. Norman Horowitz [professor of biology, emeritus; division chairman 1977-1980] was after Sinsheimer as sort of an interim chairman. When Sinsheimer took over from Ray, I remember we had a musical production that had to do with the transition. Do you know about this biology tradition, the musical production?

Aspaturian: No.

Benzer: It goes way back to the late forties when I was a postdoc here in Delbrück's group. Through good fortune, there were two talented postdocs—Ted Harold in biology and Jack

Dunitz, a Scotsman, in chemistry. Harold was very good on the piano, but he couldn't read a note. And Dunitz was very imaginative in making up scripts. And the two of them, stimulated in part by Beadle's wife, created this traditional Christmas event at which an all-musical production was put on. Some of those were recorded; I have copies of them. We published records—this was before tapes—and enough people wanted to buy them. Some of them are quite funny. Delbrück was quite a ham; he loved to be in them. In fact, at his memorial service, I played some of the recordings of Delbrück singing from those shows. Some of the songs were very clever. One was: "When I was a youth/I wanted to be/A full professor of biology." And telling how you went through all the stages.

Aspaturian: Is this a takeoff of *H.M.S. Pinafore?*

Benzer: Yes. "But that was very hard to see/Because my IQ was only ninety-three." And then he gets promoted.

I remember specifically that there was a musical when Sinsheimer took over from Owen. This had the plot of the old king stepping down, and the question was which of his princes would inherit the kingdom. We had people imitating the various professors who were competing for this, with funny names. Professor [Giuseppe] Attardi was mimicked by one of his students who was Prince Retardy. He was gesticulating, and waving his arms and quoting Italian from Dante's *Inferno.* [Laughter] Stuff like that. The greatest fun was during rehearsals. Once I remember we had these wonderful ideas to really devastate somebody, and Delbrück said, "Well, it would be funny but we must leave no permanent scars." We used to perform in Culbertson Hall, which is now gone. It was perfect for that.

Aspaturian: Whom did you perform for?

Benzer: Mostly the biology department people and their families and guests. In this play, I played Prince Heimer, and I wound up imitating Bob Sinsheimer. My feat was the creation of life—this was a time when he got a lot of notoriety for having synthesized a virus of DNA. They brought on a trash can, and I threw all sorts of ingredients into it, made abracadabra, and then out

came a graduate student. And I say, "Look, I created life." And someone else says, "That's not life; that's a graduate student." Anyhow, that was sort of fun.

This tradition has since petered out. The last one that I can recall was in '69 when Delbrück got the Nobel Prize. Ted Harold has since died; he went back to England and became a master of some student house in Sheffield, I think. Dunitz went back to Europe and is quite famous now. He's a professor—I think in Zurich.

Getting back to who's the next chairman, they never impinged on me very much. The only dealing I had with Owen was over this business of having a secretary, which I mentioned. And I didn't have to deal with the president's office beyond shaking hands with Lee DuBridge when they gave me the job. Twenty years went by that I wasn't in the president's office or the provost's office, except for a few occasions more recently. But as far as dealing with the chairmen, it wasn't necessary; everything ran very smoothly. Sinsheimer came in one day and said, we've got this chair in neuroscience, the Boswell Chair. I've been lucky. It's real nice. After Sinsheimer left and went to Santa Cruz, we had Norman Horowitz—I think he was considered an interim chairman. Lee Hood was next. And now we have John Abelson [George Beadle Professor of Biology]. So I've been under five different chairmen.

Aspaturian: How about the various presidents?

Benzer: Harold Brown [1969-1977] made himself quite conspicuous by two ideas. One was to develop a medical school relationship. He said he thought the funding was getting tough for biology—little did he know how tough it was going to get. So his idea was for Caltech to pair up with UCLA to make a medical school. We would do the first two years of basic education of the medical students, and afterwards they would be guaranteed two more years of clinical experience at UCLA. And then they could be doctors.

Aspaturian: This would be at a post-undergraduate level?

Benzer: Yes. A medical school, after college.

Aspaturian: When did he propose this?

Benzer: When he was here. He thought it was a bright idea. So two things happened. In the Biology Division, it went over like a lead balloon: Why should we be knocking ourselves out teaching these guys, and then they go away elsewhere and don't even do research—they become doctors? What's in it for us? The second was that the Caltech administration called in an advisory committee, including members of the medical school, to discuss what the funding situation would be like. And the medical school people said, if you want to bankrupt Caltech, the best way to do it is to start being a medical school. [Laughter] I think that's what killed it. That was Brown's first big deal.

The second big deal was Immaculate Heart College.

Aspaturian: How did you feel about that?

Benzer: I was horrified by it. Horowitz was horrified by it, because he had an interview with the woman who was the head of the Immaculate Heart Biology Department. They had an argument over whether evolution should be taught in biology classes. [Laughter] Ed Lewis, who's usually very quiet, actually got up in a meeting and said, "Have we forgotten Galileo so soon?" [Laughter] But what was amazing was, it was sort of an off-the-top-of-the-head idea. I don't know how it was generated, by Brown's wife meeting the wife of Immaculate Heart's president at a cocktail party, or something like that. They just came up with this notion.

