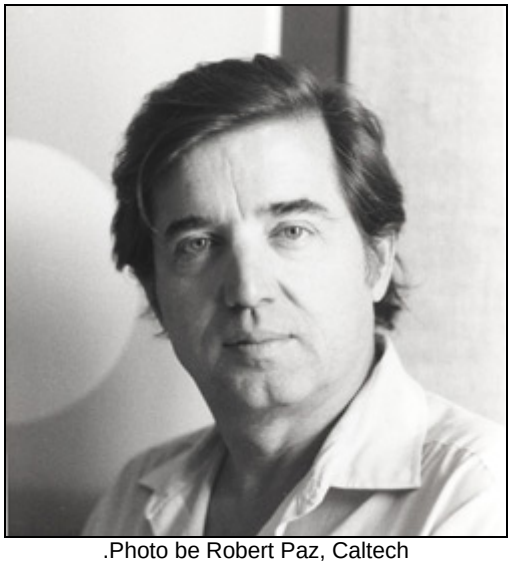

.Photo be Robert Paz, Caltech

WILLIAM J. DREYER
(1928–2004)

INTERVIEWED BY
SHIRLEY K. COHEN

February 18th–March 2, 1999

ARCHIVES
CALIFORNIA INSTITUTE OF TECHNOLOGY
Pasadena, California

Subject area

Biology, immunology, biochemistry

Abstract

An interview in five sessions in 1999 with William J. Dreyer, molecular immunologist and Caltech professor of biology (1963-2004). He begins with a discussion of how some people think visually, himself included—a theme to which he returns repeatedly in the interview. He speaks of his family history: childhood in Michigan and Wisconsin; his Norwegian father and possible inherited family traits including dyslexia and mental imaging. Recalls his education at Reed College in Oregon (BA chemistry, 1952) and graduate study at University of Washington (PhD in biochemistry, 1956); works under H. Neurath at UW. First occurrence of cancer while in graduate school. He goes to National Institutes of Health (NIH) as a National Polio Foundation postdoc, where he works on proteins with C. Anfinsen; becomes research scientist at NIH; assists M. Nirenberg in work on genetic code. Meets and works with G. Streisinger on genetic mapping with phage. Still at NIH begins inventing machinery for automating biochemical analyses.

Recruited to Caltech and accepts appointment in biology division in 1963. Together with J. Claude Bennett writes major papers on genetic coding for protein

structure, gene splicing and monoclonal antibodies. Recalls Leroy Hood's arrival at Caltech in 1963 as grad student. Dreyer's consulting work for Spinco division of Beckman Instruments; helps in the design of an automated protein sequencer; his continuing interest in new technologies. Work in 1960s with W. Gray on sequencing protein in a mass spectrometer for JPL; collaborates with Gray and Hood on 1967 Cold Spring Harbor symposium paper on antibody formation. Roger Sperry at Caltech; his influence on Dreyer. Work on the protein rhodopsin. Robert Sinsheimer as biology division chairman. During 1970s and 80s Caltech develops series of more and more sensitive instruments to synthesize and analyze genes and proteins. 1982 recurrence of Dreyer's cancer. Creation of company Applied Biosystems with Hood and M. Hunkapiller; issues arise over patents and royalties. Dreyer's work with Milton Wexler's Hereditary Disease Foundation. Caltech's Beckman Institute; recruitment of Scott Fraser and creation of Biology Imaging Center at Caltech. Study of olfactory receptors; "area code" hypothesis in embryogenesis. Capillary electrophoresis; the Human Genome Project. Recent experiments involving gene deletion and DNA alteration.

Administrative information

Access

The interview is unrestricted.

Preferred citation

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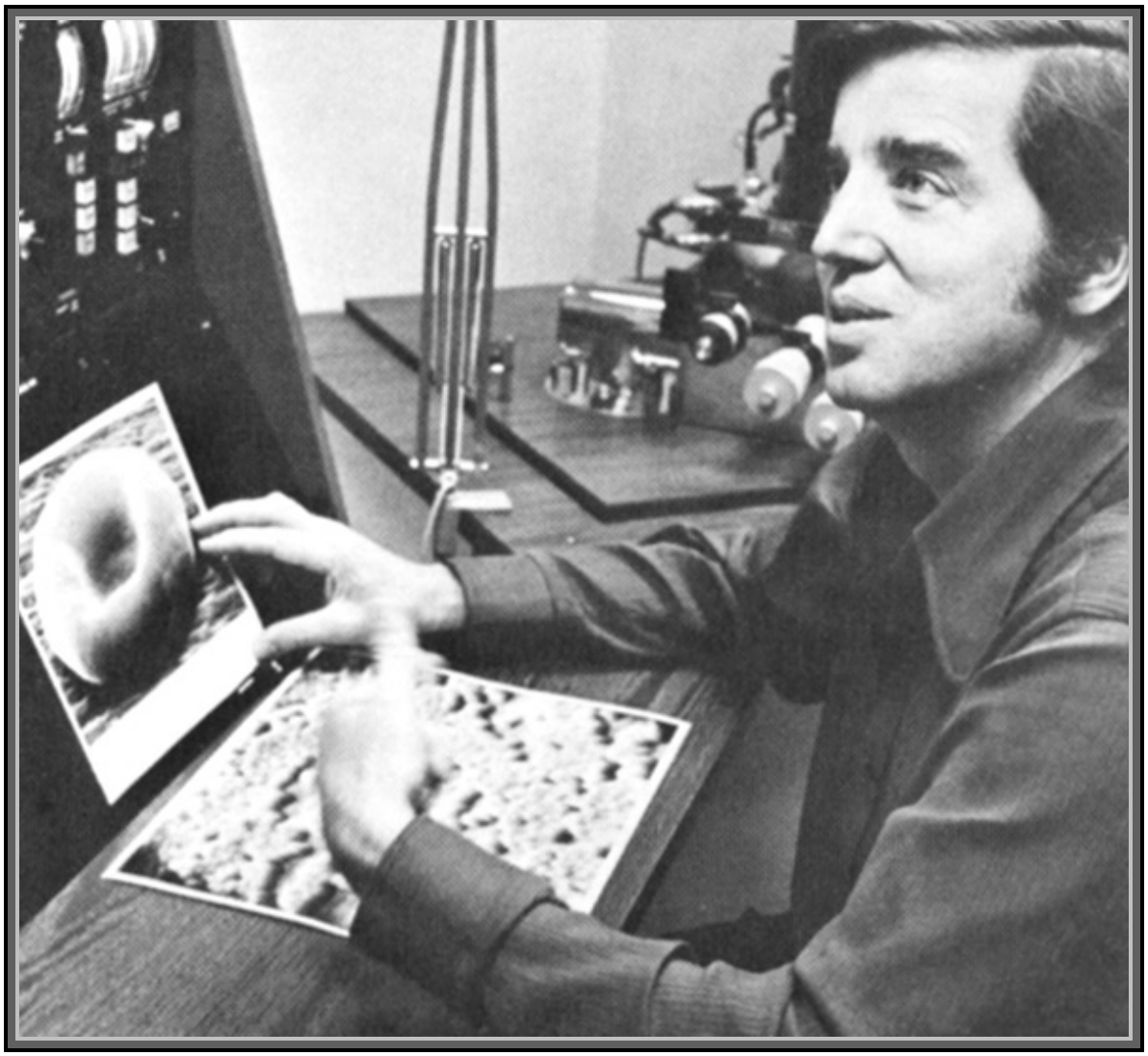

In the early 1970s Bill Dreyer developed an automated mass spectrometer to speed up the flow of data during experiments aimed at determining how cells synthesize antibodies. Photo by Floyd Clark, *Engineering & Science*, Mar-Apr 1974.

CALIFORNIA INSTITUTE OF TECHNOLOGY

ORAL HISTORY PROJECT

INTERVIEW WITH WILLIAM J. DREYER

BY SHIRLEY K. COHEN

PASADENA, CALIFORNIA

PREFACE

TO THE INTERVIEW WITH WILLIAM J. DREYER

The interview with William J. Dreyer, Caltech Professor of Biology, as recorded early in 1999, presented significant difficulties in transcription and editing. The quality of the recording itself was poor, due partly to inadequate equipment. There were many inaudible words and phrases. Unfortunately Bill Dreyer's health failed, and he did not live long enough to review the full transcript, although he did read and correct a part of the first session. The Archives is very grateful to his widow, Dr. Janet Roman Dreyer, for her invaluable help in unraveling some of the problem portions. A few of her comments—marked with initials JRD—have been added to the transcript as footnotes.

The final transcript still has a number of missing words and phrases. Some elusive segments could be teased out with great patience. Others have remained unresolved. Portions that are still questionable or lacking have been filled in or noted in square brackets by the editors, to the best of their ability.

Charlotte E. Erwin
Associate Archivist
June 2005

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CALIFORNIA INSTITUTE OF TECHNOLOGY

ORAL HISTORY PROJECT

Interview with William J. Dreyer **by Shirley K. Cohen**

Pasadena, California

Session 1	February 18, 1999
Session 2	February 19, 1999
Session 3	February 23, 1999
Session 4	February 26, 1999
Session 5	March 2, 1999

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COHEN: Thank you for coming, Professor Dreyer. You expressed some interest in giving us an introduction before we start the interview, so why don't you go ahead and do that.

DREYER: OK. Well, the introduction has to do with [the fact that] I've come to realize that scientists—and people in general—have very different ways of thinking. I was just at UCLA two days ago with people studying brain imaging, and only one or two of them understand this now—it's so new. They tended to want a uniform brain, with everyone having the same anatomy and thinking the same way. That isn't at all true; it's amazing how different people can be. And in particular, the book that I loaned you—*In the Mind's Eye,* by Thomas G. West [*In the Mind's Eye: Visual Thinkers, Gifted People with Dyslexia and Other Learning Difficulties, Computer Images and the Ironies of Creativity,* Amherst NY: Prometheus (1997)]—is about the only one I've ever seen that deals with the subject of people who have extreme visual imagery in the way they think. I wanted to preface all of this with this little story, because when you start asking me about schools and whatnot, it has a profound implication.

COHEN: But of course you didn't realize this when [your schooling] was going on.

DREYER: I knew I was different in the way that I thought, but I didn't realize why I was so dumb at spelling. I'm terrible, OK? And rote memory and arithmetic and so forth. The first time I realized how different different brains could be—by the way, I was interested in psychology among other things as a student—was when I bumped into Jim Olds at a dinner party back in the late sixties. Jim Olds was a professor here [Bing Professor of Behavioral Biology, 1969 – d. 1976]. He's famous for his pleasure center work. He was a professor here and so was I. A speaker talked about the way we think and compared it to holography. Jim was across the table from me. I said, "Oh, yes. When I'm inventing an instrument or whatever, I see it in my head and I rotate it and try it out and move the gears. If it doesn't work, I rebuild it in my head." And he looked at me and said, "I don't see a thing in my head with my eyes closed." We spent the rest of the evening, over wine and so forth, trying to figure out how two professors—both obviously gifted people at Caltech in the Biology Division—could possibly think at all, because we were so different. So then I took this up with Roger Sperry [Hixon Professor of Psychobiology 1954-1984, emeritus, d. 1994], and I realized that I had some amazing shortcomings as well as some amazing gifts. I took it up with some of the students, one of whom was Mike [Michael S.] Gazzaniga [Director, Center for Cognitive Neuroscience, Dartmouth], who is still around writing, and a few others that came out of Sperry's group of postdocs and grad students. And they typically said, "Oh, no. There's no difference. Everyone does this imaging. We're all the same." So I never could document this, and my wife [Janet Roman Dreyer] is the same way. It's called dyslexia, typically, because you have a strange inability to do stuff. If you are thinking in images, then a spreadsheet doesn't work; your brain doesn't compute well. If you're smart, you can do all kinds of things if you work hard on it. I can learn how to spell if I work hard at it, but it doesn't come naturally. The reason [is because] there's no image to it. Let me mention that [there were] other people at Caltech who never realized this about themselves. Dick Feynman [Richard Chace Tolman Professor of Theoretical Physics, d. 1988] was one. And Murray Gell-Mann [Robert Andrews Millikan Professor of Theoretical Physics, emeritus] doesn't realize that he's totally different from what Dick Feynman was, in the way he thinks algebraically. This is why I think it's interesting for Caltech to be aware of these differences that Tom West documents. Einstein thought in images, and Feynman did his work in physics in diagrams, as you well know. But other physicists just couldn't

understand it. So I have some of those problems—with other biologists not being able to understand me—and I've come to understand a little bit more why. That's the preamble.

COHEN: OK. So let me now bring you in a more formal way to the beginning of this interview. Tell us about your family—your mother, your father. What did they do?

DREYER: OK. My father was Norwegian and I still have lots of cousins there and so forth. I was born a Norwegian citizen, really, I'd expect, because my father was just in this country as a Norwegian citizen. We went back when I was three months old and many times later. So I've had a lot of contact with Norway.

COHEN: Where were you born?

DREYER: I was born in Michigan. On the Norwegian side—in terms of where this brain came from, which is one of the things I warned you I've been thinking about—I'm sure they think this way. It's hereditary, by the way; I have three daughters who are dyslexic—I like the term "high visual imagers." They all see things in their heads in images, the way I do.

COHEN: Are you telling me this is a Norwegian trait?

DREYER: No, I'm saying it's genetic. However, what I'm saying is you might wonder how the genes of a book publisher such as my grandfather would produce someone who's not very good at the normal literary things. I write, and I write well, but I'm slow at it. But it turns out that the name of the [family] company was Dreyer's *Graphics*. So in fact the heritage is not one of literary but visual graphic skills.

COHEN: Now, this was your—

DREYER: Grandfather. His father started it. They did fine, highly technical graphics things. He also invented and patented a major method for printing. So in terms of the genetics, I think it's fairly reasonable [to think] that I got part of it from them.

COHEN: What was your father doing in this country?

DREYER: There were four sons. In the old Norwegian tradition, the eldest son inherits the farm. So he set out. And with four sons of a wealthy—my grandfather was wealthy—what my father did was to defect and come to this country. He started out in a low position in a paper company.

COHEN: Because he was not going to inherit the Dreyer company?

DREYER: Well, mainly he had the good sense not to get into the squabble—which did occur—among the remaining three sons about who would control the company and all that. He came here to develop his own life, which he did. Why he went back, I'm not totally sure.

COHEN: Now, your mother is a Norwegian also?

DREYER: No, my mother is from Michigan. He met her in this country. Her father was a builder—farm community people. And again I can see this hereditary thing showing up. The very best builders and architects have this strange kind of ability to see the buildings they're designing. What they do is not fully appreciated, either. So there's the genetics, which does interest me a lot, as you will see. And not as a self-centered thing; I'm really interested in the whole subject of how human brains work and how genes build, sculpture living organisms.

COHEN: It's your profession, so to speak.

DREYER: In some ways I'm a guinea pig, which will come out in this discussion. That's why I wanted to bring up this kind of stuff.

COHEN: So then you went back to Norway, but then you came back here to go to school?

DREYER: They came back in less than a year—back to Kalamazoo, which is where I had been born, but then they moved to Wisconsin. He began to work [his way] up in the company; it was

a specialty paper company. [He was] a representative of the company, a salesman. And a regional [salesman] for big-deal butter companies and things like that. They moved to Wisconsin when I was three years old. One of the stories I remembered because of your wanting to do this interview and thinking about where scientists come from. I've been told that I was a born scientist. So here I was [at] three years old. I was told that if you threw salt on the tail of a robin—we had these little robin redbreasts that played around on our lawn collecting worms and whatnot—they couldn't fly. So what did I do?

COHEN: I have heard that.

DREYER: I went and got some salt. I decided I was going to test this. It was the first time I can remember doing experimental science—to approach this robin and throw salt on its tail. And it flew away, of course. And then, probably around the time of kindergarten, I got the Santa Claus story. So what did I do? I went and examined the chimney and examined Santa Claus and said to my parents, "No way." [Laughter] That was in Wauwatosa, Wisconsin—it's a suburb of Milwaukee.

COHEN: Were you the only child?

DREYER: I have a sister, who is two years younger.

COHEN: It sounds like your parents were very interested in your having a good education.

DREYER: Well, not really. My father was really brought up more as the son of a rich man. He did go to Germany for an education of some kind—I think it was highly technical and related to the company. My mother was a kindergarten teacher; she didn't go to college. There was no special interest in intellectual activities, in the way that someone who's brought up in a tradition of scholarly work would have. She treated me more like she would a kindergarten kid—to have fun and do what I wanted. She cut me loose, and so did my father.

COHEN: That was probably good.

DREYER: For me it turns out [that that was good], because I have dyslexia. It's the best thing you can possibly do for some kids. Because if you try to force the traditional reading and writing and arithmetic onto someone whose brain doesn't do that— It probably turned out quite well. I didn't have to constantly be told, "You failed, you failed, you failed." So—just perfectly normal grade school. But I can remember always being interested in scientific things, like shaking a jar of cream and having it [turn into] butter. And I was interested in building things. From a very young age, I had hobbies of all kinds that were scientific or mechanical. I'm talking about grade school. The kinds of things they taught in that particular system were just uninteresting to me. In history, you are asked to memorize a date. I don't do that. I want to understand the history. I do now; I'm very fond of the history channel. I'm very good at understanding and analyzing all kinds of things, but memorizing dates—the stuff they tried to teach me—was a trivial pursuit. I'd get out of school and have all kinds of hobbies. In about the second grade, I became fascinated with something, and I'm still fascinated. This came from the fact that my father's Norwegian. His hobbies included hunting birds, so he would go hunting for a brief period in Norway, and I'd get the wishbones from these birds—doves, geese, ptarmigan and turkeys. I collected these and was fascinated by how different they were and how they were made—the sculpture of the things. There was a science fair when I was about in second grade. I put the whole collection on a board and named them. I won first prize for this science project. But the interesting thing to me is that that fascination is still part of my latest paper; that is, how do genes shape, form, sculpture embryos, brains, and so forth.

COHEN: And your parents encouraged you?

DREYER: They just let me be free.

COHEN: I mean, he provided you with all the wishbones. That's encouragement.

DREYER: Absolutely. And they did not press. They weren't terribly interested in little Billy getting A's and B's or being the best in the class or whatever. So this is why I partly wonder how I wound up here. [Laughter]

COHEN: Where did you go to high school? In Wisconsin also?

DREYER: In Wauwatosa. Same story. I joined the science club. I loved it. We did all kinds of things, and on my own I built radios. I had a job repairing radios. Dick Feynman, I happened to read, also had a job repairing radios.

COHEN: What's interesting to me [is that] here you are, in a nonacademic family living in Wisconsin. How did you get to Reed College?

DREYER: Well, let me get you a little bit through high school. I never learned to do homework. Obviously, now I can look back and say it was because I was bright enough to get away with it. So in physics I got A's—but I didn't do any homework, I just understood it. In biology, when they asked me to memorize the Latin names of creatures, I always had a hard time, but after school I would raise plants with chemicals, look up the chemicals and learn about them, learn about plant hormones. I studied all this stuff that had nothing to do with what the teachers were asking. I recall one of the general science teachers saying, "You're a natural scientist. You're born to do it." But it didn't show. I never got any [high] grades—I wasn't the first in the class. I was into hobbies and all that stuff. OK—so that's basically high school.

COHEN: But you weren't miserable.

DREYER: No, not at all. I was a healthy, well-loved kid who got along with the other kids. However, I was very different. I didn't relate much to competitive sports. I could do them. No one ever beat up on me, because I was large and I could wrestle. That was somewhat of an intellectual sport in the early days. I could lick any of the big guys, so I never had any problem with being beaten up on. But one thing that did happen, that may be relevant: My dad died in 1938 in an accident with his hunting rifle—

COHEN: You would have been still in school then.

DREYER: Oh, yes. I would have been finishing grade school. So then my mother, even more, gave me credit for being essentially an adult. Neither of them had any great prohibitions or standards that said you shouldn't—they didn't have any problem with me sharing a glass of wine now and again. Of course, for that reason, I never did drink. It was the same with sexuality. They never banned it. I was pretty normal.

COHEN: Your mother was financially secure?