There were two elements of rationale in it. One was, there were no girls here, and we're deficient in humanities. The other was that Immaculate Heart was about to move, because they were on bad terms with the bishop and had to get out. They were going to move to Claremont, so that was the time to get them. And Brown had the idea that we'd set them up here between here and Lake Avenue, and that would sort of give us a buffer zone against the deterioration of the neighborhood.

The Caltech faculty was really badly split on this, because so many of the faculty were concerned about the fact that the boys were so deprived in their social life, which was certainly a serious issue—still is. And a lot of the Caltech students were all for it. They were told, "Look, the Caltech students get 750 on their SAT exams and the Immaculate Heart girls are getting 435. What do you think about that?" The boys said, "Oh, that's just great." [Laughter] So they

weren't really concerned about Caltech's welfare.

I think it was eventually killed by the Caltech trustees. So these were Harold Brown's two big accomplishments at Caltech. I'm sure he did something else, but this is what I remember him for. [Laughter]

The next thing was the rescuing of the hostages in Iran, when he was Jimmy Carter's secretary of defense. He's one of these really bright quiz-kid types; but some of his ideas were a little bit too much.

Aspaturian: What about Murph [Marvin L.] Goldberger [1978-1987]? Did you have much dealing with him?

Benzer: Yes, I had more dealings with Murph on a personal level, because we had mutual friends. So from the beginning, we've had contact. He likes Chinese food, and we'd go out occasionally for that. He and Mildred have a hobby of cooking Chinese food, although I never got to eat any of their cooking. We had a personal rapport—not too close a contact but occasionally social encounters. He was busy hustling for money and I was busy doing research. But I think we understood each other.

Apparently he bombed, though, as president. He had this terrible friction with [then Provost] Robbie [Rochus L.] Vogt [R. Stanton Avery Distinguished Service Professor and professor of physics]. I don't know too much in the way of details. In the end, Murph succeeded in getting Vogt fired after some kind of strong encounter. But I think that was just a culmination of a long period of antagonism where Vogt was still trying to run the place and ignoring Murph, and in some ways being much more effective. Like getting the money for the Keck Telescope, I think was largely Vogt's doing. So we had a lot of heads rolling. Murph fired Vogt, and Murph got fired in the sense that I think he could have been renewed, but he wasn't.

Aspaturian: Is that what happened? He had a contract that expired?

Benzer: Yes, I think he came to the end of his ten-year period. He was getting older, but I think he still could have been renewed. But they didn't do it. I don't know the details. Maybe some trustee didn't like him. He got a nice job [as director] at the Institute for Advanced Study, which

he's retiring from now. Mildred's had a terrible time with her health. So Murph has announced that he wants to retire this coming June, and earlier if they can find a successor for him. They want to move back to California, either Pasadena or La Jolla. So they may be coming back. I don't think they wanted to leave California.

And then what happened next? Barclay Kamb [Barbara and Stanley R. Rawn Jr. Professor of Geology and Geophysics], I guess, replaced Vogt as provost. And then Barclay Kamb fired Lee Hood as chairman [of the Biology Division]—well, maybe that's not the way to put it. Lee Hood stepped down as chairman; and then the next thing was Barclay got thrown out.

Aspaturian: Was Lee Hood fired?

Benzer: Well, Lee Hood was asked to step down before he wanted to. He had gotten this big center from the National Science Foundation, and part of the feeling was that that should keep him busy. He already had so many enterprises that kept him away from Caltech ninety percent of the time, if not more. And having that meant he'd have that much less time. So I think it was the right time for him to step down.

But then Barclay got thrown out after that and was replaced by Paul Jennings [professor of civil engineering and applied mechanics] as provost. So there has been a lot of stuff going on that I'm not involved in, but I hope it's settled down for a while now. But I guess that's natural to have with the transitions of presidents.

Aspaturian: I also wanted to ask you about the Mark Tanouye tenure case. I believe he was a colleague of yours, and you supported him.

Benzer: He was originally my postdoc. I was on a search committee to find somebody doing molecular genetics in the neurobiology field. We were considering various applicants. Tanouye was looking for a faculty job. He had seven offers, including Harvard. I said, "Look, he's my student, but he does fit the bill. Maybe you should consider him." So in fact he was hired. And the work he did in the six years he was here was exactly what he set out to do—it was a world-class accomplishment of cloning the potassium channel. What happened was that three of my students started working on the problem here, using the shaker-mutant *Drosophila*. After they

left, they set out to clone the channel in competition. One was Lily Jan and Yuh-Nung Jan, who went to San Francisco. And one was Alberto Ferrús, who went back to Spain. And the third was Tanouye. They all came out with the achievement within weeks of each other. But Mark had this whole prospectus all worked out from the beginning, even while the Jans were off doing something completely different on the hormone of the frog. And when things started working, they jumped in on it. Those people were good. The Jans were outstanding, especially as a husband and wife team. Somehow they got the publicity by one of these flukes where there was a notice in *Science*, I think, even before their article came out. It was very credible and good science, too. And Mark—I have the whole chronicle of this that Mark wrote out, in which I think he behaved in a very gentlemanly fashion. So as I say, this was a world-class accomplishment. The fact that other people did it, too, shouldn't be held against him. But even if it were, he kept pace with them and was not left in the dust. I was particularly pleased by this discovery, because it was something that no one had ever been able to do and could not have been done other than through the *Drosophila* mutant system. So that's one of the really nice things that came out of that work. I think to a lot of the neuroscience community who had been pretty skeptical about *Drosophila*, this was something that they could understand and that touched them where they lived. So it was an important event.

Tanouye came up for tenure. I think there were several reasons why he did not have the unanimous vote of the faculty. A number of people were against him—I'd prefer not to go into those details. But I'm convinced a good part of it was his Japanese cultural background, which favors mild speech instead of flamboyance. He was very mild-mannered and it's easy to believe that he's not very bright. But things were going on in his head. He was just too nice a person to fit the mold of an aggressive Caltech cutthroat. People just couldn't believe he was that smart, in spite of what he had done. So I supported him as strongly as I could, but to no avail. It ended with [Caltech president] Tom [Thomas E.] Everhart—everyone was very impressed by this—actually taking every faculty member in biology into his office and talking, for an hour in some cases, to find out the individual feelings before making the final decision. In the end, he decided not to reverse the decision. I think it was a mistake; I still think so. But I respect Tom Everhart for taking it that seriously. It's hard to get a decision reversed as long as some people are instilling doubt.

Tanouye started looking for jobs. He was offered a full professorship at Northwestern, tenured positions at various other places. He ended up taking a job at Berkeley, where he is very well off scientifically, because Berkeley has an outstanding group in neurogenetics. He's just reinforcing the strength of that group. So their program in this field is booming, whereas ours has suffered.

Aspaturian: I have heard that in the last decade, there has developed a kind of split in the Biology Division between the neurophysiology types and the molecular scientists. Is that true?

Benzer: It was a very real thing, a little like the Arabs in terms of shifting alliances. [Laughter] It was sort of brought into focus in a couple of cases, particularly when it came to making appointments. There's a certain blindness on each side toward the other. We also have some strong political types in the division. We have some people who act like scientific bigots, I'd have to say. But they are a minority. By and large, I think it's a wonderful department. But when it comes to a decision of this sort, there can be a lot of trouble. So there were a few occasions when there were simply very sharp cleavages between the neurobiologists and the microbiologists. But I have found since then that it's not that clear-cut. It's also not obvious to me that one could say that that's quite the case right now. There are individuals who are exceptions, but I don't think it's a valid generalization, at the moment.

Aspaturian: Do you think the shift in chairmanship may have had something to do with patching over some of these cleavages?

Benzer: The shift to John Abelson? I don't think so. There's still some soreheads, but not a lot, and nothing can be done. I'd have to say the split over the Tanouye case was not really a clear-cut neuro-molecular division. So I can't blame it on that. Even among the neuros or among the moleculars, there's a lot of heterogeneity over which ideas are important.

Aspaturian: Do you think that in terms of major issues in biology the division is moving in the right direction? Is it still at the forefront? Is it going to be there at the end of the decade?

Benzer: Well, there are a lot of good guys. When I look around in the faculty meetings at all the people, these are pretty good people. And I was impressed when we recently had a department retreat. John Abelson instituted this. We all went out to Oxnard to a hotel.

Aspaturian: When you say we, who do you mean?

Benzer: The whole Biology Division.

Aspaturian: Including the graduate students?

Benzer: Yes, some graduate students came; and postdocs. John Abelson found a pocket of money to subsidize this, to bring everyone out there for the weekend to the Mandalay Inn Resort in Oxnard. Last year [professor of biology] Henry Lester had been the sparkplug and had organized a neurobiology retreat at that place; and it worked out very well. Then the idea came up, Why not have it for the whole division? It cost a lot of money, and John Abelson found the money—where from, I don't know. Chairmen seem to have a lot of pockets, as they should. You just have to hope they utilize them properly.

It was great. About half the faculty gave short talks about what was going on in their labs. There was a real feeling of community and solidarity. How long that will last, that's another question. Until the next fight in the faculty meeting. But this is an example of Abelson's efforts to get some communal feeling. One of the first things he did was to implement caucuses representing the various biology fields. Anyone could belong to any caucus, like molecular biology or immunology. Some of these caucuses had one or two members; some had a dozen. You could belong to as many as you wanted, but you could only vote in two—I mean, institute democracy. That led to a whole lot of meetings and caucusing; and each caucus was supposed to report to Abelson on what it would like to be doing in the future. Then he had an advisory committee to which the elected representatives of each caucus were invited. I was not on that committee. But when the report of their meeting came out, I thought, "My god, this is a pork barrel situation; this is not a program." So some of us—in particular Giuseppe Attardi and I and Mel [Melvin I.] Simon [Anne P. and Benjamin F. Biaggini Professor of Biological Sciences]—got a proposal together. There were two problems. One was, What are we going to do? The

other was, How are we going to get money for it? Particularly, there was a pitch for getting a new building. We suggested that human biology would be a saleable sort of program, as well as being a field we were very interested in. Giuseppe works on human mitochondria; I'm getting into human biology; and Mel Simon works on mice, which is pretty close. [Laughter] John really went for that; he liked it. That's the kind of thing the trustees would be interested in. So that's been adopted. After all this caucusing, what came out was what three guys suggested. [Laughter] Anyhow, John is very sensitive in getting representative input from the division.