DREYER: She had insurance. But I worked always, in the summer. We were comfortable, in a duplex in Wauwatosa. We went over to Norway to live in 1939. She felt that Grandfather could help raise his oldest grandson. I had been there several times—cabin class, by the way, on an ocean liner like the *Titanic*. And I'd always head for the tourist section, which was much more fun, as they showed in the movie *Titanic.*

COHEN: You went in '39. That wasn't a great year to be there.

DREYER: No. So in the late autumn of '39 they said, "You'd better get back to the United States." As we came back, I can remember the—

COHEN: War beginning?

DREYER: Yes. The Nazi submarines were sinking ships. They'd mark the sunken ships on the maps as we came back across the Atlantic.

COHEN: The rest of the family stayed there? I mean, the Norwegian family stayed there?

DREYER: Yes. I knew all these uncles. They became surrogate fathers for me—one of my many surrogate fathers. One of them was sent to Dachau, and I've always wondered whether they had an *nth* of Jewish heritage. What I'm told is that he was a leader in the Norwegian underground. He survived Dachau, but they didn't know enough about how to treat him and feed him and give him electrolytes and whatnot, so he died just a bag of bones. And an aunt was put in Grini

concentration camp in Norway. So the war brought us back. We had already said goodbye to everyone, painfully. So that gets me through high school, more or less, with a mother who treated me as if I could do whatever I wanted.

COHEN: It sounds like she depended on you, too.

DREYER: Yes. I helped.

COHEN: So then, how did you get to Reed College? I mean, I know what kind of place Reed is. And here you are in Wisconsin.

DREYER: OK. That's a very interesting question. We decided collectively that after I got out of high school—and having been to Norway a number of times, [where] I learned this culture of fishing and hiking and being free in the wild—they'd just let the young people learn how to deal with life in the mountains and everything without being over-sheltered. To this day, I still love the great outdoors. So we moved to Oregon.

COHEN: Why did your mother move to Oregon?

DREYER: Because of the physical beauty of the place. It was like Norway.

COHEN: I see. So she had no real ties to Wisconsin.

DREYER: No, she had no ties there. She liked the idea of a change. Of course, as a teenage guy I loved the idea, but my sister went bonkers leaving her friends. So I went to the University of Oregon. I could get in, with my mediocre high school grades.

COHEN: Did you move to Portland?

DREYER: We moved to Portland. And the natural thing was to go to the University of Oregon down in Eugene. One of the things I learned about myself is that I am slow at taking tests but I

get everything right when I do these ability tests: I might get sixty or seventy percent of the way through it and still get a high score. I was in the top [percentile] of those tests, and that told me I had some ability in the life sciences. And I was in a fraternity. The name of the game at the University of Oregon at that time was to have parties, which I did enjoy—drinking beer in the fraternity and singing songs. For some reason they asked me to head up the homecoming float design. And I did that with a sorority gal, and we won the float parade, which is kind of neat. That's my big accomplishment at the University of Oregon. I soon came to the realization that I did not fit into that environment.

COHEN: How long were you there?

DREYER: One year. And we won a songfest. I got to use my deep voice to sing sort of a hymn that wowed them. It was fun—party, party, and all that. And the name of the game was to cheat. The fraternities all had piles of old tests. The profs would recycle every three years the same test, so you'd just go up and read that, and not study. I still didn't know how to study. I'd cram for the tests and memorize the answers and all that, yet I loved physics and did very well in it. I didn't need to cheat. It was the same story as high school; I just listened and understood it. And this man did not ask us to memorize equations; he wanted you to derive them and understand them. He was an influence, unquestionably, because of the fact that he appreciated characters like me. And he even knew Einstein's problems with that. One thing I do remember is that we had a test on relativity and light and waves and all these things. I took the test and when it came [back], after he had the grades, he said, "Bill Dreyer, would you please stand up?" He said, "What's the speed of light?" I said, "I don't know." And he said, "I know, because that's the only question you missed on the exam. And Einstein didn't remember it, either." So something like that can influence your life. He let me off the hook for this lousy rote memory, before I understood why. And I got an A in philosophy; for some reason I really enjoyed philosophy. And I nearly flunked French because of some memory difficulty.

COHEN: How about mathematics? I mean, you need mathematics to do physics.

DREYER: Well, I didn't have a lot—I'll come to that. So I wound up realizing that this really wasn't the right thing, that if I stayed in that fraternity I'd wind up a car salesman or something, because that's what all these guys do, even the bright ones. And I knew I didn't want to do that, especially after seeing the struggles and competition among my uncles and all of that. So I ran into—this was a major thing in my life—on a Friday night I went out dancing and drinking beer at a local pub. And a girl was there, a friend of my date's, who was very attractive. I got to talking [with her] and she told me about this kooky little college called Reed College. They had an honor principle. The professors had to stay out of the room during an exam. At the University of Oregon, they had proctors—of course, everyone cheated anyway. There are all kinds of ways of cheating. At the University of Oregon, I really didn't like these big classes. You were an anonymous person sitting in the lecture hall. You couldn't ask questions. "At Reed," she said, "what they do is they have occasional lectures but most of the classes are small, like this little table here that we're sitting at. And you read in advance and then get together and talk about it collectively, including the professor." That sounded absolutely awesome. The whole thing sounded great to me. No one had told me that Reed was supposed to be for very smart kids and that it was hard to get into. So I went out there the next day, slightly hungover. This would have been '48, probably. And I said to the director of admissions, whose name was Bob Cannon, "I heard about Reed last night, and I'd like to come here."

COHEN: Do you mean that you just took yourself from Eugene up to Portland the next day?

DREYER: No. Sorry. I was at home in Portland. That's where my mother lived. I was due to go back to Eugene the next Sunday. So he said, "Well, how are your grades?" And I told him what I just told you. And he said, "Oh. And you want to come here?" And I said, "Well, I heard about it last night, and it sounds great." And he said, "Well, how would you like to take some ability exams?" I said, "Fine." And these were tough. They were basically ability [tests], but included so-called verbal [tests], which I hadn't viewed myself as being good at. But [there were] logical questions and whatnot. And because the tests were tough, they gave me a long time, [and a lack of time] is always my downfall on the simpler tests.

COHEN: I find this very interesting. You went over there and they didn't say, "I want to see your record; I want to see all this stuff," and then dismiss you?

DREYER: Well, but wait. So I took the test and took it back to him. And he said, "Well, here are the grade sheets. Grade it." Well, I kept them for about thirty seconds and then handed them back to him. He said, "What's the matter? Don't you want to grade your own test?" I said, "I did. I just counted the wrong ones." And there weren't very many; there were only a few. I had gotten most of them right. He said, "My God. You've done better than anyone I've ever seen. You have applied. You can start Monday."

COHEN: He just made that decision?

DREYER: Yes.

COHEN: Well, that's a small private school—you can do that.

DREYER: So I started Monday.

COHEN: And you never went back to the University of Oregon?

DREYER: No. I went to collect my stuff that I had left at the fraternity, but that was it. I had to take two years of mathematics, overlapping. They had a special course. I do remember [Frank L.] Griffin was the one who had written those textbooks. I did better in the second year of math than I did in the first, and I realize now why. The reason was that this was three-dimensional geometry, graphical analysis. You do your math analysis and create the equations, intervals, and so forth graphically, and then you convert it into the intervals, the differential stuff, and all these things, which was basically looking at other tables. I did very well at that. Once I got into geometry and trigonometry and whatnot, it was just fine. And I could manage the other. I understand people like me—like Feynman and some of the other physicists—did theory graphically; they'd translate things *into* mathematics but they don't really work in algebra at first.

COHEN: It's interesting. I've taught mathematics in high school, and most teachers do not like to teach things like geometry, because either students can do it or they can't do it.

DREYER: Also, many of the teachers have been brought up in this other mode, and they're good at it themselves.

COHEN: And students who work hard can be good at traditional math, while [with] this visual stuff, some kids can do it and some can't, and working hard at it doesn't help.

DREYER: Apparently, among extremely good mathematicians—famous ones—there are those two kinds. Just as I said, Murray Gell-Mann and Dick Feynman, both winning Nobel Prizes and generally in similar areas. One has one kind of brain, completely, and one was at the other extreme.

COHEN: So Reed was really the right place for you. You didn't get caught up in the drug culture and all those kinds of things?

DREYER: No. I drank and partied. I never did really learn to study through the whole experience there. But I did OK. They didn't give grades. Again, they gave me the freedom to really evolve and try. At first I thought I wanted to be a physicist, and then the labs bored me. I wound up being bumped to the head of an elite psychology class, because I had asked questions about Plato and whatnot that got me into that. I thought, "Well, philosophy might be fun—and psychology." I didn't know then what, if anything, I wanted to do. I certainly had no intention of becoming a professor. I was expecting to get a job. Maybe medicine, but I realized—

COHEN: But many of the people at Reed were going on to graduate school, certainly.

DREYER: Yes. But I didn't—

COHEN: You didn't think about it.

DREYER: Yes. For some students there were suicides and all kinds of trouble, because they had been valedictorians and suddenly found themselves average. Well, hell, I found myself average and I was delighted. [Laughter] So I didn't have that kind of problem. And it was wonderful, because I would ask questions. On exams, if I answered a question and was marked wrong and I explained why it was right, they'd love it.

COHEN: So it was the right place for you.

DREYER: Yes. [There were] any number of times when I would correct the prof and all that. It was wonderful for me. The head of biology there, which also is one of the things I got interested in, was a butterfly taxonomist. He, or someone like him, taught a course in comparative anatomy that involved, among other things, a chick embryo, naming all the structures in a 16.5-day-old chick embryo and all of that, which, as it happens, I now know, because I wound up working with chick embryos. But I had no interest and no brain for doing that. What's relevant is that when I should have been studying math—I never got grades but almost certainly nearly failed it—I was staying up to cram for it, in a room in biology, and I found a book on experimental embryology. And I read that from cover to cover, when I should have been studying for this other exam. I became totally enthralled with how cells migrate together in sort of sheets, talking to each other as they shape the heart in an embryo. And they already knew that—these old guys—by putting carbon particles in and following the migration of cells in the embryos. They could see the carbon particles. And I just became totally enthralled. I wound up, because of the chemistry and physics I took, being a chem major. At that point I began to get turned on to the chemistry and physics of life, but that took until almost my senior year. That's when I started becoming a scholar.

COHEN: You finally found something you really cared about.

DREYER: Yes. This was an awesome mystery at that time: How does life work? It's a philosophical question, but it also is a question of chemistry and physics. Then the event that probably changed my life more than anything else happened. I had a lump in my right testicle.

This was the senior year, when you write your thesis; mine had to do with how you put amino acid molecules together, and I was excited about the thesis. I had a lump in my right testicle that changed in size over a period of two weeks. So I went in to see the school physician and said, "I really don't like this." He said, "Well, let's watch it. Why don't you come back next month?" I didn't say anything, but I did not like that.

COHEN: You didn't like that answer.

DREYER: Not at all. I was too smart and too knowledgeable. So I called a friend of mine who was a physician; we had been steelhead fishing together. He was another one of my surrogate fathers, who took me deer hunting and things like that. I told him what I thought. And he said, "I'll get you in to see the best guy in the region right now." He did, and this man looked at it and sized me up correctly. He said, "This is what I think it is. It's really serious. You have about one chance in ten of living a year with this embryonal carcinoma."

COHEN: "Embryonal" meaning that it was just starting?

DREYER: No, that's the name of the type of cancer. It makes little embryos, little parts of embryos, when it spreads. It's from the germ cells in the testes. And they can make any tissue. Women have this type of cancer also. It gets loose and gets into your brain or other organs. So I said, "Well, how can I stack the odds?" Because ten percent was not good. And he said, "Well, as soon as you're ready we can have your right testicle removed." And I said, "How about tomorrow morning?" So he arranged it. So then I asked, "What can I do next?" And he said, "Well, the drainage—the first place these cells would go to—is your whole lymphatic drainage area, through the thoracic duct up to the armpit." And that's a really major operation to remove all of those lymph nodes. But it increases the odds." So I said, "Let's do it." So I had that done.

COHEN: Do you mean that you had surgery to remove the lymph—

DREYER: All the lymph nodes. They basically remove your whole innards and set them on the table for eight hours or something and keep them under saline. I was, of course, unconscious.

But then they go in and they go through the whole duct. You'll see the scar going all the way up to my armpit here.

COHEN: From your groin to your armpit. They essentially open that up and take out all the lymph nodes.

DREYER: Yes. And I was going to have the operation at the Catholic hospital. Of course, I was reading Voltaire, which drove them nuts, because Catholics do not like some of these writings. It's on their banned list. A nun came in and said, "Oh, that operation is horrible. It's really painful to recover from," and so forth. "And Father O'Brien had that last year." And I said, "What happened?" "He died."

COHEN: How cheerful. [Laughter]

DREYER: Yes, really hopeful.

COHEN: Did they offer you the last rites?

DREYER: Just about. I'm going to back up a second. One of the things that happened when I was quite young—in Wauwatosa before my father died, and when I was in grade school—[was that] they sent me to a Methodist/Episcopal Sunday school. Neither one of my parents was particularly religious; they just kind of went along with it. I went to Sunday school, and I remember still that the Sunday school teacher would tell these biblical stories. And I went back home and said, "I can't handle this. [Laughter] They want me to believe…." I wouldn't have said it in these words, but [basically I said,] "This will not do." So they never made me go back. I just didn't buy that stuff. So naturally when the nuns tried to convert me, or whatever [laughter], I read my Voltaire instead.

COHEN: How long were you in the hospital recovering from this terrible thing? [Tape ends]

Begin Tape 1, Side 2

COHEN: OK, so you were recuperating. You had finished school. You had gotten your degree.

DREYER: Someone helped me write the shortest thesis Reed College has ever had. It was one or two pages, and then they signed me off, thinking I'd be dead. The draft board also signed me off, thinking I was going to die in a year, which was really great.

COHEN: That was something positive, right? Because that would have been, what, the Korean War? Where are we now?

DREYER: This would have been '52. I think it was still Korea. All I know is that I was very happy. I would have been inducted, because I was on a student deferral. And I never went back to tell them I didn't die. So I graduated. And to this day I really don't like wearing those gowns. Plus I have a size-eight head and those [mortarboards] always sit on top and bounce off. I have never had a fondness for this academic sort of snobbery, or whatever. I wasn't brought up that way. Nevertheless, I wore it. I struggled through graduating, and I got lots of support from graduate students and whatnot.

COHEN: I was just going to say that this operation was before you graduated. You went immediately.

DREYER: The first operation was right before graduation. I think the second one was more serious. It probably came right after graduation.

COHEN: And that was a decision you made with the doctor—that this was to beat the odds.

DREYER: Yes. If you have one chance in ten and you can do something about it, you might as well do it.

COHEN: Was this before chemotherapy was—

DREYER: Now, for the same thing, there's an amazingly effective chemotherapy. It wasn't before *any* chemotherapy, but I'll get to that. Because then how we tried to stack the odds next was with X ray. So I had X-ray therapy for two or three months, just on the border of making me nauseated. That went on through the whole summer. And I went in [to Reed] and pretended to work.

COHEN: Now, was this the medical school of the university that you were involved with?

DREYER: No. This was the Catholic hospital. It was a very good hospital. The best physicians and the best surgeon for this elaborate operation, and so forth, were there. I've forgotten where the X-ray therapy was done, but it was wherever they had the machine. And I went in to Reed and tried to continue on my peptide synthesis project, which, by the way, had radioactive stuff and all. It was a very advanced kind of undergraduate place for getting into research.

COHEN: OK. So you finished, but then you had these medical problems to deal with.

DREYER: Well, plus I had never intended to go for a PhD.

COHEN: So then, what happened? I mean, something must have pushed you into this.

DREYER: I had been offered a job before this all happened—at Hanford, the atomic energy place.

COHEN: Right, in the state of Washington.

DREYER: With a very high salary for an undergraduate. They obviously respected the students from Reed. They knew we typically would be smart, like Caltech students. I went out for an interview. I could have done the work, but then this cancer thing came up. That really was an eye-opener. So I had to decide, "OK, what do you do? One chance in ten. Yes, you can try to stack the odds. What happens if you win? Do you really want to be a technician, working for

someone for the rest of your life at Hanford? And then, if you really are as clever as Bob Cannon said you are, shouldn't you do something useful—more than you have so far—with that ability? It's a very rare, special ability. You really ought to do something with it somehow." That did affect my thoughts. And I was interested in this business of how you make this polypeptide bond, how you make proteins, and also in genetics. I had had exposure to a really good genetics teacher at Reed who taught *Neurospora* biochemical genetics. That was related to stuff Caltech scientists were just developing at this time. We even talked about enzymes very early in the game. That fascinated me, so I had gotten into that. As I say, finally, after all this bumbling around and lack of studying, I found something that really, really excited me. I read a book by the physicist Erwin Schrödinger called *What Is Life?* It's on the nature of life; he was fascinated by that. And there was a talk by Wendell Stanley, who worked on the tobacco mosaic virus—trying to figure out whether the genetic material was the protein of this virus or the nucleic acid. And that was utterly fascinating. I thought [the genetic material] had to be nucleic acid, but no one knew at that point. That talk had an influence. It was at Reed. They had invited him there.

COHEN: There's no graduate school at Reed of any kind, so this was all—

DREYER: Now they have some kind of graduate program. But to answer your question briefly, their emphasis is on undergraduate education, with very bright kids, and trying to do really good—what they did with me, in a sense.

COHEN: Yes. Let's just back up. We're talking about Reed. The tuition was no problem for your family?

DREYER: No. That was because [of] my grandfather.

COHEN: Because I know it's an expensive school.

DREYER: Yes. Even though we led a relatively middle-class modest life, my mother worked. She sold real estate, for example. And I had summer jobs in construction. We always contributed. The education wasn't even a problem, because of the Norway connection.

COHEN: I see. So the family in Norway took care of that.

DREYER: And when I needed something like that, they helped. And then there was some inheritance. My grandfather died. I don't remember the time. It doesn't matter. Fortunately, thanks to the Norwegian connection, I didn't have any problems.

COHEN: How long did it take you to recover?

DREYER: I was feeling pretty wiped out. I'm still talking about the summer, when I was undergoing radiation therapy. I was trying to figure out what to do. And just before all this happened, I married my girlfriend, who had come up to Reed. So I was now married and we had a child on the way. And here I am in the summer trying to figure out what to do. She was a nurse, so she could pretty much support me, if she had to. But that wasn't really the interesting thing. What was I really interested in at that point and how could I use this special ability? The University of Washington had a very good department in this whole subject—in biology, how you build proteins, how the proteins fold, and things like that. The head of the department [at Reed], Art [Arthur H.] Livermore, was dealing with this question of how you build these proteins, which is by starting with just one little peptide and these three amino acids—which was the next step from what I had been doing. And Frank Hungate was my thesis [advisor] at Reed.

COHEN: Did everybody have to write a senior thesis at Reed?

DREYER: Yes. And also I had a lot of humanities and philosophy and things like that that you wouldn't get here. So I trotted out to the University of Washington in sort of shabby shape, because of the radiation and recovering from all the surgery. And again I said, "I'd like to come to graduate school here." They asked how my grades were, and I said, "Well, we don't get them at Reed." And the number one person right then said, "Do you think you're smart enough?"

And I said, "Yes, I do." That's all. He just asked me, because they didn't know, because I didn't have the grades to get into grad school. They probably let me in because they felt sorry for me.

COHEN: You never took the Graduate Record Exam or anything like that?

DREYER: No. But this [admissions test to get into Reed], of course, was very similar, had they looked at it. Maybe they did. I don't know; they might have. Nevertheless, they let me in. I didn't want to talk about that super-high score. I am now, because I think it's relevant to what you want to know, about where I come from.

COHEN: Yes, of course.

DREYER: It astonishes me. Oh, I'm flipping back now, for a moment. The verbal on that advanced test—I realized later; I wondered what had happened, how I could do that—had vocabulary, which people like myself are good at for some reason and logical relationships among words; and comprehension, which I'm superb at. You'd read a paragraph and they'd ask you tough questions. Well, I can do that. As long as I have time, I'll get it. So that's why I did so well on verbal, because it wasn't the usual kid stuff. OK. So they let me into the University of Washington. I wanted to work with the younger prof who was doing these things with proteins, but by then I guess they might have gotten some more information on me. The chairman of the [Biochemistry] Department, Hans Neurath, drafted me to work with him. He's a refugee from the Germans. He came over before the war—one of the intellectuals. He drafted me to work with him, and it turned out to be great. He was notorious among his students for being both grouchy and a slave driver, but I got along [with him] famously.