Aspaturian: Human biology—would you envision that as the entire human organism? Or are you talking about a reductionist approach to human biology?

Benzer: Well, then you have to ask, What do you mean by human biology? There are two parts to it. One is what you call a program that you sell to trustees and donors. And the other is what you can actually do.

Aspaturian: Doesn't that bring the dreaded spectre of behavioral psychology onto the Caltech campus?

Benzer: Well, the idea was that it could represent everything from the genome structure, in which some of us—Lee Hood and others—are actively engaged, to development, to behavior and psychology. So it sort of covers everything. All of us, regardless of whether we work on flies or yeast or bacteria, are always putting in our NIH grant applications how important our research is to human health. And it's actually true; we believe in it.

SEYMOUR BENZER

Session 11

February [exact date unknown] 1991

Begin Tape 11, Side 1

Aspaturian: I was wondering how you felt the influx of women into the division had affected it in the last ten or fifteen years. I think biology has more females in it now than any other division on campus.

Benzer: I don't see any effect. I think the women behave pretty much like the men. There are individual personalities, just as there are among the men. So I haven't noticed any difference in that respect, except that we feel more respectable now with having women. It became a serious issue for the NIH. Jenijoy [La Belle, professor of literature] was the pioneer in this, and I think Caltech felt quite threatened by the prospect of losing all its federal grants. Caltech does seem to respond to threats. [Laughter] So no special effort was made, but I think we have some pretty good, well-qualified people.

Aspaturian: Were there any serious divisions among the faculty that you recall over the issue of admitting women to the tenure track?

Benzer: I don't recall any difficulty over the issue of giving tenure to women per se. Just like with the men, some of the tenure decisions were not exactly unanimous. Quite honestly, I think there were a couple of cases where we bent over backwards to favor women. There's a couple of cases where the administration, in effect, overruled the division's vote. The effect of that is a kind of demoralization, so far as what the meaning is of the faculty vote. But I don't think any of these cases involved the question of gender, as far as the faculty was concerned. It was rather a question of the estimation of a person's quality as a scientist. And after the administration got involved, I think there were some disillusioned faculty members, in the sense of feeling they were wasting their time. On the other hand, still being to a large extent a knee-jerk liberal, I feel that it's important to make an effort. And I believe in affirmative action. I think it's not inappropriate

to favor women and minorities in order to try to adjust things over the long range. That's my personal feeling. Not all my colleagues feel that way.

Aspaturian: Has the quality or caliber of the graduate students you're getting now changed a lot, say, in relation to the last ten or twenty years?

Benzer: I wouldn't say that, no. I'd say the students' frame of mind has changed, because now they're only too aware of how tough it is out there. It's tough to get a job; it's tough to get tenure once you have a job; and once you have a job and tenure, it's tough to get grants to keep your research going. And that is very much present in their thinking from the beginning. I think students come in today with an agenda, and that didn't used to be true. It used to be they came to do science. [Laughter] I think they were more daring in doing unorthodox things than they are now. I think that now they very carefully plan out going down a defined track on a relatively safe project, even though it might be not too different from what other people are doing. And you can't blame them. These are the facts of life. The physicist Leon Lederman recently put out a letter on precisely this topic, which has attracted a lot of attention. President Everhart's comment on that was, Lederman puts the case very well, but there was too much emphasis on what's needed for science rather than on what's needed for the country, so far as influencing Congress is concerned. Everhart felt there should have been more emphasis on that part of it. But the kids know that. And the kids who apply to Caltech for graduate studies have always applied to the same five places. And it seems that every year, we agonize over the ones that turned Caltech down. Where did they go? Well, if they went to MIT, that's OK. Or if they went to Berkeley. Occasionally there's one who went to some unheard-of university, and we wonder what went wrong. [Laughter] But that's part of this business of the defined track that we see all the time now. The students are all running around the same track. So there's a change in the whole atmosphere of doing not just biology but probably all science. I think it's probably worse in other fields, like physics. I heard a few years ago that there was one job available in high-energy physics in the whole country—something like that—and several hundred people applied for that one job. Biology hasn't come to that yet, but my students who are applying for jobs tell me they've been told there are 150 applicants. But there are also forty jobs. So it's not as bad as in some other fields. But it seems like it's going in that direction.

Aspaturian: How do you feel about the trend toward big science in biology?

Benzer: Well, it's not my cup of tea. [Laughter] And again, I think it's a matter of the realities of the modern world. But I deplore it; I think it's terrible. Again, whether it's good for the country or good for the scientist can be two different things. One is how much science needs to produce. Another is the fostering of individual thought and creativity when there's no more ivory tower. Everyone is caught up with practical concerns.