COHEN: Now, you started right in on research? You didn't have to do coursework?

DREYER: Oh, I had to do coursework. I became a scholar, an instant scholar. I studied. I did superbly well—even in organic chemistry, which is rote memory, which I'm terrible at. But three of us would get together, and I would listen and understand it. Someone else would take

notes and someone else would type it up, and we'd get together and study, and so I got through this organic chemistry thing. After that, I became very good at chemistry. I'd typically get better and better and better with more difficult things. When you get to where you have to do 3-D imagery to see how these molecules all work together and the quantum stuff and all that, that's what my head's built for. For rote memory, I'm not. So yes, I had a surprising number of courses there, but I started research, too.

COHEN: And then, after that [period of] feeling lousy and recuperating, that was the end of that?

DREYER: Yes. I never had any recurrence of the cancer.

COHEN: And with all that X-ray therapy, you still went on having even more children.

DREYER: Yes. Well, we're bilaterally symmetrical; one testicle's quite enough. I have three daughters now, and they're all high-visual—in other words, dyslexic.

One other thing we did there was to take qualifying exams. You could take a total of twelve, and you had to pass six of them. I immediately passed the first six, with flying colors. But I can remember—again, relating to the psychology of the brain—that there was one question on there that wasn't about understanding biochemistry. It was, "Who did this work?" I didn't know the answer. "Who worked with insulin?" and so forth and so on. I just couldn't do that. I didn't pay any attention. I didn't care. There was nothing interesting about who did it. I still passed, but it's another piece of the story, isn't it?

COHEN: How long were you [at the University of Washington]?

DREYER: Four years. I could have gotten—scientifically I had done very good work in three years and I could have graduated. Neurath—who is still alive; he has an office there and I saw him just a few months ago—viewed me as his best student, which is kind of fun. But at that time they had a requirement for two foreign languages. They started off being easy, like scientific French and German. But someone decided that if you got a doctor of philosophy degree you should have some serious language, so they kept upping the ante when you'd take the exams. I

had to pass a test in French that was on French political philosophy, which I did, but that's what took me the extra year. I was happy with doing science, perfectly happy. What really slowed me down were these damned languages, again.

COHEN: I've heard so many PhD stories [where] they do everything and then, all of a sudden, this language business comes up.

DREYER: And yet, as a kid when I was in Norway, I played together with other Norwegian kids, and they learned English and I learned Norwegian in four months, or whatever. At age four [this] was not a problem. But now that I'm a smart guy getting a PhD—yuck! So in the brain there's a profound change.

COHEN: By now you had your family already—a wife and children?

DREYER: I had a family, yes. She worked as a nurse. I helped take care of the kids. We bought a—

COHEN: You were in Seattle, which is a very nice city, also.

DREYER: Yes. And we bought a house in the university district. We managed to scrounge. I guess it was from this Norwegian connection. [We had] a modest amount for a down payment. We took over a very low-interest loan. And this house had a not-so-legal second-floor apartment, which we rented out to a couple. The rent they paid us more than paid for the payments on the house for about four years. So there seldom were real financial problems; I didn't need a huge subsidy to take care of that.

COHEN: So those were good years.

DREYER: Yes. Of course, then I totally became a scholar. I got good grades, learned a lot, loved the theory, and everything else.

COHEN: You then went to NIH [National Institutes of Health].

DREYER: Yes.

COHEN: We'll start that next time. OK.

WILLIAM J. DREYER

SESSION 2

February 19, 1999

Begin Tape 2, Side 1

COHEN: You had some thoughts after the interview last time.

DREYER: Well, if you're a professor here involved in teaching all these brilliant students, [there is the] question, "Where do creative scientists come from?" So I thought it might be appropriate to go back and mention a few things that had to do more with science, when I was brought up. And that would start with the fact that my father died in that accident, and my mother had the good sense to realize that it would help me a lot, in the summertime during vacations, to go visit her brother in Michigan and have a male [role model] and learn things that she couldn't begin to [teach me]. She realized what kind of guy I was, and she couldn't deal with that, but he could. [His name was] Ed Richards. As an aside, again going back—both sides of the family came from seafaring communities. Hers was Cornwall, in England.

COHEN: She still had family there?

DREYER: She still had family there. They went to sea a lot. And so did the Norway family, in history. And this goes back to the question of, where does this kind of brain come from? Perhaps this is the wrong place in the discussion, but if you're a Viking going to sea or climbing mountains or fishing even, and you don't have the ability in your head to create maps—before they had written language or maps—you'd die. So it was a powerful selective advantage for the visual abilities I have. I see maps, I see rivers, I see whatever, in my head. I'm willing to bet [that] that came from selectivity. Because [there are] parts of the world where you die if you don't have those abilities—literally, because it's critical if you don't have maps. Sorry: I'm going into a little bit of theory about all this, but it becomes important if you're thinking about the huge differences in brilliant scientists here at Caltech, which is part of what you're interested in. The first written language, it turns out, was for bean counting in Egypt.

COHEN: Bean counting?

DREYER: Meaning numbers and counting—basically to keep track of goods in societies where they had domesticated plants and animals, which is the Middle East. It wouldn't surprise me if there was a big selective advantage for those people who were literate and who could handle the—

COHEN: Mathematical concepts?

DREYER: Well, just arithmetic, really—the stuff I'm not terribly good at. And maybe they even lost some of the primitive qualities that led one to be able to do what wolves do—move around territories.

COHEN: Yes. Certainly the seafaring and the map and the visual make a lot of sense.

DREYER: Well, and it's again relevant to try and understand scientists and where different kinds come from. OK. So my uncle Ed had a city job. He was middle class. His job had to do with knowing all about heavy-duty equipment, like the [kind] that lifts freight at docks and warehouses. He handled all the parts that dealt with that as his job at this company. But he had a farm. It was his farm that I went to.

COHEN: Now, these were Depression years. This did not affect your family too much?

DREYER: Well, my dad had his accident in 1938, which would have been almost post-Depression. Our family didn't seem to suffer. I didn't even realize there was a Depression as a kid. It probably had to do with the combination of the fact that he was very good at what he did and that they still sold paper during the Depression. And the connection with a rich grandfather.

COHEN: A rich family.

DREYER: Very well off.

COHEN: So you spent your summers with your uncle.

DREYER: And he had an amazing number of hobbies, which he taught me. These included photography. I'd take pictures and movies. I'd make fancy things with a very special kind of movie equipment—special effects and all these things—as a young kid. And [I learned] how to develop film and that sort of thing. He collected weapons: guns and whatnot. He said [that] when I was old enough he'd give me a .22, which he did. He taught me how to use it safely.

COHEN: Did he have his own family?

DREYER: He had a daughter, who is still alive. She was maybe eight years older than I am, so it was not relevant, really.

COHEN: I see. So it sounds like it was nice for him to have a son, also.

DREYER: Yes. He didn't have a son. I haven't really asked Mary Jane how she felt about all that. But she was enough older so—

COHEN: It wouldn't matter.

DREYER: She was off in college. He was also interested in wood and woodworking. He would harvest black walnut—cut it himself. He did lathe work and built things. So I learned all that. He did mechanical things, fixing pumps and making his own watering system, and he loved to camp and fish. We would go on two-week trips up to northern Michigan, way out in the woods, photographing, boating, all that sort of thing. So this was really great, because [back at home I was] living with a mother and a sister. And Mother was really interested in finding a man for herself. She dated a number of different guys; so it was very good. It was a nice way to get away. I learned all those things. When I went to Norway—which was a fair number of years over the period right after my dad died—again, I had three uncles, and they taught me a variety

of things. They were nothing like an intellectual family, literate and whatnot, living in the city. They were outdoor types, basically, brought up to play and hunt and fish and boat. One uncle in particular—Uncle Paul; this would have been after the war, now—was returning a large, forty-four-foot sailboat down the coast, and he invited me to go along. That was quite an experience. It started out very calm; then we had this horrendous storm. It was a great adventure. I wasn't afraid, or whatever, because—

COHEN: Maybe you didn't know enough to be afraid.

DREYER: No. The boats are very hard to sink.

COHEN: And I gather you don't get seasick.

DREYER: No, I don't get seasick. And I enjoy adventure. So he provided those kinds of experiences.

COHEN: It sounds like you had a wonderful, wonderful childhood in many ways.

DREYER: Yes. Camping up in the mountains with backpacks, both before the war, when I was much younger, and after. Grandfather had a wonderful home; it was the home of a rich man who had servants who'd cook whatever he wanted. And he doted on his oldest grandson, so I was pampered. And he also had a hobby of science, because in the house he had steam engines and a telescope, which he gave me—a big-sized telescope. He gave me some exposure.

COHEN: Now, all these people—this family of yours was fluent in English?

DREYER: Oh, yes. All the Norwegians spoke English. I mean, they were bright people. And they traveled. They spoke multiple languages. They just weren't intellectuals in the normal sense. I guess my grandmother was more that kind of a person. [My grandfather had] a large factory. He was very fond of art, and they printed volumes on art, and he collected. He had [works by] Edvard Munch, who is a famous Norwegian artist; he collected his paintings, and

they became worth millions. They also did—when photography became publishable, and etchings and all that sort of thing—books that were scenic, about mountains or whatever, and books on the arts. High-quality sorts of things. And I got to learn quite a bit about the way that was done—how the machines worked. So I had exposure to technical science through that.

And then [there was] another surrogate father. We lived in a duplex in a suburb of Wauwatosa, and the man below us was the head of Children's Hospital, a medical doctor. He sort of took me in also as one of his sons. He had a son who was a good friend of mine. But he clearly liked me and appreciated that I had some very special qualities. And I was more stable. His own son was a bit wild. He had a farm also. I'd go out with him to his gentleman's farm. But there was nothing [in all of this] that made me think of being a professor. I did think of going into medicine, because I was interested in those matters. But it became clear that my brain wasn't right for that; I probably wouldn't have made it. No way was I going to wind up enjoying memorizing all this stuff that you really had to do. So that [medical ambition] kind of faded away. I nibbled at it at Reed.

I was going to mention something about Reed College. First of all, I realized that the name of the man who did the N*eurospora* work was Frank Hungate. And with Art Livermore, whom I [mentioned] yesterday, I learned a lot of chemistry and how to make radioisotopes and handle them well. I had become interested in [these questions after reading] *What Is Life?* I was clearly a philosopher by bent, and I still am in many ways. And then this Wendell Stanley lecture was very provocative. It clearly led me to be interested in Art Livermore's lab. At that time, I guess, it was really leading-edge research in these areas, with radioisotopes, showing where these amino acids went, using paper chromatography and separation techniques. Those were the state of the art. Part of it, also, was undoubtedly because they were close to the Hanford atomic energy [installation]. Undoubtedly they had grants. They probably cultivated students like me, who would then work at Hanford, which is why they gave me an offer, I realize.

I clearly had, throughout all of this, the ability to invent with great ease, because I'd see things in my head. As a kid, I made little gizmos to deliver food to birds out in a tree. All these things I did. But as an undergraduate I wanted to know, what is life and how does it work? The question was very clear, and even some of the theory, but the methods were [not there]. So even there I worked on finding a better way to do electrophoresis, building a little instrument. Then

when I went on to grad school—they didn't mention it much, but I realize that when Hans Neurath drafted me, it would have been after they found out—

COHEN: That you were able to do this kind of thing?

DREYER: That I was their top student. He didn't do that until I was starting to get the top grades and qualify and all that stuff. And even then—clearly, I would have been more successful in many ways with theory than with experiments. As a new grad student, I went into Neurath's lab, read all the things, and put together a diagram of theory about how all this stuff was supposed to work—how the proenzymes [interact?], and what bonds, and all this stuff. I started working on it, and it was good enough so that they put postdoctoral fellows on it, which kind of miffed me a bit. He had a very high-tech lab. He had the best, newest ultracentrifuges, electrophoretic equipment, contacts with Beckman Instruments. And I helped advance the state of the art there. We made this elaborate optical-auditory equipment. They are still methods used, even today. And I had a chance to use them all.

COHEN: How many students, postdocs, did Neurath have?

DREYER: He had quite a few technicians. I had the benefit of having technicians work for me from the start. He probably had four or five grad students and postdocs.

COHEN: I see. But not like the stables of people we have here at Caltech.

DREYER: No. But for then, he had—

COHEN: For then that was a lot.

DREYER: He was well supported.

COHEN: You didn't have to worry about—?

DREYER: I had my students write my grants for me. He just said, "Go do the work." He wrote my papers. [It was a] great place for a dyslexic. I've learned since then how to overcome—you know, how to become rather good at that, but not easily. But he spoiled me. He did give me a dictating instrument. As you've noticed, I don't seem to have a particular problem dictating. That's a very old thing in human evolution: speech and verbal transmission of history. This business of the bean counters, I'm talking about—written language—it's brand new.

So there, again, there were instruments that I invented, as it were, for fast-flow analysis. It made some very nice science possible there. That becomes recurrent—this ability to, when I need something, invent the instruments you need to do it.

COHEN: Yes. Well, I'm going to spend considerable time on your lab here. So you then had a postdoc at NIH. How did that come about? That's where we were going to start.

DREYER: Well, basically I had the chance to go wherever I wanted. In that era, too, things were getting quite well supported. And because of my work on these proteolytic enzymes, as they are called, I was offered a postdoc at the Rockefeller Institute working on enzymes—a very high salary, with all kinds of perks and things. But by then… It's one of my faults, in many ways; I tend to get bored with something once I understand it. I also like to leapfrog. I don't like to just compete head-on with other scientists. I could see that a French group was going to do what I would do next in this field. And there was no way I wanted to go on with it. Basically, it would waste my time. By then I had the knowledge that I could probably do whatever I wanted. What was the point of doing what someone else was doing? I mean, I went into all this because I didn't want to waste my life. So the question was still there of how life works; that is, how you get an active enzyme out of an inactive one. I began to learn about these bigger molecules. And there was a guy at the National Institutes of Health—Christian B. Anfinsen—who had theories about how you make a protein. By the way, this was post-Sputnik, and the government was pouring money into medical research at the National Institutes of Health. And DeWitt Stetten [associate director of research at the National Institute of Arthritis and Metabolic Diseases, NIH] had been able to help identify extraordinary talent at the various labs. One of the things that he wrote and told me was that, when you are trying to recruit—as we are now in the Biology Division—when there's someone really extraordinary, it's just obvious. You're at a seminar and

you know it. And that's what they had done at NIH. That's what I wish they would do here at Caltech.

COHEN: So you went there and you gave a seminar.

DREYER: OK. So Anfinsen was one of these people. Stetten had set up this wonderful place. It wasn't just Anfinsen. But Anfinsen had a theory about how you make proteins. I didn't believe it, but I went to visit him and I enjoyed the way he thought and the interaction. In fact, he was excited about this subject. So I applied for a National Polio Foundation postdoc and got that. It was about half of what I would have gotten at Rockefeller. And I went to NIH.

COHEN: So you moved to Bethesda or to Washington?

DREYER: Bethesda, which is just outside Washington. We lived in Rockville. We sold the house in Seattle and we used the profits from that to buy a house in suburbia—in Rockville, Maryland. The Anfinsen lab was extraordinary as a place to go. And even though my theories as to how you build these things were quite different, he tolerated that. He loved to stir the pot. He had these brilliant people; what they had by the late fifties, or early sixties, was a research associate program at NIH. And it was very hard to get into; they took the very best graduates from the very best medical schools who also had research interests, who clearly had shown evidence of research ability. And if they could get into this program, they escaped the draft for physicians; there was a physicians' draft. And I got to play with these guys. There weren't any women that I can remember, as a matter of fact, at that time—there are plenty now. It was a really great place to be, and thanks to the nature of Anfinsen I got to develop my own program right away. I made a pact with him that I would help him with one of the things he wanted to study, and that was the evolution of proteins. But then I completely changed fields. Without Max Delbrück, I learned phage work. What I was after, and what others were [after] at that time, including Max Delbrück—Seymour Benzer [James G. Boswell Professor of Neuroscience, emeritus] was trying to do some of these things. And Sydney Brenner, who was a very famous scientist, was trying to do [it] in England. I wasn't trying to compete; I was just very interested. This was a topic—

COHEN: Was the Cold Spring Harbor business going on already? Were people gathering for the summer?

DREYER: Oh, yes. But there happened to be someone at NIH who did phage work. So I could go up a few floors and learn how to do it. And basically what I wanted to do was to find a protein made by the genes of this virus, where you could do the genetics and correlate the genes with the protein. And I knew the protein work from both Neurath, when I worked there, and from Anfinsen's lab. So if I could get the genes and get a protein small enough to work with, then I could crack the genetic code and find out how the code works—because no one knew at that time. That was part of this whole theme: What's the nature of life? So, thanks to that background, I could do things that were amazingly novel for those who didn't have that background. I found a way that the phage coded for a very small protein. These other [people] were working with huge things [molecules?] that were hard to study. I dinged around with one of these big ones where you had [gene?] genetics, but it was just intractable to do any of this code-breaking. And typically of me, my best friends don't believe the stuff that I said I would do. I felt that this phage, the virus, coded for some [form?] of lysis [words unclear]. That made a lot of sense: to get it out of the bacterium after it made copies of itself. And that turned out to be right. I also wound up being involved with a really cool assay for mutations, by just exposing the plates to chloroform, which turns the bacteria into a substrate so that the enzyme just makes halos around the plaques. That allowed [word unclear] and, based on protein chemistry, made what are called conditional lethals. If you raise the temperature, the enzyme can't work. So it couldn't get out if you'd lower the temperature. It can't [lyse?], so it's temperature-sensitive, things like this. So these things then allow the genetic map [of the protein] to be made. Phage lysis is what it's called.

So I went to Cold Spring Harbor, which you mentioned, and there was one of the people who was a Delbrück phage group member, named George Streisinger. [I] basically talked him into helping make the genetic map using this phage lysis [word unclear]. And, again, one of the things that's happened to me [is that] when you have something really exciting and someone who has never had anything like that happen, you get into this strange personality thing—taking credit, wanting to be famous, maybe get a Nobel Prize, and things like that. Some of that came

up with George Streisinger and Anfinsen, so there were some interactions. [Streisinger] was especially jealous of Anfinsen publishing some things of mine and George's. So this is the negative side of things, but mostly it was fun. So we wound up getting a genetic map and starting the process of cracking the code.

COHEN: Now, where was this work being done?

DREYER: That was at NIH, in Anfinsen's lab. I mean, they promptly made me a permanent research scientist and wanted me to stay around, I know.

So that work got a lot of attention, because it was better than any of the others that [words unclear] working on and clearly would have cracked the code. Marshall Nirenberg was just a couple floors above, [and he] asked me to help him do an amino-acid analysis of a funny protein strata that he'd gotten with his biochemistry and test tube whatnot. I did it, and it came out to be all phenylalanine, one amino acid. What he had been able to do was basically use an artificial template in a test tube that had a certain code, and it made a protein that was just phenylalanine, and that was the break that cracked the genetic code. So I helped him do that, which was the thing I had been trying to do, too. I wasn't downhearted or anything. It was just fun stuff that was a hobby.

COHEN: He was a much more established scientist than you.

DREYER: Well, not a lot. I mean, I was young, but by that time we were both research scientists at NIH. He kind of bumbled into it. His wasn't as planned as my project was. It was one of these things [where] anyone who was interested in life wanted to know how the code worked. I don't know what spurred him to do it. So that's the work that clearly got the attention of Bob [Robert L.] Sinsheimer [professor of biophysics 1957-1977; chairman of the Biology Division 1968-1977] at Caltech.

COHEN: When you did this work with Nirenberg, did you publish something together?

DREYER: No. I just did [him] a favor. I didn't contribute, really. I was just helping him find out what he had. In no way did I contribute to that. He could have done it. Well, others could have done it. This happened to be the best method around for what he needed. I could do radioactivity and show it. I told you [that NIH] was a place with a lot of talent. [It was] a really exciting place to be.

COHEN: And people cooperated with each other, which is interesting, too—from what you're telling me.

DREYER: Well, I've always had people cooperate with me. It's my nature. At the University of Washington I'd wander around. At NIH I wandered around. And here, at Caltech. And that may be partly a matter of just expecting people to be interested and cooperate, and they do. I'm not in science for some of these other reasons. I just have never been that way.

By then I had given a talk in Moscow. It was the first genetics thing they had ever had in the Soviet Union. [James D.] Watson was the chair of my section. And clearly people realized that this approach was going to lead to cracking codes. Nirenberg was there also. I realized that he really had the answers already. He had the critical problems solved, but nevertheless there was a Brookhaven symposium where I presented this work. This would have been about 1959 or 1960. I had been at—I think it was—a Brookhaven meeting and presented, as a little bit of a publication, this assay I told you about. And amazingly, Bob Sinsheimer and others here were determined to get me to come out and give a seminar. By then I had been asked to go all kinds of places. But I loved NIH. So he kept at it. Finally, I agreed to come out to Caltech and give a talk. One of the other things—again, this theme I want to keep pointing out—was that we were again limited by equipment at NIH. I had helped develop the equipment that Nirenberg used—the methods and whatnot. Anfinsen didn't—he said he always liked test tubes. But he totally tolerated my instrument-developing activities. I was active in trying to build instruments and invent them. It was very tricky, because they wouldn't let you work with private companies, unless you took vacation time, which I did. I worked with one private guy to get something I wanted. Again, I could always invent it, but you've got to find a way to make it. And sometimes in private industry it's easier to get whatever you want.

COHEN: Now, is this because NIH didn't want to fund any equipment buying? I mean, what was the problem?

DREYER: No. For decades money just dropped on me.

COHEN: So then, what would have been the objection to building the equipment?

DREYER: Well, at NIH we could, but there was often a waiting line. There was a lot of demand for the shops.

COHEN: Oh, I see. So it was just getting in the shop and getting the proper technicians to do the work.

DREYER: Getting the right skills and the right people. It was a good place to be, but it took time. Whereas when I met someone who was very interested from the private sector, and who wanted to do it rapidly and give me the equipment—Warren Gilson was one of these people. I had to take time off to be able to talk with this guy, or possibly get in trouble with the rules of—

COHEN: I see. What company was this, now?

DREYER: Gilson's. He was the boss [of Gilson, Inc.].

COHEN: Well, I suppose there's a conflict of interest. You were in a government lab.

DREYER: Well, yes. Now they realize that to keep people they have to change their rules. But what was so neat about getting to know Warren Gilson was the arrangement we had, which did include some royalties on things I invented for him. We just shook hands. We never had any worry about contracts, talking to lawyers, and all that junk. But I got the equipment, and when I needed something different that was better, I'd call him up and say, "Hey, Warren. What would you think about so-and-so?" Three weeks later [it] would arrive gratis. That happened here at Caltech, too; I kept it up for a long time. And then you get a whole team immediately working

for you. And he benefits, of course, because I use this stuff to do leading-edge work, and [I] publish it. But that annoyed me, because I really wanted equipment to do my job. So what happened was I realized that you needed automated equipment to do this stuff. Machinery was just not up to the job, even with this little protein. It was horrendous, trying to do what you needed to do. We could do it; we had invented some methods that made it a lot faster and a lot easier—some not even published. But a man named Charles Sibley—Sibley was a visiting prof who came to Anfinsen's lab, and he was famous for evolution of birds. I don't know if he's still alive [d. April 1998]; I'd like to go back and see if he is. He came to Anfinsen's lab both for the protein chemistry and molecular evolution stuff. Anfinsen wrote a book [*The Molecular Basis of Evolution* (1959)]—the first book ever on the evolution of proteins, molecular evolution, which I helped proofread, reading as he wrote the chapters. So I became quite knowledgeable about that. Sibley came there for that reason, too. But Sibley wanted to do his study on lysozymes. [It was] the same thing—small molecules you get from eggs. It's basically a penicillin-like thing that does the same job for [word unclear] and for the egg white and birds and [word unclear] as penicillin. So he came there wanting to compare birds and study their [family] trees by sequencing the [word unclear]. Well, the methods were really primitive for what he wanted to do and for what I wanted to do. So we wound up with a document that basically was a proposal to build a set of automated instruments to make all this much more reasonable.

So I finally agreed to come to Caltech and give a seminar, in which I of course told about this phage work, but I also mentioned the new project… [Tape ends]

Begin Tape 2, Side 2

DREYER: OK. So what happened next? Here I was in my early thirties. In 1961 I got a letter from Caltech offering me a full professorship and what was then a high salary of $18,500. I had been raised way up in NIH, fifteen, sixteen [thousand] or something like that. Here I was this young squirt with a full professorship offer, and I didn't want to do it. For obvious reasons, I liked NIH—I didn't have to worry about grants. But they [Caltech] had promised they had a grant and that I wouldn't have to write grants and that they would put me on a program project. The big deal thing at that time was that they [NIH?] were giving away money to different places they felt were top notch, hoping they could help spend their money. It was a different world.

And partly because of this desire to build instruments. And also I talked with DeWitt Stetten, this guy I said I admired for his ability to pick really gifted people. I showed him the letter. By then he was my boss. I had moved in with the microbiology lab he had set up. He said, "They've made you an offer you can't refuse. You've got to go." I wasn't trying to get him to match anything, because [my salary] was pretty close to that already.

COHEN: Well, Caltech was a place that had *the* reputation at this time.

DREYER: But I didn't feel that I belonged here, because I was dyslexic. I knew that I wasn't a good writer. I knew I did very good science, and I knew I was great at a research institute. But academic life I really had reservations about.

COHEN: Had you ever taught before? Coming to Caltech means that, if you are a professor, you have to teach.

DREYER: Yes. But what I taught here is more or less the same as I did there. We would have group sessions with discussions of advanced topics. And amazingly I got away with doing that kind of advanced teaching, which included postdocs, grad students, eventually some undergrads, and professors. I've gotten away with that through my whole time here. Lecture courses—as you know, I left the University of Washington because I thought that was a terrible way to teach.

COHEN: OK. So you made the decision to come. How about your wife? Was she happy to come here?

DREYER: Oh, sure. We came in '63. She didn't really care one way or the other. We liked the West Coast, the mountains and the ocean. The smog, by the way, was horrible.

COHEN: Those were the bad years.

DREYER: Yes. It was really horrible. But I'm not very sensitive to it. Swimming in a chlorinated pool does more harm. So I accepted [Caltech's offer]. I still am not sure which

would have been the better place for me to be, frankly. But this is certainly not that bad. And a major part of it was the instrumentation. The shops here were great—many different kinds of shops. And JPL [Jet Propulsion Laboratory]. And the one that had built the telescopes—central engineering. And shops in chemistry and in biology. So that was a major part of my decision—my desire to build the tools that I could use to find out about how life works.

COHEN: This is the early sixties. Who was the chair of the Biology Division at that time?

DREYER: I think Ray Owen [professor of biology, emeritus; division chair 1961-1968] was the chair. And, by the way, before we leave NIH—I warned you of my habit of moving on to a new kind of very challenging project once I find the answer, or others do, in an area of science where I'm into it because I'm curious and want to know. And I had already started doing that. Caltech didn't know; they thought I was a phage geneticist, because I was doing this leading-edge [science]. Clearly, they were impressed by this squirt who suddenly left Neurath's lab and was with the top of the whole field of phage. They undoubtedly made this ridiculous offer based on the phage work. They did not realize that I thought it was all over and not worth pursuing at that point. So what I did was I wound [things] up at NIH. Speaking of interactions and all that, I was at a coffee shop and bumped into this MD at the National Cancer Institute named Mike Potter. He studied cancer, and he had these mice with multiple myeloma. Like humans, they secreted proteins into their urine; they're called Bence-Jones proteins. And they had proteins in their bloodstream that were homogeneous and spiked. I understood all of what that meant. And he thought these were the key to cancer. But I looked at it, and what the myeloma cell basically did, before it turned into a cancer, it was basically a cell in the immune system that made antibodies.[1] And I realized that these were homogeneous antibodies. They were monoclonal antibodies, before you could make them to order. And that was controversial. A lot of people in immunology didn't believe that at all. I'd go to meetings and say this—blah, blah, blah—but it was true.[2] And that a lot of protein chemists like myself use these tools to map these molecules and start looking at them and use some of the new techniques I helped invent for protein

[1] Bill realized then what we now know to be true, that the protein in the urine is the product of the myeloma cancer. Each myeloma is one antibody-producing cell that has transformed into a tumor and is producing a single antibody. –JRD.

sequencing to study these molecules and ask, "How do genes make them? How can you make a million different cells with a million different antibodies from genes?" And nobody knew.

COHEN: Now, was anybody working on that sort of thing here at Caltech?

DREYER: No.

COHEN: And they didn't even know you were working on it—well, they must have—

DREYER: No, they didn't—not when they gave me that offer. So they set up equipment for me to do the phage work. I went along with it, but I really didn't want—

COHEN: That wasn't your interest anymore.

DREYER: But I felt I had to. So we began to get very provocative, extremely curious answers, combining immunological techniques with protein chemical techniques, and so forth. Electrophoresis I had done as an undergrad, [words unclear], and things like that—putting it all together. And it was beginning to take shape as a most extraordinary project. We turned people at Rockefeller on to it. So that's the main thing I had been doing back then by that time. You see, I came in '63 but the offer was made in '61. So I felt obliged to go on and do some of the phage work, but I never even got off the ground there, really. People were angry with me for not caring. Like Francis Crick, who wanted to prove one of his theories with my enzyme, and I wasn't moving fast enough with that for him. He threatened to do it himself, but— [Laughter]

COHEN: [Laughter] But he wasn't here. Where was he?

DREYER: He'd come by. What he did—what they did, also—was scour the world for ideas, which is a good thing to do. So he'd make a circuit. He was in England. OK. So I brought along Claude Bennett, who was one of these superb MDs. J. Claude Bennett. And he and I,

[2] Having a large amount of a monoclonal protein was the key to being able to map these molecules. –JRD.

because of the phage work, were asked to write for the *Annual Review of Biochemistry* a paper on the genetic code, which we did ["Genetic Coding for Protein Structure," *Ann. Rev. Biochem.* 33, 205 (1964)]. Thanks to Claude, it was well written. We worked as a good team. But really he was interested in immunology, as I was. That was the project we both wanted to pursue. There was a guy who was a Caltech graduate who went to medical school at Johns Hopkins for three years and he had applied to Caltech for grad school—Lee [Leroy E.] Hood. So Lee Hood came to the lab, probably in '63.

COHEN: As a grad student?

DREYER: As a grad student, and also to finish his fourth year in medical school. He never had, really, an MD.

COHEN: He didn't do any clinical work.

DREYER: He didn't do clinical. His fourth year was [in] my lab. And he was, like all first-year grad students, kind of a klutz, working very hard. He was very motivated, and a very competitive guy, but he didn't get an awful lot done that first year. But we carried on with these peptide mapping methods and improving all these things. One of the things, by the way, that happened at NIH—Beckman Instruments made the ultracentrifuges we used to prepare a lot of these things. And remember, I had worked with ultracentrifuges before. And we had problems with the rotors heating up in the vacuum. [Beckman] clearly hadn't been working on these; their really big interest, I expect, was the atomic [word unclear], separation of things; same tools I used for chromatography [words unclear]. And I said, "Look, if you have trouble with heat transfer in the vacuum, why do you make it like a thermos bottle—silvered? Why don't you make these rotors black?" On my advice they began doing that. It obviously helped them a lot, and they asked me—I didn't have any patents or anything like that; I just said it was crazy not to do that—to consult for them when I came out to Caltech.

COHEN: This was Beckman Instruments?

DREYER: Yes. The Spinco division. Spinco, as in centrifuges. So I said, "All right. I'll consult for you. But what I want is an automated amino-acid analyzer—not one where you have to have a technician working all day long counting dots. I want to make it so it puts its own samples in and a computer analyzes the data." Surprisingly, they agreed to do that. So, again, I had this ability, and by then I knew it, and I dreamed up how to do this, and told them. But the people there—a lot of engineers don't have this spatial ability. They make diagrams with rulers and squares and all this sort of thing, and they draw it out and analyze it and all that. I'd show them ideas for how valves could do this stuff, and they didn't get it. It was a real strain.

I love to fly, and I was a member of a flying club. I flew myself up to Palo Alto, which then was quite a nice thing to be able to do.

COHEN: Now, that's where Spinco is?

DREYER: That's where it was. It still is, I guess. They had made a contract with Caltech to deliver the prototype here for such-and-so-many bucks—a reasonable price. And everyone knew I was consulting on the design; I've always kept things that way. And I didn't take any money for it, except just maybe a little consulting fee for travel. I really wanted the instrument. But that dragged out for a couple years. They just weren't able—they weren't moving on it. They did market research, as big companies do. One of the people they interviewed was John Racs. He's still here, by the way.

COHEN: He's a technician?

DREYER: Hungarian. He has the patience of Job and he was counting these dots and running these hand instruments. I hired him because he had that kind of patience. They asked him whether he wanted an automated instrument, and of course he said, "I don't need it." And that's what happened.

COHEN: [Laughter] He had plenty of time.

DREYER: Yes. That's what he gets paid to do. And they weren't even sure that there was any need for it. So I finally got fed up and spent a long weekend in here, taking parts from various things I had around the lab that were really designed for something else. And I built the working breadboard instrument, with a fraction collector and little hummingbird-like things that went down in there and would just activate pneumatic cylinders and things. It wasn't classy, but it showed the feasibility of the concept. It was very workable. And I did that in just three days or less. I called up Arnold Beckman and Paul [name unclear], who was chairman or something like that. I said, "Look, how about coming out and having a look at this instrument? Because I'm frustrated with your Spinco." And they did. And I showed it to them, and I got the instrument. They understood. I said, "Look, if the competition, like TechniCon, comes out with something that will do this, you'll never sell another amino-acid analyzer." And they did it. So that was one of the first things—

COHEN: That was one of the first things that you did here.

DREYER: Yes. This all had to do with Charles Sibley and his dream. You asked what I meant by better equipment—what was slowing us down. This really was slowing us down. And we hooked it up to the computing center. I'm not good with writing software; I refuse to learn—but graphically I could do it. I designed the software, and thanks to being at Caltech, there's a programmer there. And lots of money, again, was not the problem. She wrote the software, and it was a leading-edge instrument that was copied by others to make a lot of new things.

COHEN: So you had your instrument. This would have been…?

DREYER: This was '65 or '66.

COHEN: Let's see. I have written down here [something about] a microchemical facility.

DREYER: This was its first instrument. I also had some very high voltage—10,000-volt electrophoretic equipment that would have been—

COHEN: Where did you have all this stuff? Where were you located?

DREYER: In Church [Norman W. Church Laboratory for Chemical Biology]. I just got out of there a year and a half ago. I wanted to close down my chemistry. But we'd better go back, because I learned something else by '65. I told you—this is the side of the instrument development after I came here, and the high-voltage equipment.

COHEN: Now, what was the high-voltage equipment?

DREYER: That was separating the amino acids very rapidly—again, for the ability to sequence very quickly. There was mass spectrometry, with a postdoc who came from Fred Sanger's lab. Sanger won the Nobel Prize twice [1958 and 1980]. Anfinsen won it once, by the way [1972]. But he and Bill [William R.] Gray and I helped dream up instruments that were leading-edge.

COHEN: Now, Bill Gray wasn't a professor?

DREYER: He was a postdoc; his name is on one or two of these things. And he and Claude Bennett and I—and I had technicians—kept on with this myeloma project in collaboration with the guys at NIH. And that led me to become increasingly convinced of a radical thing that had to do with the genetics of the way you made these. The data were overwhelming by then, from what I could see. Lee [Hood] didn't get it quite, just because he didn't have the experience. Plus, he's never been—he's a different kind of person. He's superb as a scientist, and he's superb as an administrator and fund-raiser, but he wasn't a risk taker, or an imaginative innovator, or whatever. And I am to a fault, so we make a good pair. We still do, to this day. OK. So Claude Bennett and I wrote a paper. ["The Molecular Basis of Antibody Formation: A Paradox," *Proc. Nat. Acad. Sci.*, USA, 55, 826 (1965)] That caused a furor, because what it said was that good old Caltech—George Beadle, I guess—[and the] one-gene, one-enzyme [leading to] one protein [theory] was wrong. [The paper] was radical. It said that you take a gene here and a gene here and you have little genetic machines that cut and splice those genes, like you would a film, and paste them together and make a new gene. And that gene is now the gene for that particular cell. And that's how you remember how to make that antibody, with this end

made from that gene and this end made from the other. And that's what a monoclonal antibody is—it's made from a cell that has had its genes spliced.

COHEN: And nobody had talked about splicing genes before?

DREYER: No. In fact, they didn't for twelve more years. They still don't today. I'll come to that.

COHEN: How did *you* arrive at this?

DREYER: We had the data. We had all this evidence, starting back when I was at NIH, which I could understand because of my background. The fact is, the people in the field of immunology, including Ray Owen, the division chairman, didn't get it. They just didn't see how this could possibly be true. I had to ask myself why that was so, and part of it is the old [Thomas S.] Kuhn story [about what happens] when someone from the outside comes in to a field where everybody believes a different set of beliefs, like a religion. [Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 1962.] Of course, from the outside it seems like nonsense. And you have a paradigm shift. I was the guy from the outside who said, "This is crazy. This is the way it is, really." So why was it so hard for Ray Owen and others to understand this? It violated the paradigm; it said you really do alter the genes as you make cells different in your body. I want to come back to that, because the old paradigm may just now, as we head into the next century, be about to change. The dogma is still there. Very few people believe [that genes can be spliced and rejoined to make new sequences], even today, except in the immune system.

COHEN: You're saying this is true for other systems also?

DREYER: Yes.

COHEN: Which has not been accepted.

DREYER: That's true, it has not been accepted, but my latest paper concludes that, and it's probably right. The dogma that all the genes in adult cells are the same as in the egg or sperm has been around for a very long time, but I am sure that it is wrong. So the fact that my theories about antibodies bucked the existing paradigm is one reason they were not readily understood or accepted. The other is that [getting it] depended on understanding the results of a variety of different technical procedures from different fields, some of which the biochemists did not understand and some of which the immunologists did not understand. You had to understand double diffusion assays, which tested for whether proteins were similar or not. You had to understand protein chemistry and what peptide mapping told you. Peptide maps gave a whole bunch of spots that were always the same—representing the constant regions of the antibody molecule—and other spots that were always different—representing the variable regions. You had to understand molecular evolution. You had to put together data from many disciplines. I felt that the fact that antibodies are the products of gene rearrangement was all very clear in the data, so why was it so hard to understand? This is one of the things that's really interesting. Why could I see it and most of my colleagues could not? Again, part of it is clearly this issue I've been talking about. I have a strange brain that thinks in images. Everything I'm trying to say, I realize, is pretty much images. And some brains don't do images; they can't see it. So I actually suffered in salary pretty much, because Ray [Owen] would get feedback from other scientists that they had this kook in the department. [Laughter] And he didn't understand at the time—I don't know what he'd say today. But that was fun, because I knew I was right.

COHEN: Now, you and Bennett: Were you alone in the wilderness, or did other people see it?

DREYER: We were alone. Even Lee [Hood] didn't see it at that time. Within a year he got it, but there was no one else.

COHEN: Now, did you ever do an experiment? Well, you said you had the data, so you must have been doing—

DREYER: Yes, we had the data. It was there, if you read it. I did do one paper. It basically was when there was a seventieth birthday celebration, I guess, for Anfinsen, and they asked a bunch

of us to write something out. I took the occasion to explain how much we knew and why we knew it.

COHEN: But it just plain wasn't accepted?

DREYER: No, not for twelve years. And, again, I wasn't unhappy about that, because I knew it was right. Somehow or other, it's fun to know that you know something that nobody else knows and can't understand and whatnot.

COHEN: But would you give a paper when you would go to a meeting or something?