Aspaturian: I've heard Lee Hood express the opinion that if the current and future generation of biologists don't come to grips with the fact that the science is becoming increasingly computerized and quantitative, they're going to fall by the wayside. Do you agree with that?

Benzer: Well, that's Lee Hood's idea, and he's riding with the tide. I don't think the history of creative thought has been built by people who were riding with the tide. It's been built by freaks who were using their brains. So I don't like it. As Max Delbrück used to say, the universities are a haven for freaks. Delbrück was a freak; Einstein was a freak; Kurt Goedel was a freak. I think there's some kind of natural evolution in a science when it becomes too successful. In practical terms, chemistry was way ahead of biology in becoming industry-oriented and in developing large groups. I remember when I was just beginning in microbiology, talking to Sydney Brenner about a chemist who had a fleet of twenty or thirty graduate students and postdocs. And I said, "Oh, my god!" And Sydney said, "Well, that's the way chemists work all over the world." But this was almost forty years ago, and now biology has arrived to that stage of ripeness. I think this comes partly from the agenda. The agenda these days is that you find someone very prominent and you work in his lab, so that he will be able to give you a letter of recommendation at the end and, with his connections, get you a job. Also being a large group gives you the momentum of many people, a lot of expertise that can grind out a lot of papers, even though there may be six or ten authors on the paper. So, that way, you build up your CV. Et cetera. Biology, in my lifetime, has come to that stage. Physics has gotten to where you now need several billion dollars to do a physics experiment. It's a natural evolution, but what it means is that the science is almost like an industry. A very large lab is very much like an industrial operation. And in fact, more and more

people are depending on industry as the source of their funding.

Aspaturian: Are there areas of biology that you think will be able to remain unaffected by this?

Benzer: Only temporarily. I remember a mathematician telling me with pride that what he was doing in number theory could never be practical. And a month later, an article came out in the *Physical Review* applying that theory to nuclear structure. So you can't avoid it, nor should you, but whether you as an individual want to go along with it is another question. My own history has been just the opposite. I started in the semiconductor business at Purdue; great developments came out of that. And other people in the lab were saying, "Semiconductors are going to be a great industry; let's form a company and we can ride in on the tide." They thought I was crazy to shift to biology. The same was true when I was in molecular biology, doing rather well, and decided I'd be interested in neurobiology. Some said, "You're crazy to be shifting; ride in on the tide." Well, some people ride the tide, and more power to them. But that's not my style.

Aspaturian: Do you know what I think when I hear you say this? You told me your mother emigrated to America first, and then brought the rest of her family over. And that your dad was the only one in his neighborhood who drove a car. I see a certain family connection there.

Benzer: Well, maybe. [Laughter] I believe in the inheritance of behavior. It also gets boring, trying to keep up with a field when it proliferates so that you can't really follow what's going on. And there's the problem of redundancy, when you get to the point where six people are doing exactly the same experiment in a frantic rush to publish it. That gets unpleasant. But I don't think I've ever actually run away from a subject. I've always just gotten intrigued by something else. But you can't divorce that from the positive push as well. It's always very refreshing to be able to just make a clean break, start over again with something you're completely ignorant about. That's very exhilarating; nothing's expected of you because you're a novice. And with luck, you come up with something that other people were saying was impossible because they know too much. So being ignorant has a certain advantage.

Aspaturian: What are you working on now? What direction has your research gone into?

Benzer: The work over the last few years has been largely focused on the development of the eye in *Drosophila*. It's been through several stages. In the earliest days we were asking what's the relationship between genes and behavior. We got all kinds of *Drosophila* mutants and all kinds of behavior and found that every kind of behavior could be analyzed with mutants. There were several periods in that. The first was finding out about the behaviors; the second was a method of analyzing them. So there was also a period of doing electrophysiology.

Then I got interested in the neurospecificity. My original reason for coming to work with Roger Sperry was his research on what he called chemospecificity of neurons—how does the nervous system wire up? Each neuron comes in and is connected to another one. There must be some kind of labels or molecules, so they know when to match. I was to some extent disappointed; when I came, Sperry had lost interest in that completely. There was also the feeling that there was no clear way to tackle the problem by identifying these molecules. But along the way, monoclonal antibodies came out. This is a way of developing an antibody toward a very specific molecule. People working on the leech showed that specific neurons could be identified with specific antibodies. To me, that was a big breakthrough. I thought that was a way of tackling the problem—putting some chemo into chemospecificity. So we thought of making monoclonal antibodies, and that turned out to be very fruitful. I have the burden now that everybody in the world is asking for them all the time. We're running a shipping service, sending out antibodies. I just got a request from Germany. I've become a dispatcher, and that's become a bit of a burden. It might be nice if I could give it all away.

But that became an important approach, something we were the first to develop here. If you have an antibody that identifies a specific neuron because of a particular protein in that neuron, what is the function of that protein? So we took this approach with our photoreceptor-specific antibody. We used the antibody to purify the protein—then we obtained the sequence of the protein. From that, we could predict the sequence of the DNA and use that to isolate the gene. And then we could locate the gene on a chromosome, make a mutation of that place, and see what goes wrong.