DREYER: Sure. And I'd wind up at international meetings, of course, because this was nonstop. One of them that happened early was in Israel, which was kind of neat—to visit there and tour around at the Weizmann Institute. As it happened, one of the main people at the Anfinsen lab, Michael Sela, was by then the head of the Weizmann Institute. That was an amazingly talented group of people. This was immunologists—the midwinter conference on immunology. And I gave a talk on it. They just had a very hard time understanding it. There's nothing hard to understand, today.

COHEN: No. I feel like I understand it.

DREYER: Yes. That's what I mean. It's an amazing psychological phenomenon. But they just had been taught that it couldn't be true. And they also missed the knowledge of the molecular genetics of protein chemistry and all these other things that I had brought to the party. So there was a partial excuse. They were so interested, though, that we were supposed to be playing in the afternoon but whoever led it said, "Is anyone interested in having a special session with Dreyer and asking questions about all this?" And the whole place showed up. One guy, whose name I don't know, got it, understood what I was saying, and got up and helped me try to explain this to 300 people, or whatever it was. And it was just amazing. It wasn't that we couldn't communicate. It was just—

COHEN: Going against what everybody felt was true.

DREYER: And those two factors. It relied on background knowledge that most people didn't have. It was a unique combination of protein chemistry through molecular genetics that nobody in immunology who worked in phage [word unclear] genetic code [word unclear]. No one had read Anfinsen's book on molecular evolution.

COHEN: So the people were just in their narrow—

DREYER: Yes. So it's really interesting to me, independent of the fact that I happened to be the object of it all. But it was fun. And then Gerry Edelman—this is, again, the same old theme that I've been harping on—Gerry Edelman was at the Cold Spring Harbor meeting in 1967, which was held for this topic. Francis Crick was there, and César Milstein, the guy who invented monoclonal antibodies and eventually won the Nobel Prize [1984]. And Milstein told me that he was doing the experiments that led to his monoclonal antibody discovery [and that they] were being done to prove me wrong. He's a great guy. A lot of these top guys were at this [meeting]. They'd somehow, again, collected a nucleus like Anfinsen's, like the NIH was doing. And each of these had published papers saying that you make these antibodies by just recombining a couple of genes. That's all in the literature. This is after all these data were available. Lee Hood by then was just getting his PhD, I guess [1968]. And we set it up so he gave a talk and I gave a talk. He covered some of it—some of the work he'd done for his thesis—that helped support this. And I gave a talk in which I had some fun—going farther, way out—but pulling it all together and talking about how you do similar things to build brains, and whatnot. We'll come back to that. But the amazing thing is that [out of] all these people, none of them—as you read the discussions—got it. They didn't get it.

COHEN: They weren't ready to give up the other idea.

DREYER: It's an amazing story, to me. So that's '65, basically, going on until '67—the antibodies. And, of course, by then I really didn't want to fool with phage lysis anymore.

COHEN: So you went on with this other work.

DREYER: Yes. But Lee Hood was indoctrinated by me into the importance of instrumentation and methodology when our theories clearly were way beyond what we could do experiments for. He bought into that, too.

COHEN: Building the right instruments?

DREYER: He didn't have the inventive ability, but he was very interested. So he went to NIH for a postdoc.

COHEN: And then he came back here?

DREYER: He sort of was a partial postdoc, being that he had an MD. But after his PhD he went to NIH. He came back here [1970, as an assistant professor], and eventually he became division chairman [1980-1989].

COHEN: OK. Maybe this is a good place to stop. [Tape turned off]

WILLIAM DREYER

SESSION 3

February 23, 1999

Begin Tape 3, Side 1

COHEN: I was looking at this paper, this review article, on a microchemical facility for the analysis and synthesis of genes and proteins. This certainly brought fame and fortune for a lot of people, I think.

DREYER: Including me.

COHEN: Including you. So maybe you'd like to just talk about the whole thing.

DREYER: Well, what I have been telling you so far is that I had a conviction to build instruments and tools and methods—microchemical things and things like this. It started way back. And I think it would be a good time to recapitulate some things I said before. I was not at all a scholar for my first three years at Reed College—and high school and grade school and everything else—because I never did study. I did cram, so that's how I could learn my mathematics and keep good grades. I really enjoyed physics and philosophy, but I wasn't a scholar, and I hadn't figured out what I wanted to do with my life. I didn't have any particular desire to be a professor or anything else. However, I did tell you that when I got to my junior year, probably, I became fascinated with something I wasn't supposed to be studying, which was memorizing the chick embryo. This was experimental embryology—that is, how the cells know how to come together and magically construct a brain or a heart or a body or make identical twins totally identical and all of that. And [I was] so fascinated [that] I stayed up all night and read that experimental embryology book. I did a terrible job on the test, I have no doubt at all. So I became really fascinated with the philosophical questions of how does it all work? How do we build ourselves? Around the same time, I had a course from Frank Hungate, who was not very popular with his department chairman. The department chairman was an old-time biologist, but Frank Hungate was into things that were going on at Caltech at that time.

COHEN: Where did that connection come from?

DREYER: That came from the study of *Neurospora*, which was work done here: one gene, one enzyme, and so forth. So I learned about that and actually had a laboratory where you could look at these little round black spores and learn about genetics. This is now called molecular biology. You could just see it starting—this was just the very beginning. And then, thirdly, right around the start of my senior year or during it, I read the book [by Erwin Schrödinger], *What Is Life?* It was a philosophical question. Nobody had a clue. The philosophers, of course, would be into these very mystical whatevers about what life's about. But Wendell Stanley, who was at Berkeley, had a whole institute to study the tobacco mosaic virus. He came [to Reed] and gave a talk. And I found that absolutely enthralling, because it's a very simple "live" organism that's only protein and nucleic acid, and they didn't know—and he didn't know—which carried the hereditary material. They didn't have a clue, really, as to how it reproduced itself, yet it did, very quickly, destroy the tobacco plant. And they used advanced instrumentation—it's the only way they could get as far as they did—including an ultracentrifuge that was being designed at a start-up company called Spinco. And I certainly became aware of the critical importance of these tools. I chose to do my thesis basically on that question, starting with the very earliest steps of how you make a protein, which, in this case, was a molecule called glutathione. It's only three amino acids. [That was] the first step in my deciding that what I really wanted to understand was life, at the level of physics and chemistry. And that commitment remains today. That's really what the thread is, through all the electrochemical things. [The idea] isn't just to build instruments; it's to get more tools to find out what it's all about.

And then I also told you that with the cancer and one chance in ten of living another year—and knowing that I had abilities that were unsurpassed, basically—I could hazard a chance as needed to do something, provided I became a scholar. I did. I talked my way into the University of Washington, where they were studying the next step: How a protein folds—and how it's made—to get to the genetics of it. And we used the ultracentrifuge back there, too. I helped in various ways to invent—when I needed a change in the work being developed—the tools we needed to just eke out knowledge one step farther. So those would be called microchemical instruments, those things I was using all the way through. You can use whatever

word you want, but they're the tools, the methods, and the automated instruments—the various tools you need to eke out the knowledge of the chemical-physical basis of life.

COHEN: Now, would you get a patent on each of these instruments as you did them?

DREYER: No. For the things I did as an undergrad, it might have led to patents if I had bothered. But I didn't. I was developing new ways to separate things related to what I was working on, and clearly had the ability. And I'll say it again: The reason I could invent [something] when I needed a tool [was because I] had the confidence that I could do anything or build anything—[that] was critical. With this confidence—call it arrogance or whatever—it was just plain experience. I know, just because I can build it in my head. I see it in 3-D Technicolor.

COHEN: So in some sense it never would bother you that somebody else would use these instruments and you wouldn't get first chance to use them.

DREYER: Oh, it was quite the opposite. One of the things I'm most proud about—and we'll come to that—is that, as we go through all this, tens of thousands of laboratories have used these various tools. It's by far and away the most impact I've had on science.

But what happens is that, if others want to use the tools that you've invented, they have to nag you to death to make something for them that you don't want to be doing. Or they have to be able to buy it. If [it's] a commercial firm—[it was] usually venture companies, as you'll see, that I got involved with—they're going to take the risk to build an instrument. As Applied Biosystems did with the instrument I invented—just me, not Lee Hood or anyone else. They developed this protein-sequencing machine. They needed a patent. The guys that funded that machine had filed for those patents; they needed patents. Because they don't want to invest hundreds of thousands—

COHEN: That's right. And not get a return.

DREYER: I came to appreciate that if you want to get funding to do your work, [the best place] probably is the private sector. So patents are sort of a necessary by-product.

COHEN: OK. Now, did Caltech at this time have a policy that you signed over before you started?

DREYER: Let me move on through this other thing. So I did a lot as a graduate student. And then I went to Anfinsen's lab [at NIH]. He, again, was a great guy. He was just respected by everyone, mostly because he knew he had the most gifted people in the world in his lab. And he cut everybody loose. He didn't try to tell them what to do. He stirred up discussions and tolerated dissidents and verbal explosions. It was an open environment. But one thing he did not have was the ability to invent; he didn't like it. Charles Sibley and I and others there knew [what] we needed. [Sibley] wanted to study the evolution of birds, and he needed protein sequencing and other methods so he wouldn't spend his whole life [words unclear]. We had invented some things and methods that were really important—new methods to do protein chemistry. And this peptide MAP [multiple antigenic peptides] thing that I told you Gilson made. There probably were 10,000 labs that used that and the amino-acid separation. This had a huge impact on being able to do good science. It also provided the tools and some of the knowledge that I needed to crack that antibody problem. I did build some things [at NIH], but I really wanted to go on and continue this quest to understand what life is—the genes and proteins—how it gets made. And that was frustrating at NIH. So when I came here, I told them. Maybe that's partly why they gave me that full professorship at that young age. But clearly Bob Sinsheimer and some of the others must have felt that was an outstanding thing for Caltech. I did. So as soon as I got here, I started doing things—

COHEN: Building this equipment.

DREYER: Right. By the way, speaking of credit, one of the things I did as a graduate student [at the University of Washington] was show that you could unfold a kind of trypsin, a crooked [?] enzyme, leaving the [cell itself?] intact, and you could show, with one of these new inventions that—minor detail—but with the fast-flow things you did, that it could refold itself, as soon as you got rid of the thing that made it unfold, and make an active enzyme. So the molecule itself had the intelligence to know how to fold itself back up. Well, I helped encourage Chris Anfinsen

and those guys, but I wanted to move on to the next step. And probably that's what he won his Nobel Prize for—going on and doing much better work [words unclear] and showing that you could refold proteins. So there again, there are these prizes that I wasn't really after.

COHEN: You planted the seeds.

DREYER: Yes, but [the prize] wasn't what I was after. OK. So at Caltech, then, I really set a course to start building this kind of instrumentation. Bill Gray was probably encouraged to come work with me by Fred Sanger, a two-time Nobel Prize winner, because he had developed methods. He [Sanger] had sequenced penicillin and by methods that were really tough, and I was improving on those methods. So Bill Gray came here. He had done his PhD with Fred Sanger. Between what he'd learned from Fred Sanger and from me, we developed—I'm not even sure it was in his paper—a really good way to do this microsequencing with fluorescence. He was very, very important in getting the data that led to this paper. This was '65, when I had published this paper with Claude Bennett that revolutionized, ultimately, immunology. That's what that paper talks about. It mentions all the data that we had that led to the conclusion that this had to be the way it worked. It was all there, but others couldn't see it. And, to recapitulate, we could do that because of the new tools we had. The methods I had helped develop let us get data and understand the implications of the data. The other standard non-biochemical immunologists [like] Ray Owen had no way of understanding. So he had serious problems, and so did his cronies. And I got as far as 1967, telling you about the meeting at Cold Spring Harbor about all this. And one of the things I did: If you want a protégé to take off and get fired up and work hard, you let the protégé take credit. And that's Lee Hood. He was a very gifted student, very competitive, and very hard-working. He sleeps only three or four hours at night. He's a very interesting, different character. These guys—even Thomas Edison—had cat naps. I do that. It may have to do with the energy required for this enormous computing power of a silicon-graphics-like brain.

COHEN: [Laughter] Needs more downtime, huh?

DREYER: I don't know—it's funny. So, at Cold Spring Harbor I set it up so that Lee Hood gave the talk about the main data. And I gave a talk about where I really thought this all led, beyond immunology. And I included in there some work of Roger Sperry's that was very controversial, about how neurons know exactly where to go. [Dreyer, W. J., W. R. Gray, and L. Hood, "The Genetic, Molecular, and Cellular Basis of Antibody Formation: Some Facts and a Unifying Hypothesis," *Cold Spring Harbor Symp. Quant. Biol.*, 32: 353-67 (1967)]. I knew that was controversial. I knew it was counter to winning prizes and things like that. Gerry Edelman was there. Everyone knew there'd be Nobel Prizes; it was just dynamite, exciting; it still is. But he wanted the Nobel Prize. He and I wound up on the circuit with one or two others—Mel [Melvin J.] Cohen in San Diego and I think David Baltimore. We would go on these circuits like Mutt and Jeff with Gerry and Mel Cohen just not understanding what the hell I was talking about, even though it was there. Anyone could see it today. Once you know that it's true, you have an easier time seeing what [that 1967 paper] says. Roger had that problem, too. He was one of those people that I could always relate to and understand. I immediately understood what he was trying to say. When he got his Nobel Prize [1981], they explicitly ruled out the stuff I had written about. They thought it was so crazy they didn't mention it, because it was not believed. They gave him his Nobel Prize [for his split-brain work]. But I mention that [1967] paper now because what I was really trying to do was to understand how genes build brains. This is not the right time to insert this, but a paper just came out in the journal *Neuron* that references that paper, and basically it says [that] the new data support it. [Chun, Jerold, and D. G. Schatz, "Rearranging Views on Neurogenesis: Neuronal Death in the Absence of DNA End-Joining Proteins," *Neuron*, 22: 7-10, Jan. 1999]

COHEN: Now, you were just concerned with genes and the brain? Or were you concerned about the rest of the body?

DREYER: Everything. I used the brain because you had the most powerful evidence that there was very high precision for putting cells together, as there had to be in the heart. I had read an experiment on embryology, but Roger had produced really good evidence—it was clear and should have been accepted right away—that genes program our construction with extraordinary precision. This is well into my first few years at Caltech now, when we were doing this stuff.

But what's happened in the past months is that I may very well be right, even though no one's accepted it. Because of the new data we have. But what it's about is saying, again, that genes are actually changed as you make [words unclear] and that molecules are put on the surface [of the cell] that act as the construction code—where to put this building block, very precise structure. So that's where I'm going to go with all this. And to be honest—

COHEN: Is this your telephone metaphor…? What is the analogy you use?

DREYER: Area code and telephone number.

COHEN: Area code. That's what you're talking about?

DREYER: Yes. Well, it's a metaphor—there probably could be better ones. But the construction code—whatever it is—is easier for a lay person to understand. When you want to build a castle or a steel girder building, each little steel girder has to be marked so that you know exactly how to place it in the whole structure. That's what this is about—and how you use the same marks again and again. When someone says, "North," you can use the same marks as when you say, "South." You can have a combinatorial code—that's what it's called. So this, too, to be honest—I can't imagine there won't be a Nobel Prize in this area.

COHEN: Now, are you saying that this is not accepted yet or that it's starting to be accepted?

DREYER: I think we're going to start to see—and what this Tom West thinks is going to happen is that this is just the start of a whole paradigm shift in biology, a major, major shift. And that shift will be from the view that the DNA in all cells is the same to the view that the DNA is programmed to be different—edited and spliced—in order to put these codes on it and have the brain cell know that it belongs here and not there, and so forth. That paradigm shift hasn't happened yet, but it's very close. In this *Neuron* paper that just came out in January, they point out that that was written twelve years before the antibody [theory] was even accepted and it's thirty years before this new evidence [words unclear] that basically says that if you block the

splicing of DNA, you can't make the brain, and you can't make antibody cells. It's the same thing. You have to splice DNA, it looks like, for both of them. That's what I was talking about.

So it's an exciting time. I think people are going to start taking this seriously. They haven't. Nobody's taken it seriously, except a few, so it's been lonesome out there. But Dick Feynman was somebody I could tell those theories to, and he immediately understood them—again, as I said, we could communicate. We'd go out to the desert together and stuff like that. He was interested in biology.

So what happened with the antibody thing: Lee Hood wanted to win the Nobel Prize for sure. He worked like hell. He had [to do] more and more work on antibodies to build up his image in the field. And he did—he did superb work. This is a wonderful thing, that people are this way. And I already said that Gerry Edelman worked like mad on it. The pedestrian thing to do was the structure of an antibody. He won the Nobel Prize for that [1972]. [Susumu] Tonegawa is the one who actually did do what everyone knew—including me from the start—you needed to do. But you couldn't, because you didn't have the methods; you needed to wait twelve or thirteen years before the tools [became available]. Paul Berg was involved [words unclear]. And then Lee Hood couldn't do it. But Tonegawa was also aggressive and wanted the prize. He was the smartest of all: You couldn't use those tools yet in this country—they were banned—but he went to Switzerland.

COHEN: Explain to me what the tools are.

DREYER: The tools you needed to clone the genes in sequence, the parts of the antibody region, to find out if they really were cut and spliced and changed from what [words unclear].

COHEN: So why weren't the tools here?

DREYER: Because there was a lot of concern by all of us. There were meetings with Bob Sinsheimer, who was maybe still chair of the Biology Division—I can't place the exact date. This would have been—

COHEN: In '77?

DREYER: In ’77 or somewhere in that range. And there was concern that you might introduce a cancerlike virus into people and things like this. They didn’t know enough about the potential dangers of manipulating all these genes. So they called for a study—a one-year moratorium, or something like that—of these techniques. They were basically splicing together cancer viruses—

COHEN: Oh, you mean the “create a monster” kind of thing?

DREYER: Well, or create cancer—create a virus that spreads, create an AIDS virus. They still might. I, and probably others like me, if we wanted to, could work on germ warfare. We probably could create a stealth monster virus that would get past the immune system.

COHEN: I see. So there was a fear of developing something like this and its getting out of control.

DREYER: That’s right.

COHEN: But they didn’t have these qualms in Switzerland?

DREYER: Well, if they did, they didn’t have laws against it. Here they had NIH rules or something equivalent to law, that no one could do that. You had to wait until the study was completed. But Tonegawa went there, and he did it and proved me right.

And, again, I really wasn’t interested in spending the rest of my life working on that. So you’ve already heard that I invented a robot to do amino-acid analysis, with a computer tied in through a cable all the way to the mainframe—a time-sharing computer. Lee Hood used to stay up all night long, manually pipetting chemicals into test tubes and whatnot to eke out data on this sequence stuff by hand. It was important to develop automated instruments to do this stuff—methods that would make [our work] a lot easier, because he worked very hard to collect data that he then could use and I could use.

Bill Gray and I were developing more tools. He and I worked with JPL on a really neat trick for sequencing proteins in a mass spectrometer. Basically they were the end of the protein chain—chopping [them?] up [in] the mass spectrometer into differing lengths of pieces. And that worked. It was really nice. It was too cumbersome to use routinely, but I could bet that Fred Sanger, his mentor, paid a lot of attention to what Bill was doing. That approach was what Sanger then used for nucleic acids. Basically the idea was to label the ends and chop them into pieces. We really needed to do amino-acid analysis better than what I was doing, with very high-voltage separations, [which] was fast but not very quantitative. Around this time, a man named Per Edman in Australia published an instrument that automated the sequencing [words unclear]. It required something like ten milligrams or more of protein, which is a lot, but it would do [the sequencing] automatically. The proteins we were working on were cancer cells, or myeloma, or monoclonal [antibodies], or whatever you want to call them. We could get that amount of protein, so [that instrument] could work—it could do our jobs for us. And we had a lot more we wanted to learn about these things. And so did Lee. He went to NIH and did his postdoc somewhere around [that time]—probably after I started this. Because he then, at NIH, bought one of these instruments that evolved from Edman's. I, again, wanted to build one and had the confidence that I could in fact just design whatever I needed, using [Edman's] paper. That's all I had for an engineering diagram or anything else, because he wouldn't come to this country. He was ticked off because—

COHEN: Was he a Communist over there?

DREYER: A leftist, or whatever. And that happens. He wouldn't come here. So I decided to heck with it, and I built one with the help of the people in central engineering. I needed money, and there was a fund to do just that. And I didn't see any reason why it shouldn't be a justifiable thing for me to get.