Aspaturian: You didn't sequence the gene? You just located it?

Benzer: Yes, but we also sequenced the gene, once it was isolated. So that was the first time, to my knowledge, that that whole paradigm has worked out that way. Now it's commonplace.

First, we were going from the function, from the behavior to the gene. But with the monoclonals, we were going from the gene product back to the function. You can also start in the middle, with cDNA, which is a DNA copy of messenger RNA. With the *Drosophila* eye, for instance, what you do is take the eyes, grind them up, extract the messenger RNA, and make that into a copy-DNA sequence. From the cDNA you can immediately find out what the gene is on the chromosome. You can go in the other direction to the protein via so-called fusion protein. Use the cDNA and hook it to some other elements, which enables you to make protein out of that cDNA, with the right sequence.

Aspaturian: Do you put it on some sort of ribosome?

Benzer: No, this is all done *in vitro*, with the right kinds of polarizing enzyme. You can do it with ribosomes, but that's done more generally when you have an impure extract. But once you have a pure cDNA clone, you can make very large quantities of it. You can make an artificial protein out of it. And then, you make an antibody to that, and then you see where the protein is located. So with cDNA, you can go in both directions.

The particular way this technique is applicable to the eye development is that the *Drosophila* eye has a very repetitive structure. It's a compound eye, with about 800 facets on each side. And within one facet you have 8 photoreceptor cells. These 8 photoreceptor cells were originally in early literature thought to derive from one cell that undergoes three divisions and gives you 2, 4, 8. But we were doing experiments on a retinal-degeneration mutant to see whether retinal degeneration is due to the photoreceptor cells themselves or to some other general problem that is feeding back and causing degeneration. The way to do that is to make mosaics, so we made flies where half the eye was mutant and half the eye was normal. And sure enough, one half degenerated, and the other half didn't. But when I looked at one of these photographs of a section, I could see that sometimes among these groups of 8 at the boundary, between mutant and nonmutant, they didn't all degenerate. Within the same group, you could see two or three

nondegenerating cells with others that were degenerating. And that couldn't be true if they were all derived from one parent. So this was one of those "Ah!" moments. My graduate student Donald Ready did a detailed study of the development of the eye and how these clusters form. And sure enough, they were completely nonclonal—they all come together by neighboring cell-cell interaction. And that discovery raised the question of how they do it. It turned out that this development is happening during the larval stage, when there's the so-called imago—the preadult disk. In this disk, you have a single layer of cells, and there's a wave of differentiation that goes along behind, out of which these clusters form. And you could see that at first there's a kind of furrow in the disk where this was going on.

Then we did sections and analyzed them under an electron microscope. The first clusters we were able to see were just groups of five cells. And then two more were added. The last one to be added was one that, according to the numeration, was called Number 7. And then we found that in the mutant, Number 7 never appears—called sevenless. This was picked up behaviorally by the defect in this phototactic behavior; when you looked in the defective eye, you said, "Everybody's there except Number 7. All these cells are fine, except Number 7 is not there." This was a discovery of an important developmental event, where one gene is affecting the differentiation of just one specific cell. During all this time, all the molecular technology of cloning genes was developing. I remember once, in the seventies, we actually made a rather intrepid remark in one sentence at the end of a paper, saying, "You know, you could use this behavior to point to the gene and thereby you would be able to clone the gene." That had to do with excitable channels in the nerve membrane. But we thought at the time that this was a very risky type of statement to make. [Laughter] And then came the flood of all the recombinant DNA technology.

I was shocked recently to look back and see how recent that was. It was in the late seventies.

So now, everybody's cloning every gene in sight—clone and groan, as we call it; or clone by phone, because you find out who has what clone. It's become unbelievably exponential in its development, and big industrial development, too. So that's what happened to the sevenless gene. We started cloning it in the lab—there was a big race over who would publish first. It turned out to have an important function related to oncogene receptors. So just sevenless alone has become a whole field. My students left, set up their own labs for working on sevenless. In

just a period of three years or so, you have eight guys spread all over the world, working on the same thing. [Laughter] I'm not working on sevenless—I've shifted to other things.

Aspaturian: I took a look at your proposal to the Markey Foundation. Obviously you're working on genes that are homologous to *Drosophila* and humans to some degree.

Benzer: Well, if you remember, from the beginning, I was always interested in human beings. And I think it's time to have the courage to undertake that. It's exciting. People say, "Why go to humans? At least go to the mouse." But I'm interested in humans. I'm willing to use the mouse as a sort of intermediary. But I can afford to take a chance and do something crazy. And people who say it's crazy now are going to be doing the same thing next year. I may be wrong, but I doubt it. Max Delbrück was wrong. He thought that when he dropped phage and switched to *Phycomyces* that that would be the new revolution, just like phage was. And it never happened. Well, that's where I'm at. Some of it comes from my association with my wife [Carol Miller]. I'm interested in human behavior, and so is she. So we're trying to develop that. It turns out, we're no longer unique in this; a lot of other people see the obvious possibilities as well. So this is no longer a fringe science. It's the kind of thing that peer review groups will probably look down upon for another year or so. [Laughter] Remember the monoclonal antibodies. I never had problems getting support for monoclonal work—I was already well established on an ongoing NSF grant. But others who put in had terrible difficulties. I remember speaking to someone on a review panel, who said, "Anything with monoclonal antibodies, we just throw it right out. It's useless, a waste of time." What the whole community objected to was the way we were doing it. Because there was the established way of doing it, where you take a protein molecule that you know is important and interesting and you purify it, and then you make an antibody against that, and that's the way you go. What we were doing was taking a whole mixture of proteins, the whole tissue, grinding up the whole brain and sticking it in a mouse. I don't know if you're familiar with the system, but the lymphocytes in the mouse get excited about all these different antigens. Then you take them out, more or less one by one and fuse each one, in effect, with a myeloma cell that just compulsively makes antibodies but doesn't know what type to make. So the lymphocyte hybrid myeloma cell makes the type that the lymphocytes are sensitized to. Then

you separate out all these cultures. And then, what we were doing was to take a slice of the brain and test each antibody on it to see what lights up. So it was a quite different approach from the conventional one. It's absolutely amazing how hard it was to sell that to these people, who had this rigid idea of the way things must be done. And now, those same types of people are saying, "Well, human to fly. What's one got to do with the other?"

Aspaturian: I'm surprised people would be saying that, given discoveries about the homeobox.

Benzer: Yes, well, it's changing. But this is all within the last few years. Part of it is just sheer numbers—there are so many people in the field. So that's a problem. If you have an idea, you have to run real fast. And that engenders an atmosphere of secrecy and double-crossing, which is not nice. [Laughter]

Aspaturian: You've won practically every prize in biology. Except one. Are there any that are particularly meaningful to you?

Benzer: I remember once getting a letter from a colleague that said, "Congratulations on getting the Wolf Prize, but I thought you had it already. You better check your records and make sure they're not giving it to you twice." [Laughter]

Aspaturian: Do you regret not having won the Nobel?

Benzer: Well, if you give it to me, I'll take it. [Laughter] But it's not up to me. My mother always regarded me as a failure. [Laughter] Because I didn't get the Nobel Prize. She wanted to be able to tell the neighbors—"These other prizes don't mean anything to the neighbors." [Benzer was awarded the Crafoord Prize in 1993, presented by the Royal Swedish Academy of Sciences "for work not covered by the Nobel." Ed.]

Aspaturian: Is there any particular prize you've been especially proud of for the work that it recognized?

Benzer: Well, there's a short exhilaration; it's nice to realize that people like you and respect you. Followed by, "Oh my god, I have to go on a trip to a meeting and give a lecture." But it's nice to be thought of. I remember Feynman's story. They called him up and said, "You won the Einstein Prize." He said, "Well, what's that?" And they said, "Well, you get $15,000. Don't you have anything to say?" He said, "Hot dog!" [Laughter] That's what it amounts to. It's nice. But you know, a lot of people feel that these prizes should be abolished altogether. Other people go out and very actively campaign for them and make real fools of themselves, subject themselves to practical jokes. You know, friends calling them up with a Swedish accent at five o'clock in the morning to tell them they got the prize. [Laughter] There's a book about the Nobel Prize in the Caltech [Millikan] Library. It was brought to my attention that I'm identified in there as the holder of the "forty-first chair." This refers to the French Academy, which I think has forty seats. There's a whole series of people who are referred to as holders of the forty-first seat. [Laughter] They called me that with respect to the Nobel Prize. Well, that's something.

Aspaturian: I remember reading in *The Eighth Day of Creation* that when Marshall Nirenberg presented his findings on the polyuracil triplet, Delbrück said that his speech struck everyone in the audience with astonishment. And the author went on to say that you mailed Delbrück a photograph showing half the audience fast asleep at the time Nirenberg was talking.

Benzer: It was a photo of Francis Crick. The story was that someone had written that he was electrified. And I happened to have a picture of Francis Crick, sitting in a meeting asleep—but to be fair, it was not while Nirenberg was speaking. But I just showed that as an example of how Francis looks when he's electrified.

Begin Tape 11, Side 2

Aspaturian: If you had to single out, say, three or four areas of biology that you think are going to be very important in the next century—leaving out the genome project, because obviously that covers everything—could you do that? Are there things maybe not very well known right now that you think are going to have major significance?

Benzer: I think I'd have to say the brain and behavior, which also includes everything. I think the problem of neurospecificity—how you get from the genes to the wiring up of the nervous system—is still a big question. A certain amount of progress has been made. And I think that will accelerate now that we have the methodologies, the molecular techniques, combined with the genetic approaches. So I think that's moving rapidly. But we're still very far from understanding how it works. So that's one area. Just sequencing the human genome I think is a boring project. I'm glad that other people are doing it. I think it's worthwhile to do, compared with spending the same amount of money on a B-2 bomber or two. But I wouldn't want to do it; it's boring. Watson once said to somebody else within my earshot, "If Seymour wanted to sequence a *Drosophila* genome, I could give him $5 million." [Laughter] It might come to that, if I can't get grants for what I'm doing.

Aspaturian: You'd have to sell yourself.