COHEN: Now, the fund was here at Caltech?

DREYER: Yes. I think it was Sloan money. I think it still exists. And I knew I'd never get a grant—although I was well supported then. There was a big block grant that Maxine Singer and

I shared through our most productive scientific years. We never had to write grants or think about it. She was at NIH when I was at NIH, in a building right next to me. She stayed. It was just an awesome place to be.

So I went to Ray Owen, who was chairman [of the Biology Division], and he wasn't about to give me any money.

COHEN: He didn't think you should build this instrument?

DREYER: He was already ticked off about this theory, which he thought was bullshit—he couldn't understand it. And he was getting harangued by his colleagues, who said, "How could you let him publish such junk?" He had been head of immunology, and all the immunologists would get on his case and whatnot. So he wasn't excited about it. And so when I went to him and wanted money—even as little as $15,000, which is unbelievably small to build an automated instrument—I couldn't get it. That was probably in '67 when I went looking [for jobs]. I [had] all kinds of possibilities for a job. I went to Buffalo. There was a center there that wanted me to come.

COHEN: You mean you were just so disgusted with—?

DREYER: Yes. No way was I going to stay in a place where I was blocked from building instruments—when they had the money. If they didn't have it, that was different. I wanted to carry on with what I told you I had a commitment to from undergraduate days. To carry on with this whole dream of eventually understanding life—how genes make creatures, that stuff. So I don't remember the details, but I got the $15,000.

COHEN: You mean, when he heard you were having other offers for jobs?

DREYER: I suspect that people like Bob Sinsheimer and others said, "You can't let him go." I was serious. I was really fed up with the chairman. [Laughter] He didn't believe my theories.

COHEN: And he wouldn't give you any money.

DREYER: He didn't give me raises. You know. I'm not going to hang around there if I have all kinds of offers from elsewhere.

COHEN: Sure. So you got your money and you built the instrument.

DREYER: So I got my money. That instrument actually got built. I have a nice picture of it, along with the team. And this will come up later. One thing I know about doing that sort of thing is you have to have a creative and authoritative and strong leader who can make decisions, because there are many, many things where it really doesn't matter. But you can't have a committee of twenty people sitting around debating which kind of solenoid to use. Someone has to say, "Use this one." So I did that. I was a strong leader. And they were great. They were just wonderful in following [words unclear]. We got an instrument built, and it worked. And then Beckman Instruments came down and I just openly showed them how to do it. I gave them the advice they needed to build one.

COHEN: So they proceeded to build this thing?

DREYER: Yes. They didn't have one that year, but they had my machine. So they copied what they could and improved it in a lot of different ways. And I automated it by some funny rotating switches—thirty-point switches that rotated around. I hooked them together in a way that was bizarre, but it worked. I followed my brain. And the fun thing to think about is that that turns out to be a lot like the way our brain works. John Hopfield [Roscoe G. Dickinson Professor of Chemistry and Biology, emeritus] and I share some views on how the brain works. It has to do with cycles and simultaneity and timing delays and all that stuff that I used to make these switches.

COHEN: Now, were all these instruments in one place?

DREYER: Yes. We had a facility in Church. And we had high-voltage things that Bill Gray helped bring from England.

COHEN: So then, were there students working on it?

DREYER: Oh, yes. Sure. But I never have been totally enthusiastic about graduate students.

COHEN: Why is that?

DREYER: Postdocs are so great, because they—

COHEN: They're motivated.

DREYER: Yes. You can look through the whole world to find a Bill Gray or a Claude Bennett. Lee Hood was halfway in between. He knew what he wanted to do. There have been students, and some good ones, but not a huge number.

COHEN: So you really prefer the postdoctoral students.

DREYER: Yes. [Tape ends]

Begin Tape 3, Side 2

DREYER: So we've gotten as far as having built a sequencing machine. I tried not to reinvent Edman's machine, because why invent it if he's already done it? And I tried to glean as much from his paper as I could—just this ordinary paper—and invent what I had to to make sure that I could get what I needed to make it work.

So I wanted to move on from immunology and get started with this thing I published in '67, how you put other cells together. And that had to do, again, with the limitations of the tools. That means both the methods and tools, fluorescence, and all that stuff. One of the things that I could do was study—how do I say this? There are neurons in the brain that form the nose and give you the ability to smell ten thousand different odors. That reminded me of the complexity of the immune system. Each neuron detected one odor; we knew that from the genetic

[expression]—from people who can't smell something. So that [the olfactory system] sounded like an outstanding way to go to study the possibility of genes being switched to tell one cell what to do, versus the next cell. But [in those days] you couldn't begin to think of getting [a sufficient supply of] molecules [to study]. They were just too scarce. But a very similar kind of neuron in the brain—it turns out it really is a similar molecule; I didn't know that—it's the rhodopsin in your eyes. There you could get hundreds of milligrams. And that was enough.

COHEN: How do you get that material?

DREYER: You buy the retinas from [Armour?] or you go to a slaughterhouse and you get eyeballs of cows and you dissect out the retina. The first time I and my friends did that, we threw the retina away—[it was a gossamer?] white thing—and collected the pigment. [Laughter] But we learned quickly.

So you'd get these [gossamer?] things and you'd study the protein rhodopsin. I've gotten citation index awards for the method, including some of this high-voltage stuff, but it's at huge numbers of labs here, so they reference that. Usually they reference the company that makes it, but even then you get [cited]. But we've gotten an award for our work on rhodopsin. We did fundamental work on how you—

COHEN: Were you still working with Bill Gray at this time or had you gone on to someone else? Because a postdoc stays three years and moves on, usually.

DREYER: Yes. I think he stayed five. He came in '63, then he moved on to Salt Lake City. He didn't shine after that. It's too bad. Once he was out on his own, he didn't have the synergy. David Papermaster was the one who came. And Hermann Kuhn, a German postdoc.

COHEN: Now, who was funding you on all this?

DREYER: Again, I was funded at this point by a block grant the division had gotten. NIH was giving away money and letting the division decide. And thanks to Sinsheimer, I think—

COHEN: Who appreciated you.

DREYER: Yes. He said, "Do whatever you want."

COHEN: Those were easy days.

DREYER: Well, and I think he had become chairman at that point [1968]. That made life very easy for me.

COHEN: You got on well with him.

DREYER: Yes. He appreciated and understood a lot more than [words unclear] I had worked with. He appreciated what I was trying to do, and the goals and everything else—he had the same dream. And I respected him. He was a very smart guy—a physicist. And you know that people in physics are smart. [Laughter]

COHEN: They just know everything. [Laughter]

DREYER: So we studied this molecule and we in fact found out some very fundamental things about how you adapt to light [words unclear] and things like that. So it was a productive thing. I was not really doing what I wanted to do, but nevertheless [I was] producing something that was important in the lab and for the postdocs. And these people went on and continued working with [vision?]. The instrument I had built, the sequencer, was 1,000 times—or 10,000 times—less sensitive than what I really needed. So I undertook to dream up something that could be 10,000 times better, and did that. And then I tried to get money.

COHEN: To build this. This was not $15,000?

DREYER: This was not $15,000. And NIH and NSF [National Science Foundation] turned me down. I had done prototype work, cheaply, to convince myself that—

COHEN: It could be done?

DREYER: It was really poor-quality data, but it was the right track. And about this time [1970] Lee came back from NIH. And he, of course, was extremely interested at the thought of a new and better sequencer, for the same reasons I was.

COHEN: So he came back from NIH?

DREYER: Yes. And I, of course, was delighted to have him back and share this dream. I know that he didn't have a dream of understanding all about how the embryo goes together, but the dream of the instrument we did share. And he and I together tried to get funding for this job. And we couldn't.

COHEN: What kind of money were you looking for?

DREYER: $100,000 to $300,000. You couldn't do it on $25,000. And by then inflation hit. $15,000 was—you couldn't build much with the shops. We had a period of high inflation. So that's when I visited [Spinco at] Palo Alto. I think I was still consulting with Spinco. They wouldn't touch it. They did a study and didn't believe that it would be helpful. By then, this nice small company had been bought by the big giant, Beckman Instruments [1955]. And that's when the creativity tends to disappear, when little companies get bought out. So I was up there—having found that I could not talk the Spinco division of Beckman into building it, or even doing a prototype—and we also visited a place that had supplied me with [words unclear]. That's where I met a venture capitalist. They are willing to take the risks. Everything I do is risky; you have to be willing to fail.

COHEN: What was the name of this small company you went to?

DREYER: This was Chromatronics [name unverified]. They said, "OK, we'll put up $200,000." This was one man. He could make the decision. The capital gains taxes had been reduced; they were really quite low and regular taxes were very high. So why not send it to the appropriate

person who's interested in science, enough to cough up $200,000. That was a lot of money—more like a million, actually. If you do win, you win big, because of taxes. So he funded it for Chromatronics to start a prototype, which they did. The terms were [that] they would file the patent so that they [would] wind up with it. I didn't have to bother with it. And I'd get royalties for making the instrument, which is typically five percent of the gross sales. They did. They built a prototype. But then they were bought by—this I know I said before.

COHEN: I don't remember.

DREYER: They were bought by another big company [word unclear], and they decided that—

COHEN: They didn't want to go with it?

DREYER: This wasn't going to be a useful instrument; nobody would want it; stuff like that. So they gave me the prototype, with permission from all parties—[including] the division chairman here. And all they needed were the patent rights that had been filed and whatever. I brought [the prototype] down here to begin to try to— Oh, yes. I forgot. Part of the deal with Chromatronics—it was like a pact with the devil—was that I would help them build an instrument to compete with Beckman Instruments. And I said, "Look, in my life I don't do that." I always want to see a project go on for the next generation as long as I can, [I want to] have the experience to build something far better. I don't want to fool around competing with a giant like that [Beckman Instruments]. It's crazy. But I did help them do that. So this machine was made to be able to do both things.

COHEN: So you brought the prototype down here? And it was working?

DREYER: No, we were trying to develop it. It wasn't working. It had glitches in it, and all. This was the early days of microprocessors. They would freak out with high voltages, and stuff like that—technical stuff. But somehow the opportunity arose to get Durham Instruments [name unverified] involved. And I said, "Great." I knew the president. I always seem to get along best with the president of Caltech, the president of companies, Arnold Beckman.

COHEN: Well, they're not answering to anybody.

DREYER: Yes. And they're also very smart, so they understand.

COHEN: Where is this Durham company?

DREYER: That was also in Silicon Valley. This stuff—it's bound to bore you—

COHEN: Oh, I don't find it boring at all.

DREYER: But this is critical. This is an instrument that's 10,000 times more sensitive than the commercial one, which by now Lee Hood's bought, NIH has bought from Beckman Instruments. Because this [the commercial one?] did help, right away, immediately. They started making [word unclear]. Edman, of course, had published a paper, but they couldn't make it work. OK. So Durham, who was the head of his own company, thought it was great and was willing to take it over. And his lawyers set up a contract that basically said that Caltech also knew that I was working on my own time for this and that they [Durham] would file the patents in the US and foreign countries, everything. It's expensive.

COHEN: So Durham was filing all the patents?

DREYER: Durham did that, with Caltech's acknowledgment. And I was getting some money from Durham to help nibble away at this thing. So they got started, and filed all these patents. And they made a commitment in writing to me, which I learned— By the way, along the way I had also consulted for two or three more companies. One had to do with new types of medical assays. That was a division of [word unclear], helping them do some fluorescent things. That led to a better pregnancy test. So along the way there were other things I was doing as a consultant.

So here we are at Durham. They made good progress, and they had good engineers. They built a better amino-acid analyzer than the one that I had built, or Beckman Instruments

had built. And I think it probably began to take over from the one I helped invent; it was a better model. So I naturally had a great respect for this Durham guy. They were making good progress on this 10,000-volt better sequencing machine. They were bought. After patents were filed, the patent lawyer helped me with one of the things that I had done in another outfit to do with these medical tests. He licensed some of the patents that are in there and paid me $6,000 a year, which was quite a bit in the beginning, but forever. And they never used it. So I was stuck with my patent license, and unable to use them for exciting medical tests. So, because of that experience Russ [Russell R.] Palmer helped me write something for this Durham company.

COHEN: Who is Palmer?

DREYER: He was my patent advisor. He never wrote a patent for me, but he taught me about it. He's a patent lawyer in Pasadena: Christie, Parker & Hale. He wrote this agreement that basically held [Durham] to a timeline. I met with [words unclear] prototype of the—we call it a gas-phase sequencer. It's not all gas but [words unclear]. And when they would start building the models to ship, and when they would ship them, and so forth. Again, I wasn't given any up-front money at all, but I would get a royalty and they would take care of all the [patents]. I hate patents but nevertheless appreciate that they're important. OK. So [Durham] got bought—same old story: a big company, committees, no vision. They couldn't see it, or didn't want to, or whatever. It was just astonishing. They didn't know that this was the key to all kinds of stuff. They had funded me to have someone here, too, to help with the prototype. Then they got bought. Bill Dreyer, private consultant, gets the rights to these patents. [The company that bought Durham was] delighted about that, because they wanted to get off the hook for all these commitments that were in writing. They didn't want to have to do that. So I said, "Sure, I'll take the patents for all of them."

COHEN: So you became your own company.

DREYER: I didn't call it a company, as you will see. So at that point, we had enough exact details on how to kludge together prototypes. And at that point, the patents were filed and

everything else. I think I finally got an insignificant amount of funding from NSF to help support that. But they wouldn't get patent rights, because [the patents were] already filed.

So we did some work with this kludge here. We were using radioisotopes. We showed that it could really so micro, micro things. [It did] extraordinarily sensitive sequencing, with a proof of the concept, and goes way out on the [amino acid] chain—sixty, seventy amino acids. It was a real winner. So at that point—again, in order to make it work on a shoestring, basically—I used some tactics for the way you program and whatnot. Commando tactics, let's put it that way. But it worked. I did that with a technician helping. Her name was Suzanna Horvath. She's still here. Most people who worked in my lab tended to move over after they got tired of [me], but Suzanna is still there. John Racs—the one who did the amino-acid analysis—they were both from Hungary. She could hardly speak English at the time. She has a PhD in organic chemistry. That made her good for this sequencing. She knew that with a chemistry PhD she could handle the chemistry required to modify this first instrument and the peptide synthesizer and others—once you have this first one, which I'll come to. So she continued to work on that. At that point, I decided that I wasn't going to be able to get an instrument from Durham [and that] I'd build one here. How did I fund it? I don't know. Lee got funded. By then, he was back.

COHEN: And he knew how to raise money.

DREYER: Yes. He knew how to raise money. And he had a strong interest, including his own ego. He wanted credit for this stuff, and that was fine, especially if you raise money to build it. So there, again, I went to Central Engineering. There was a guy named Mike [Michael W.] Hunkapiller. His big thing was to develop the same thing—better sequencers. [He started that] as a postdoc with a PhD in chemistry from here. But his approach was to search the world for a commercial instrument and then tweak it, modify it, with a valve—a woman had invented a special valve that he needed—and tweak it to make it better, significantly better than the commercial instrument, so he could publish on that and get famous for it. He was very proud of that. In the meantime, I was building this gas-phase instrument. I think it probably was Lee himself, and some other people, who didn't believe that I could do what I said I was going to do. And I even used a programmer the shops had made for one of the things Mike had made,

because it was cheap and already available. So I used that. I used the valve the woman in Germany had made—the basic design. But I miniaturized it way down, by convincing the guy at the shop [that] they really could make a tiny little valve. So this thing then started developing out real data that showed that it *was* [word unclear]. And it was still getting better. In the meantime, part of the whole idea was to have a mass spectrometer. And Aron Kuppermann [professor of chemical physics] worked with me on a mass spectrometer that was so sensitive that it could analyze derivatives. And we built that; there's a patent on that and also a publication with Aron Kuppermann. [Dreyer, W. J., A. Kuppermann, et al., "Automatic Mass-Spectrometric Analysis: Preliminary Report on Development of a Novel Mass-Spectrometric System for Biomedical Applications," *Clin. Chem.*, 20, 988 (1975)] And what Aron and I knew was that a mass spectrometer can be so sensitive that it can count individual ions. This was a radically new design and, again, I dreamed it up to do this by basically putting an electronic film in the focal plane. It was so sensitive it could count almost every ion. And that thing was working on the level of atomal—just hugely sensitive.

COHEN: Now, this was being built at JPL?

DREYER: Yes, with the people up there. So it's clear that this thing was indeed ready. The big one, the prototype, had been used to design the small one that actually got built, with the help of people at JPL, and it really did work. It was just awesome. So all we needed then was a way to get the samples in, either from the DNA-sequencing [words unclear] the protein sequencing, and already there were robotic devices that would do almost the whole job. They just needed this interface. It must have been the early eighties by then. The gas-phase sequencer was clearly working. And the results were being analyzed, again, by a robotic thing that automatically took the samples, but it ran on gas chromatography [words unclear] high-pressure [words unclear]. And it was just dynamite for delivering the goods. The mass spec [spectrometer] now just needed [the interface]. Again, I had scrounged trying to raise money; I had gone to the National Cancer Institute and gotten $100,000 from them to help with the mass spec. But I couldn't get the kind of money we really needed. But the dream of that, and the sensitivity of the instrument—I could use that in the presentation to Monsanto with the help of Lee himself. They coughed up about $250,000, just to make this little interface thing. And we really knew how to

do it. It was just bringing stuff done somewhere else, but it was a new way to do it. And it was getting droplets of liquid or even particles. If you imagine a spaceship that has air pressure in it, and you want to get it out into outer space and have it sort of [words unclear], and if there's water there, or liquid, it vaporizes [words unclear] stuff you want to look at keeps going to a target. That's what it needed.

COHEN: And that had not been built anywhere yet?

DREYER: Well, it almost had, yes. I mean, it hadn't been automated. But the conventional way to do mass spectrometry is to take this metal probe and pull it out and put something on the tip. Then you push the probe back in and it's heated and—

COHEN: It vaporizes, yes.

DREYER: So we had this money, and started up there. And I got my second major cancer, which was colon cancer. There I had a forty percent chance of living, so the odds were really good then.

COHEN: How old were you then?

DREYER: Twenty-eight from eighty-two.

COHEN: Twenty-eight from eighty-two. You want me to subtract twenty-eight years from eighty-two?

DREYER: You don't expect a dyslexic to do that.

COHEN: [Laughter] OK. Fifty-four. Did you have symptoms or was it a routine examination?

DREYER: I saw blood in my feces. I got myself in right away. Same thing—I said I wanted it out. But this one was a very major operation, because it was close to the sphincter. I also got

myself up to Seattle, because I knew about AIDS and hepatitis, and they had no way to test the blood [supply in 1982; Seattle's blood supply would be safer]. And also, there was a very good surgeon up there, and he had worked on some of my medical stuff. So I went up to Seattle—the Fred Hutchinson Cancer Research Center. And I knew the Helstroms, who are cancer specialists and scientists, so I also had people who respected me [words unclear]. By the way, I've always had respect for and been able to work with MDs. That's part of why I thought it was such utter nonsense to worry about having nurses and doctors and medical schools here at Caltech. It's so easy to find the very best in the world.

COHEN: I have a question I'm curious about. Why did you feel that if they weren't testing the blood here that they'd test it there?

DREYER: They didn't have anywhere near the number of AIDS people [in Seattle].

COHEN: I see. So it was just a question of where the blood was coming from.

DREYER: Yes. They didn't have the drug users. They didn't have the [same] level of homosexuals. Seattle was a much safer place at that time—who knows now? So I went up there. But one of the things the physician said was that the tumor was very close to the sphincter. They thought they'd be able to save that, meaning you could still have normal bowel movements. And I said, "Look, please, if you think it's too close possibly, save the patient, not the sphincter." So I had a colostomy, which means I wear this little pouch here, which is no big problem. Every day or two, I use a tube to irrigate it. I run it in there and it's basically like an enema. It takes me about an hour. And I can read or work at the computer while I do it.

COHEN: You've lived with this all these years?

DREYER: Well, since then. It's really not a problem. In some ways I'm better off. If I'm in my airplane and have diarrhea when I fly, I can put on—it's just a little patch. And I go between these irrigations at home usually without a problem. If I have diarrhea, I can have a bag on there

so I won't have any problems. You guys—in a plane without a toilet, you've got troubles. [Laughter]

COHEN: A silver lining to every cloud, huh? OK.

DREYER: You're getting this on tape? All right. You asked for it; I'm telling you. So the point of bringing that up is that that operation wiped me out for over a year. You've heard about these hospital staph [staphylococcus] bugs? I had one of those that formed a pocket. And it releases twenty different toxins that reduce your mental acuity. I wound up finding a specialist in infectious diseases at USC. She gave me the right prescription to get rid of this. But I couldn't function at a full level—no way. So here's the $250,000, and old Mike Hunkapiller really wanted to get credit for this spec job, and for the gas-phase [sequencer], so he took over that while I was wiped out. And I kind of thought—he was very good at just modifying something. You don't have to invent it. He designed a machine [words unclear] which mechanizes the whole [words unclear]. So, in the meantime, that instrument—the mass spec part—continued with [words unclear] to the point where it could do what I really wanted, which was to take, in this case, a single bacterium [words unclear] and put that in there and zap it with a laser and then analyze the whole bunch on the fly—*bang, bang, bang, bang*. That's what I wanted to do with both the DNA sequencer and the protein sequencer, because the sensitivity, speed, and automation just would have been mind-boggling. But at that point, I wasn't willing to do battle fund-raising day and night and whatnot, so I just let it go. That's one of the sad things, because I know it could still do that. It's just a wondrous way to go. But we've got enough now. The things we did do worked.

Then what happened was it came time to publish this gas-phase sequencer. We put together a publication, and I did have Lee Hood on there, obviously. He really hadn't known much about what was going on himself, and Mike Hunkapiller had had an awful lot to do with it. And [there was] another postdoc, Rod Hewick, whom I recruited from England. So we sent the first paper off. I guess my name was last, probably. Whose was first? Probably Rod. [Hewick, R. M., M. W. Hunkapiller, L. E. Hood, and W. J. Dreyer, "A Gas-Liquid Solid Phase Peptide and Protein Sequenator," *J. Biol. Chem.* 256, 7990-7997 (1981)] But shortly after that, I came on to—I don't know how—I guess Rod showed me a paper that Mike Hunkapiller and Lee

Hood's names were on, period. [Hunkapiller, M. W., and L. E. Hood, "New Protein Sequenator with Increased Sensitivity," *Science*, Feb. 1, 1980, 207 (4430), 523-25] On our instrument. And Rod's name wasn't on it. I wrote on that paper, "This will not do." I actually kept a copy of it. For a reason I can't understand, Mike Hunkapiller would not let Rod Hewick's name be on this thing—for [an instrument] that's in my lab, built by me and Rod! We're the ones who talked to the engineering shop—he didn't have any involvement. It was just crazy, literally. He wanted credit, to be famous. OK. So that's sort of the negative side. One of the things that happened next was that Hunkapiller was going to wind up helping start a company for the instrument he had modified. But suddenly it became apparent, after they started talking to these people that [my machine] was going to totally wipe them out. So Lee introduced me to the guys who were going to start Applied Biosystems—it was not yet Applied Biosystems.

COHEN: And you became part of this enterprise?

DREYER: Yes. Lee and I and Mike were going to then work for the company to help build the instrument and make them [available] on the market. We each got stock in the company. I had the sole patent—the dominant patent. That's the first one. They'd keep trying to sneak patents in with tweaky little things to get credit, which helps, but it was my patent, my rights, everything else. So I had to say yes, and I did. I couldn't get Caltech—I thought it was really appropriate that they have an equity interest free [words unclear]. Jack [John D.] Roberts [Institute Professor of Chemistry, emeritus]—I think he was the provost then [provost 1980-1983]. Who was the guy who was the business man—

COHEN: [David W.] Morrisroe [then vice-president for business and finance]?

DREYER: Yes, Morrisroe. Morrisroe would be at these meetings. Morrisroe and others would not allow Caltech to accept, on principle. It's vast millions of dollars. There are several companies like that that have been [words unclear]. Caltech would have a huge increase in their endowment, no question—Amgen. We did—Rod Hewick and I—sequence the [word unclear] for Amgen. We had a minute amount of material, and we had this prototype. And just as a

favor, [we] sequenced that for them. That started Amgen. They, too, were willing to give Caltech stock.

COHEN: But at that time Caltech wasn't accepting it?

DREYER: They refused. It wasn't just because I had gotten them [sense unclear]. It was partly that. They knew that's what got them started. Once you had the sequence of these things, at that time you could then clone the gene, patent the gene. And they'd make billions, literally. Amgen's a very good [company]. Their stock would be worth [word unclear]. Whatever they gave Caltech for this.

COHEN: Were you involved with this, then?

DREYER: No. I didn't need to [be].

COHEN: OK. Well, should we stop now and pick up with these companies next time? [Tape turned off]

WILLIAM DREYER

SESSION 4

February 26, 1999

Begin Tape 4, Side 1

DREYER: Well, throughout this talking, rambling, we've been doing, you've asked me to explain the instrument program, developing tools. And I've told you that that wasn't really what I was after. I was after the answers to the questions that, I guess, started when I was in third grade—I think it was third grade—when I was fascinated by the sculpting of the bones of the birds, my wishbone collection. I also told you that that fascination continued in various ways, including at Reed College, on the question of how these cells migrate and [make up] hearts and bones and whatnot. They're called neural crest cells, by the way. They basically come pouring out of the center of the embryo when it's very small, and they're programmed to build all kinds of things, including teeth and bones and hearts and parts of the neural system—lots of stuff. And nobody knew about those things or knew how they did what they did. Also I mentioned Roger Sperry, and that he was here right near me in the same [building]. [His office] was just above [mine] when I came here in 1963. I was really fascinated by Roger and his students. He published a paper in [1961]. [Probably: "Cerebral Organization and Behavior," *Science* 133:1749-1757 (1961)] Basically he laid out the view that I also had—I also saw what he saw. And that was the whole story about how precise the molecules must be—how [precise] neurons [must be] in order to produce brains and vision and things of that sort. He didn't know anything about genetics or molecules or whatever, but I did. And I still agreed with him totally. No one else did to speak of—I mean, very few.

And I also said that I had put his work into my '67 paper at Cold Spring Harbor. That was a piece of work that could have been included in a Nobel Prize. But I wouldn't give myself a Nobel Prize for that—these crazy ideas that were the same as Roger's were in this paper.

COHEN: To this day, has it been accepted?

DREYER: I think it will be accepted, as the details [come out] of having very specific molecules on neurons to tell them precisely where to go. That has not been accepted.

COHEN: Do you mean the fact that there are messenger molecules on a neuron to give it directions?

DREYER: That there are address molecules that give broad help. It's part of a thing I haven't told you much about. I had a whole project on finding those. I did find a lot, and so have a lot of others. But the fine details of how you really home in on the way Roger and I think/thought/believed was true have never been discovered.

COHEN: Now, this had nothing to do with—you know, toward the end of his life, Sperry became very involved with religious ideas of one kind and another.

DREYER: I never understood that. He clearly was going downhill in various ways. What happened is that he gave the problem to me and other biochemists and so forth. He says that in his [1961] article. He also told me in person. He said, "Look, this is not my kind of thing." He essentially turned it over to me, like in *Doctor Zhivago.* If you saw that movie, the old lech—the old guy who seduces Lara—when he's through with Lara, he gives her to Zhivago. Sperry, when he was through with this, gave me the problem. [Laughter] In that [1961] article, he says, in effect, "I'm going to turn that over to you guys." But also, he, in that article, refers back to prior people, all the way back to the last century, who said the same kinds of things. And I also saw what they saw. Charles Darwin knew the same thing. He wrote a whole book on the expression of emotions in man. And I think you can understand these things better than the people who couldn't understand Sperry or me. What Darwin saw was that dogs and primates and humans have very similar expressions to express when they're hostile—snarls. Dogs even smile—or my dog does. There are a lot of nonverbal expressions that are read by us, because they're the same. They're basically very close. And that meant to him that all the pathways for [expressing] emotion are wired in the brain, and the wires coming out of the brain go through the face and cause the smiles and expressions—all hardwired, in a sense.

COHEN: Not environment in any way?

DREYER: Well, no. Never say, "Not environment," because environment's powerful, and it changes, especially with our huge cerebral cortex. We can modify and take out the damnedest things that aren't really what our genes are telling us to do. But Darwin, over a hundred years ago, sent people around all over the world, asking them to check on the expressions of emotions. And that book is wonderful. Do they smile—these Stone Age tribes and whatnot? Do they indicate the same thing we do with a smile? Do they frown? Can you read their expressions in the same way? [He] thought that if it's environment that makes these expressions, there would be differences somewhere, because theirs is a hugely different environment. There weren't. Darwin knew, just by looking at and observing creatures. And dogs, by the way—domesticated animals—were one of the things he was fascinated by, as am I. When I look at my sheepdog and what he was born to do, he's profoundly different from a retriever, and so forth. The genes program this propensity. I could probably train my dog to be a killer dog, or a retriever, but it would be hard. And that's what Darwin knew and Roger Sperry knew. And that's what I knew, just by looking at what's around us.

I was invited— One of the people I told you about at NIH—who was one of these super-bright, neat people—was an MD named John Haas, and he became a very good friend. John became the chief of medicine at Harvard, Mass General Hospital. I'm trying to place the date—it probably was the late seventies or around that time. A friend of his named Fishman [name unverified] was trying to set up a meeting [at Harvard] about developmental neurobiology, and he and John were talking. And John said, "Well, try and get Bill Dreyer there, because he'll sure stir things up, because his views are"—as based on this Cold Spring Harbor paper—"really different, and we should talk about them. It might help. If anyone can solve the problem, Bill can." That's what Fishman told me. It's probably typical of John Haas to say that. So I accepted. I was intrigued. And I tried to give them what he asked for. I prepared a talk [in] which I did in fact show slides of Darwin's work, and Sperry's—the figure of Sperry's that I included in my Cold Spring Harbor paper, the one that's in his 1961 paper. And I knew they wouldn't accept Sperry's work, or Darwin's or mine, but I gave a talk. The general idea of one of the things Darwin shows in that book is that—I think I probably used two slides showing this old guy, with his funny smile and snarl and frown and stuff, and then what Darwin actually used.

I guess he was the first to use photographs in a book of science; I was surprised to read that. He showed a picture [of a man] with electrodes, [which were] causing this guy to have a very readable expression, but it was just by signals to the neurons that wired the muscles to the face. And joking, I said, "See, it's all hardwired." And I got a big laugh out of the audience, because hardwiring was a big no-no to them. But they knew I was talking about this business of [word unclear], as was Sperry, as was—in a sense—Darwin. An older, very famous scientist, Ramon y Cajal, was another one. He was, back in the late 1800s, studying neurons. Sperry refers to his writings. Only a few people in history have studied the brain and its parts. Again, this is the Tom West [visual thinking]. He hasn't studied biologists yet, but I'm willing to bet that they are the extreme high-image types, dyslexics. Darwin absolutely was. I have done a little Tom West-type study of Darwin. He couldn't spell worth a darn. It's documented. They couldn't figure out how Darwin could be so bright, when he had such terrible spelling. He was a disaster in school—all the symptoms that Tom writes about. I don't know about Sperry. But I've learned that when I can see the same things as someone else that easily, they almost certainly have a funny brain.

So these people [at Harvard] couldn't see that at all. Nevertheless, that was what I was after. And that explains to you what the real issue, the real challenge, for the past hundred years has been. It's to figure out how the genes do this [hardwire the brain]. And as of yesterday, we have the data that say that the theory I published in August is right. [William J. Dreyer, "The Area Code Hypothesis Revisited: Olfactory Receptors and Other Related Transmembrane Receptors May Function as the Last Digits in a Cell Surface Code for Assembling Embryos," *Proc. Nat. Acad. Sci.*, 96:16, 9072-9077, Aug. 4, 1998] And that's exciting. In order to get the data for the theory, I had to use all the things I told you about—all the tools that I was working to develop so that you could do this. And one important aspect of that was the starting of Applied Biosystems to actually produce these tools and sell them all over the world, by the tens of thousands or something, so that people could do the Human Genome Project. I haven't told you much about the Hereditary Disease Foundation either.

COHEN: No. We'll get to that, because I'm interested in that.

DREYER: Milton Wexler knew an awful lot of the Hollywood types and helped make a film for propaganda to help get the human genome initiative going. He and his daughter lobbied in Washington. He is a major character in the whole business. And a lot of this stuff has happened because of this guy, whose birthday party was just a couple of months ago.

COHEN: Was his party down in MOCA [Museum of Contemporary Art]?

DREYER: Yes, it was. How did you know? Did I tell you?

COHEN: No. A friend of mine was there.

DREYER: That was a fun party, mostly because I had known him. I helped start the [Hereditary Disease] Foundation. He embarrassed me by saying how important I was. Milton and others knew that I could invent these instruments and had that nature. I contributed to that, along with Lee. And he asked if I wanted to play a role in the genome thing. And I said, "No. Let Lee do that. That's his kind of thing." Because you had to be an executive and want to get involved with committees and be a librarian, putting stuff into databases. None of that was my bag. I didn't want the glory of that, for that thing. But I said, "When the database and the library are open for business, I'm going to drop this other wet chemistry and take up genomics and use the library." And I did that, about a year and a half ago. Something like a year and a half ago, it was good enough to get started. And I actually offered to close down my wet chemistry labs in Church, on the condition that I move over to the Beckman Institute. And that was agreed to by our division chairman. When the time came to move, by the way, I had to create a giant roar and behave like a lion and refuse to do anything until I got an office in Beckman Institute. He reneged on his promise, but I got it.

COHEN: But that's up to Harry Gray [Arnold O. Beckman Professor of Chemistry; director, Beckman Institute], isn't it?

DREYER: Well, Harry helped me get there. I'm not going to tell you the story of this, but Harry knew that I was responsible for starting the Biology Imaging Center—because I also knew that

was another set of tools that was really important for the institute. And recruiting Scott Fraser [Anna L. Rosen Professor of Biology; principal investigator, Biological Imaging Center]; I started recruiting him twenty years ago and I got him over here to start the Imaging Center.

So, in order to pull together the data that led to the theory, the general idea of it is that there were published papers, very reasonable, that showed that the neurons that come from your nose for smelling things do have very specific molecules, like I had published and believed, and Sperry and Cajal and these few people—

COHEN: And these molecules are different from any other molecules?

DREYER: Well, no, they're not. That's what I'll get to. They're ubiquitous. They're all over the place. They were thought to be just for smelling, but they not only did the smelling in the nose—the other end of them that had to wire up to the brain had a far more difficult job. They had to target those particular ones that had smell receptor number 666, say, to one out of a thousand spots on the front of the brain, the olfactory bulb. Now, that's what Sperry wanted. That's what I wanted. But people believed that these were just for smelling. They still do. But I thought, "Wow, that's what I'm after." So I started trying to come up with theories. What on earth could the target be for these things? They look like what I've been after. But if they go up and recognize something in the brain, what can it be? And I know an awful lot about cell surfaces—these address things that are more general. So I had the background to be able to say, "I don't think there's anything [word unclear], yet they do it." They home in on a target with very high precision—a GPS [global-positioning satellite], or something. So if I made the assumption that the target is in fact cells they like to interact with, it's called homophilic interaction. Then things started to come together. As I told you, Dick Feynman and the other theoretical physicists can't really write the equations down for something; they make the best darned guess they can and see if it starts explaining things. And that's what happened with this. So it looked as though in fact you could explain how these axons come together. They are called vesicles. There's more to it than that. They like their neighbors almost as much as themselves; that's called heterophilic interactions.

COHEN: They like everything around them?

DREYER: Well, they can find their exact target partly because they like the neighbor and then they move over to the really exact one, but a gradient receptor [word unclear] switch. It answers questions Sperry was asking, but in a much different way than what the dogma is now. People talk about gradients of very nonspecific things doing this one-in-a-thousand or one-in-a-million targeting. Even though I helped find those molecules, I didn't buy it. The stuff going on in Scott Fraser's lab, which is basically where I am now—we'd look at these very nonspecific things. He's great. He'll let both things happen. He's excited about what's going on.

COHEN: So he thinks there's something to this story?

DREYER: Oh, yes. Oh, yes. He's one of a small number of people. And I think all of them are high-visual [thinkers]. It's very interesting. John Allman [Hixon Professor of Psychobiology and professor of biology] has already put it in his neat new book [*Evolving Brains* (New York: Freeman, 1999)]. And Mark [Masakazu] Konishi [Bing Professor of Behavioral Biology] is sort of that way. He's the one who, after reading it two or three times—and, I think, letting John read it—had the courage to submit it [reference unclear].

So you have this neat mechanism—that I only briefly described, but I think you'll understand; it's not that hard—as to how these things crawl out and find one out of a thousand targets. There are other cells that come to form that part of the brain, which also follow each other. They sort of tailgate—like an elephant hanging on the tail of the one in front—as if they know whom to follow. So I assume they have the same molecules there to take them to the target. And they come from a place that's just one small part of the ventricular and subventricular zone that earlier in development makes all the rest of the brain. It's more or less way back in the brain, toward the center. Actually, we keep making [these cells] throughout life, because your nose is exposed to all kinds of nasty things, so you basically need to make new neurons. And they travel out. And earlier in time, cells are generated to make other parts [of the body]. Well, are you going to have an entirely different mechanism to do it for those other parts, when you have this most elegant way to do the part I've told you about? No way. So I just began making the assumption that the other parts of the body might use the very same molecules and codes to tell the cell how to sculpt the heart or whatever. I had already started learning to do

the genome [sequence searches on] the computer and all that, to read the genome data that went into what's called the dbEST—database of expressed sequence tags. This is a way to find out what different organs of the body actually make. They make the RNA and the connective proteins. They take this RNA from, say, the prostate or from breast or heart, or the embryo or all kinds of places. There's a big program—there are millions of them by now; then, there weren't that many here—to tell what these different organs are making. So the first thing I did was I thought, well, there's no way a prostate has anything to do with the nose. So I went into that.

COHEN: This was a huge database—

DREYER: Yes. It was coming from our machines. That's what's cool. They buy the machines from Applied Biosystems—they're robots basically, or semiautomatic; they could be much better. But nevertheless, they buy these instruments and set them up, [let's] say a hundred of them, and they create, almost by semi-robotics, these so-called libraries made from all the different RNA—

COHEN: So you mean all over the world people interested in this set up one of these labs with your machines?

DREYER: Yes. To my knowledge they are mostly using Applied Biosystems machines that came out of that thing you've been asking me about. So I get to use the data they're dumping in the database as fast as they get it.

COHEN: Now, does anybody have access to this database?

DREYER: Yes, all over the world—everyone. There are some private ones you can't get into. There's one company that has at least one or two million more of these dbESTs.

COHEN: So has there been some understanding about what part of the genome you work at, because they don't want duplication?

DREYER: Yes, they've worked on that, but I'm sure they've duplicated. Sydney Brenner, another old friend of mine, started this project with the *C. elegans* worm as a model organism, because it only has 800 or 900 total cells and 600 or so neurons. I don't remember the exact numbers. And that one's just begun. This is all coming together. You are recording live action, not history. As of December 1998, the complete sequence of the worm came out, and I've been using it. It's amazing stuff that's beyond what I've got together now.

The point, though, is that as a consequence of those instruments, you have this marvelous database, including the whole sequence of the worm. You can go in and ask questions about this theory. And the worm sequence is part of it, in a sense. I knew it before the complete [genome] was done, because it has only sixteen neurons for a sense like smelling, with a thousand of these receptors. So I also went in and found the prostate for these things, the heart, the liver, everything. They're all over the place.

COHEN: The specific molecules?

DREYER: And there are seven or so papers, maybe more by now, that happened sort of after this was published. But it's ongoing. It's all coming together right now. They've proved with other approaches that you really do express these things in the heart [word unclear] testes and just a few of those. But the database says they're all over, everywhere. What [my August 1998] paper basically does is pull all that together and say, "These are the key molecules of the address code that I was looking for in a prior paper." All those prior papers by myself and Lee. These add the final digits, like getting the last four digits of a telephone number, [which are] used again and again. But if you had beacons on every house or building that had, say, 4-5-6-7, you'd see them as specks around LA and Pasadena. They wouldn't be in the same place, because they'd have different prefixes and different area codes and different whatever.