Benzer: That's happening. That's happening to people who have difficulty getting grants for what they want to do, and suddenly get interested in sequencing the genome. Economic pressure does work.

Aspaturian: Do you see a solution for some of these problems with the money? It's in every area of science.

Benzer: More money. [Laughter] Well, as Tom Everhart was saying today, this is sort of an explosive exponential. Each professor trains several students. They go out and become professors. Then they apply for grants to train their students. And at some point, it has to reach some kind of limiting factor. That may be what's happening now. I think that a lot of these people who can't get academic jobs will take industrial jobs. And there's going to be a real tightening up.

What I don't like is that the selection of who gets to be funded begins to depend more on their skill in grantsmanship rather than just on their ability in scientific innovation. Because I think innovation is suffering from this situation. People don't dare propose a project that is not funded, or already on a recognized track. A guy I know who reviews projects once told me this

story about a panel he was on: One scientist was saying she thought it was getting very hard to get funding for new ideas. And this guy who was on the same review panel said, "Yes, every year I get a hundred applications with new ideas, but I can't tell which are the good ones and which are the bad ones; so I turn them all down." This is an exact quote. And I think that may be an exaggerated case, but it's not all that exaggerated. That is what's happening. Now that, in itself, may not be new. But the general competition for the funds is so severe that it could make the difference.

Aspaturian: Do you think there's been a decline in the quality of biology research as a result of all this? Or has it not come to that yet?

Benzer: I don't think so. I think it's been really great; just a decline in the quality of life of doing biological research. [Laughter] We spend more and more time grubbing for money. And it's becoming quite serious. You know, some of the sections at NIH have gotten to the point where they approve every application but they fund only ten percent of them; I've heard as low as eight or nine percent in some panels. That means the other ninety percent are going to be applying again, and maybe in two or three different places. So it's come to be a very severe situation now. NIH is claiming that this is just a fluctuation because they've adopted a policy of funding for longer periods of time, which means that a lot of money is committed ahead and less available for new projects. So they're constantly soul-searching on how to reconcile that. At the same time, they give multimillion dollars to some center, just because someone high up in the NSF thinks centers are a good thing.

Aspaturian: That brings up an interesting question. Do you feel, or do you find, that there are some areas of biology that are getting a lot of funding that shouldn't be—that are basically blind alleys?

Benzer: Nothing comes to mind in terms of blind alleys. I don't think there's a lot of money going down the drain, being wasted. I don't have that feeling. But I do think the trend is sort of a reflection of the whole economy of the Reagan era, the rich getting richer and the poor getting poorer. There's an imbalance.

Aspaturian: Where do you put science in that particular equation?

Benzer: I think science has become the same way. People with big grants are getting bigger grants, and people working on a modest scale are being cut off, because it's become a business. Being a good businessman means you know how to work the system and get more stuff. So people are busy working the system rather than working for science.

I think all the universities are changing entirely. The president has talked about how that's a good thing, because if we train students who go into industry, they become CEOs and then they'll be giving money to Caltech. [Laughter] Something like that. And he said, this is the way it's been with engineers. You look around and see that a lot of the Caltech donor graduates are engineers. And that's because they go out in business, make money, and feed it back. But there are a lot of my colleagues who fancy themselves ivory-tower scientists, or at least would like to be. It comes as a bit of a jolt to them to be told this, to realize that it's probably absolutely true and necessary—that the golden age is gone. I think the handwriting is on the wall. It would be nice if Caltech would feel that this could be an enclave that resists that trend. But I don't think it's going to happen. I'm not sure it can happen, with the times being what they are. But I feel the character of Caltech is changing, perhaps less rapidly than at places like MIT and Stanford, who have essentially become adjuncts of industry. They have big industrial complexes right next door, research parks. Professors are going off into companies. It's happening here, too, finally. I know of one professor who has an interest in six or seven companies. If Caltech accepts this kind of situation, I don't see how such a person could possibly be doing the kind of creative thinking for and at Caltech that one classically expects of a scholar. It becomes more a matter of using Caltech facilities as a platform for extracurricular activities, which, granted, feed back, and bring income to Caltech—training students, and so on. But it's a completely different ballgame from what it used to be.

Aspaturian: I have one more question. The Indian physicist [Subrahmanyan] Chandrasekhar—he and Willy [William A.] Fowler [Institute Professor of Physics, emeritus] shared the Nobel Prize in 1983—is famous for completely changing the direction of his field every ten years or so. He's said he does it partly for the reasons you enunciated and partly because he feels people tend to

stagnate in their own fields. Did you consciously think that as well when you moved from one field into another? Was it sort of to rev yourself back up?

Benzer: I'll say it again. In every case I switched, it's because of interest in something different. But I can't divorce the excitement of that interest from the fact that it also meant getting away from the trappings of another subject that was getting too big. So subconsciously, that's surely part of the motivation, partly an escape as well as an attraction. When a subject develops very thoroughly, there's too much you have to know. It gets sort of overwhelming. So that's why I was saying the big attraction is starting something new and being very stupid about it. Ask stupid questions, and you often get amazing answers.