COHEN: But the last numbers are the same.

DREYER: Yes. If you looked for 4-5-6-7, you'd see specks. If you looked for the olfactory receptors—we call them serpentine receptors instead, because they're not there for olfaction—the worm has a thousand of them. These receptors are doing another job for the worm. The

prediction is that they'd be expressed in a whole lot of places and not as continuous blocks but as specks. And yesterday, using Imaging Center instruments that are also just coming together—as I say, it's just an explosion of all these things happening—we got the data that say, "Yes, we can really confirm that these specks are as you form teeth," a particular thing I focused on for a friend. And you can imagine [that] you need some very complicated abilities—many different kinds of teeth. It's even more complicated than my wishbones when I was a child. And that's exciting. And technically how we did this doesn't matter, but we used the Imaging Center. That lab, by the way, has a high concentration of people who, not surprisingly, are high-visual processors.

I don't think I told you, but because I met the chairman of neurology at that Wexler party, I was invited to UCLA by him. I said that I didn't want to give a seminar but that I'd like to meet with some of the key people who study brain imaging, to explain to them how it's now possible to think about the high precision with which genes shape our brains—sort of phrenology, almost—so that people are different in different ways. They have the ability to study it, but there, too, some of the people in that field want brains to be all identical and force it all into one kind of model, like those lobes over there—trying to make them all look the same. And what I discussed with them is [that] they shouldn't look the same.

COHEN: So are you saying that these people who say, "OK, hearing comes from this section"—that's not true anymore?

DREYER: Oh, no, no. That's absolutely true. It's all mapped. What some people are trying to do is say, "We all have the same maps," as if it were like a globe of geography. In fact, I'm convinced, and some of *them* are, that genes create very different [geographies]. For example, this high-visual type—if you do the kind of imaging that can be done, and compare high-visual twins so that you can show you have a control, they should look the same. I dragged out some papers on that—on twins—and we discussed some things I'd seen on dyslexia. And take people who are the other extreme, like the Murray Gell-Mann types or people who are superb auditors and use spreadsheets—en masse, their brains are going to look very different, as Africa, say, visually versus South America or something. One can be enlarged in one and much smaller in the other, with more real estate devoted to Africa than South America, and things like that. At

least one of these [UCLA] people is already on the case, and he's got the ability, and he does the software, too. So it's already started to get exciting on the front there. We're going somewhere with it, including knowing where the genes are [on the chromosomes]. There's one more thing that's exciting that just happened, again in December. It just got published. [Probably: Trask, B. J., et al., "Large Multi-chromosomal Duplications Encompass Many Members of the Olfactory Receptor Gene Family in the Human Genome," *Hum. Mol. Genet.*, 7: 13, 2007-20, Dec. 1998] Barbara Trask, a woman up in Seattle, has found that there are many more of these receptors in humans than what the textbooks say. There are supposed to be a thousand, but she's finding thousands of these things. And people are very different in these clumps of receptors—where and how big they are. That's perfect for trying to relate the genetics of how you build a brain—or how you don't, when you have problems, like autism. There is one deletion in autism that would be an example of what you'd like to look at. Does that deletion actually delete some of the very receptors? The techniques are easy. So what this opens up is a whole story of how you study human brains and differences in people. This would be a case where you don't have thousands of people saying the same thing—that's when I leave, when you start having—

COHEN: When too many people are working on something.

DREYER: When I already know the answers. But, see, I'm already moving on to this next area, which Tom West is so interested in—some of his theories of these things. He's working with the head of the National Library of Medicine to set up a meeting to discuss imaging, inheritance, all this stuff. John Allman would like to go, and one of the people from UCLA, and people from NIH. And I'll do that. I'm moving on to that. So that's history as it happens, or whatever you want to call it.

What's nice about Scott [Fraser] is that, like me, he actually gets in and understands instruments. When there's a problem with something, they call on him to get in there [and fix it]. He was doing that yesterday with a brand-new thing which I need next week [laughter] called a two-photon confocal microscope.

COHEN: And what would that machine do?

DREYER: It will allow us to go in and look at these fluorescent cells. I'd look at them and see where they are and watch them crawl as they form a structure.

COHEN: You work on a live animal, then?

DREYER: You can. That's why I say it's remarkable. Dave Crotty, who's a postdoc in Scott Fraser's lab, is just getting a system ready to be able to look at mouse embryos outside of Mom in a culture. This is before you'd worry about whether they're live or dead or whatever, but the tissues are alive and continuing to grow in culture. And the neural crest cells continue to crawl out of the culture. People like to study neural crest cells—these ones I'm talking about—in chick embryos and whatnot. I worked with the chick in my study. It's not too bad because you just crack an egg open. Or you watch it. You don't need to worry about Mom and the uterus and all that stuff. So you can watch these tissues themselves migrate with time-lapse photography and these fancy tools that are in the Imaging Center now, thanks to Scott Fraser. And Dave, who had no idea that we might come together on this project, is now in a position to—maybe next week—if they're present at the early stage of the embryo that it works in. But it will only be one out of 1,000 or 2,000 cells that lights up bright green. And [it will be] in the midst of the rest that he can watch with normal light-wave microscopy, and he'll be able to watch it crawl with the rest of them but know that this is the one for this particular receptor, and get a movie out of it. This is mind-boggling science. [Tape turned off]

Begin Tape 4, Side 2

DREYER: I'm going to continue with just a little bit more about how exciting it is to have these things coming together now. One more thing is that David Baltimore—again, these are all sort of coincidences—has come here [1997] as our president. Well, David Baltimore and I have known each other for a very long time. He's followed some of my wildest writings and been very interested. And he and I had a discussion of [my August] paper. He was the most interesting person I've had to talk with anywhere, and he happens to be here!

COHEN: You would say [that] he gets it?

DREYER: Oh, absolutely. [He] more than gets it. We ranged into why protease inhibitors of AIDS are causing strange things to happen. And he understands. And I understand. And it's just fun. The August 4 *PNAS* paper has a big color picture in it that is modified from a paper of people back at Rockefeller—Carlos Lois. Carlos did his PhD work reducing the data that I used as a key part of this theory. Well, Carlos, it turns out, has come out here with David Baltimore and is working in Baltimore's lab. And Carlos helped me perfuse these mice in a way that preserved them much better than I knew how to before. I used Carlos's embalming method to create the tissue that I used yesterday to get these exciting cells. That's astonishing. Another one who did work in Germany, Rainer Friedrich, is here also. He did some very critical work.

COHEN: Now, he also is in David Baltimore's lab?

DREYER: No, no. He's in Gilles's lab [Gilles Laurent, professor of biology and computation and neural systems]. He did work imaging the olfactory part of the brain of the zebrafish to produce data that showed that these receptors were closely related and next to each other, so that I could confirm the possibility of this gradient of receptors being organized in that way. I haven't actually worked with him. But one other thing I wanted to mention is that I was here when Eric Davidson [Norman Chandler Professor of Cell Biology] was recruited. He's an old-timer also. But he's never believed a word of my [antibody] theory. He has a sense of humor about it, but he seriously doesn't believe it. So I made a bet with him about the antibody [theory]; the basic idea says that the genes are altered when you make antibodies. And part of this theory which was published August 4 says that genes are altered so that the olfactory—these receptors—which one turns on which cell. So if it's cell 666, it can remember how to make 666 and not 667 or 665 or any one of the other thousands. And David Baltimore is very much into that possibility. Very few other people in the world are.

COHEN: Is he actually conducting work?

DREYER: The postdoc that worked on this nose [?] stuff is in fact working on that and trying to find the genes that switch. What's fun is that Carolina Livi—she's South American—

COHEN: Another postdoc?

DREYER: She's a first-year grad student working with Eric Davidson. But she challenged me when I gave a talk to the first-year grad students. Later I explained to her that there were some papers about this whole thing, and she's become fascinated by it. Eric Davidson made me a bet, which he repressed, way back—twenty-five years ago or something. He likes to drink a very good whiskey, a special brand. The bet was that I said that I'm right on the gene splicing, and he said, "No way." But he forgot that. So finally, just a few weeks ago, I said, "Look, it's high time you paid off on that antibody [bet]." He certainly knows that he was very much against the theory for twelve years or whatever, until he was forced to give in. So he finally gave me a bottle of that fine whiskey with a little note on it. Well, here's the thing I wanted to say: Carolina got interested in this theory of mine, and she's started an experiment, as of yesterday, to screen the sea urchin libraries. They happen to have one of the best ways to do this, with arrays. They have these big flat things that have all the different library things on it. All you do is take the probes and look for these. So she's already started looking. It would just be diabolically fun if she wound up proving the theory. I haven't made a bet with her yet, but I've got to hurry over there before—while she still thinks it's [word unclear] just awful, probably, [word unclear] the second bet on that. So those are little vignettes that are not history yet. They're current events. That's probably about as much as I want to say about the current events.

Now, during the break you said that you wanted to know more about Applied Biosystems. Henry Huang, who was one of the very good graduate students with whom I got along very well, was in my lab at the time I was working to develop the gas-phase sequencer and the mass spec. And I felt, and so did he, that we really needed to automate this god awful DNA-sequencing. Sanger and others thought it was superb, but it was time to automate that as well. And I had done a lot of electrophoresis, which is the method they use for that. And I had done a preliminary thing with very small capillaries and fluorescent-labeled compounds. They weren't nucleotides; they were peptides—but on high voltages, with this very small diameter. The separation was astonishing. The capillaries could do what these normal flat plates [couldn't]. Henry was interested in starting the process of automating, so we talked about it. And the idea of doing capillaries in fluorescence or him starting maybe with absorption of light [word

unclear]. So he got started on a project like that. And then he got his PhD and moved over to Lee's lab.

COHEN: As a postdoc?

DREYER: As a postdoc. And he continued to do [word unclear] or whatever. I'm not sure exactly what happened there. And then he wound up with Mike Hunkapiller. And I've already told you that Mike was not one who had this imagination-creativity thing. He was very good at taking things already done elsewhere and tweaking them, improving them, modifying them, where you don't need to see it in your head—a new generation. He went back to the way it was done by hand. [It was] just like I told you: he did that with the mass spec and wasted $250,000. I was angry about that. I don't get angry too easily. I wanted to see that mass spec delivering—I told you the story. But that was when I was wiped out by cancer. But he also did that with the attempt to do the DNA sequencing. And it works, and it did work at Applied Biosystems. By then he also got stock in Applied Biosystems. He became their research director. He became a part of the company.

COHEN: Where are the offices located?

DREYER: It's up in Foster City, basically in Silicon Valley. And that's what came out as the instrument that people have used for all these years. I went up there. Sam Eletr is the name of the [cofounder of] Applied Biosystems. He was in instrument design at Hewlett Packard [and did] some of their chromatography things, including some automated stuff, and [he] wanted to start a company. The way this works is you find these wealthy people called angels.

COHEN: Venture capitalists?

DREYER: Well, they're before the venture capitalists. Typically there are angels first, with a small amount of money—$60,000 or whatever. Sam started writing a business plan; he kept his job for a while when he started this. And, of course, that's whom I met when it was clear that my invention was in no way going to be what they wanted to build. Lee introduced me to Sam

Eletr [words unclear]. I told you what happened then at Caltech. It worked out with the people at Caltech—an agreement to license Caltech's patents. I agreed to license my private patents if Caltech gave me five percent of that. I didn't have to, but it just seemed appropriate. And I also didn't want the hassle of being involved in this stuff. So they said, "OK. You give us the controlling interest." And this dominant patent clearly was the thing to do. So I did that. That machine was ready to go, almost, and Sam agreed not to change it much. Of course, [they] improved the computer; they made it cheaper and cut out some of the things that weren't necessary. And there were companies lining up with $100,000 to $125,000 funding this company before we even made an instrument. Once they had that sequencer, like Amgen, they were in business for billions. All these start-up companies benefited from that machine. So there, again, this is the start-up of the early days of this whole revolution in biotechnology.

COHEN: Now, what I don't understand is [that] I thought you signed something when you went to work for Caltech—that they owned the patents on whatever you did here. That's not true? Am I wrong about that?

DREYER: No. If it was funded by Caltech. With the gas-phase sequencer, if I had succeeded in getting the grant, or in getting Caltech to fund it—which I couldn't.

COHEN: I see.

DREYER: So the story is that whatever I do, or whatever Lee did, or anybody else—Norm [Norman R.] Davidson [Norman Chandler Professor of Chemical Biology, emeritus], I'm sure, has an interest in Amgen. By now there are a bunch of millionaires in biochemistry and chemical biology, because they had consulted and companies got started. I could consult, and that's what I did. I could take money, not as a Caltech person, but for Chromatronics [name unverified] I could consult.

COHEN: That's OK. That has nothing to do with patents.

DREYER: Yes. Then they'd file the patent.

COHEN: Oh. They'd file the patent.

DREYER: Yes.

COHEN: But your name is on the patent. OK. I'm understanding. Now, if you had done it with money given to you by Caltech, or by a grant, then that's Caltech's patent.

DREYER: Then Caltech works it out.

COHEN: But if you're doing it as a consultant to a company, then that's your patent.

DREYER: Yes. I told you already that I had joined a patent committee [here], trying to lobby to make things more attractive or better. I didn't need it by then. I mean, I was very disappointed not to get those grants, but he who laughs last. [Laughter] I got a lot of money because they *wouldn't* fund it.

COHEN: OK. That's called ironic.

DREYER: If I had gotten funds from one of these Caltech or grant things, then at that time, thanks to the people I've already told you about who didn't view it as an acceptable thing for academics to be doing, I would have probably shared the royalties with three or four other people.

COHEN: Here?

DREYER: Here. If it were the normal rules they had then, it would have been fifteen percent—divided up three or four ways—of what Caltech got. It would be a trivial amount of royalties, and not worth a penny. Whenever I write these patents or work with all those patents, it's a hassle. It wasn't worth the hassle. I would report inventions to these guys, but that would just mean lots of work, and then they'd botch the job of licensing.

COHEN: The only conflict of interest is if you have a graduate student that's working on this. How does that work? I mean, isn't that a possibility for a conflict of interest?

DREYER: Well, you see, if this were being done up in Silicon Valley—and the critical work was done up there—

COHEN: OK, well, you don't send a graduate student up there.

DREYER: No, but you could have. And you can now. Fortunately, people realize that these things are very important intellectually and academically. They are revolutionizing the world, as has the stuff I'm telling you about. You can see [that] I'm really proud of it, because these tools have not just helped me to find my little—and big—things, but they've helped medicine. [Caltech is] getting much better at making sure people are rewarded—getting contracts made that will allow us to do those things, and allowing students and professors to start companies, even if they are funded by grants, and all kinds of stuff. They've got a whole office to encourage that [The Office of Technology Transfer]. And what's exciting to me is that Caltech is taking an equity interest in these companies. They don't *buy* that interest, they just accept it. And if the companies are successful—like Amgen and Applied Biosystems and others—the institute will make vast amounts of money, which will help fund the place in time. But that's my dream, and that's what's happening. And I think it should happen. It's not conflict at all, if you are aboveboard. You ought to interview Larry [Lawrence Gilbert, director, Office of Technology Transfer], the man responsible for this sort of stuff now at Caltech, if you want more on that. He's the man in charge of it—he works all that stuff out. And they don't allow companies to own work done here. They do work out ways to give them, in a sense, a short time period in which to file patents and stuff.

OK, I want to get back to where I was. I was talking about Sam Eletr. Sam started [Applied Biosystems], and he of course won big with the instrument on which I had the dominant patent. And he and I got along fine and all of that, but they were starting to do other instruments with Mike Hunkapiller as their research director.

COHEN: I gather you don't get along with Mike Hunkapiller.

DREYER: Well, I feel sorry for him, because he must recognize his problem with creativity, or else he wouldn't behave the way he does. Someone who behaves the way he does, does it for a reason. He even accepted, along with Lee, an award for the instrument I made [amino-acid sequencer] that he sold patents on in Germany—an award with money. He accepted that, but did not insist that I be part of it.

COHEN: On your instrument?

DREYER: Yes, my instrument.

COHEN: How about Lee? Why did he do that?

DREYER: Well, same thing, sort of. OK. So when Janet says, "How can you put up with that?" I say, "Well, remember that my aim is not to spend my time with lawyers and arguments. After all, I didn't build the instruments to get famous. I built them because I wanted tools." Also, as director of research, he [Hunkapiller] tweaked the machine in a minor way that, according to patent law, doesn't count, and then insisted that it was outside the claims of the patents—all of them. Caltech and I had a discussion about all this. Caltech, of course, by then, was losing royalties, too, and they had committed to me that they would do all this, pay the bills and deal with the patent. The question was, "Do we challenge [Applied Biosystems] in court?" Basically, there's a law that says that if it's equivalent, then you can't say that you're doing an equivalent thing.

COHEN: Then it's not a new machine.

DREYER: Yes. He just slightly changed the way you add one [words unclear]. It's so trivial. So we had big discussions, and I had my guru patent lawyer there, Russ Palmer. And it seemed very likely—I was virtually certain there'd be a lawsuit. There were millions of dollars involved, because, I told you, royalties were five percent of the gross sales, when they were

charging $100,000-plus for this instrument, at least at the beginning. Now they are sort of obsolete. But the net result was that Russ said, "Look, Bill, I've known you for a long time. As you say, you don't need money. That's not what runs your life anyway. And if you do this litigation thing, it's an incredible pain. You're going to have to go into old notebooks and drag it out. It's going to take the better part of a year out of your life with just hassles and stress and all kinds of stuff. I don't think you need that." And so we worked out a settlement. I took his advice and said, "To hell with it." Oh. He asked me, "What would you do with the money if you did get it, after all this?" And I said, "Well, I'd figure out a way to worry about whom to give it to." Because I had set aside enough for retirement to be comfortable. I have my airplane and I have my house. That's all I really want. And I can write a check when I want to buy computers. I support my own research right now. So we arranged a negotiated settlement that was substantial, but it was much less than what [it could have been].

COHEN: You have nothing else to do with this company then?

DREYER: Oh, no. I backed out of it. [But] I really felt that this capillary electrophoresis was dynamite and would be very appropriate for [Applied Biosystems] to get started on. This was not too long after they got started [1981]. They were successfully making instruments that I designed with Rod Hewick and others. So I set up a meeting up there.

COHEN: Now, we're talking twenty or twenty-five years ago? How long ago are we talking about?

DREYER: The company got started in the early eighties. This probably would have been in '83 or '84. It was early in the game. They didn't have this thing called capillary electrophoresis. That's what the fluorescent thing had done. And I went out there and set up a meeting. Mike wasn't there for, I suppose, obvious reasons. But some of the key engineers were there—good people, really dependable. I found out that I could work with those guys. I tried to convince them that they should take up capillary electrophoresis and fluorescence and so forth, including for the DNA sequencer that I don't think they actually started to build yet. I'm not sure. I don't remember whether they had the old way of doing it. But, for whatever reasons—probably Mike,

because he was, after all, the head of research at the company—they never did it. Other companies started making capillary electrophoresis [instruments]. I believe [that Applied Biosystems] then, as typical, jumped in on it. I'm not sure. But finally, as of the news last year in '98, they actually did go ahead and make the capillary DNA-sequencing machine. They automated it much the same way as Henry and I imagined it should be done. And it's far better than using [words unclear]. David Baltimore, who was actually at a meeting where the fact that they were doing capillary electrophoresis now [using a] much better machine, putting in the genome initiative, heard me say, "Oh, at long last they're finally doing it." So he asked me about that. They're making it now, just as of last [word unclear]. This is [J. Craig] Venter [president of Celera Genomics]. He said [that] he's going to beat out all the rest of the people working on it funded by the government because of a bunch of committees and terrible decisions and all that stuff that I, of course, hate. Barbara Wold [Caltech professor of biology; from 2001, Director of the Beckman Institute] is very much involved in that. He's going to do it his way and use the new capillary machines. And do it in a year or two—way ahead of the Human Genome Project funded by [the government].

COHEN: Have you been involved in any other businesses?

DREYER: Yes, quite a few. As a consultant, with Hybritech. That was long ago. They were the ones who were working on pregnancy tests, working with little latex particles. And the tests at that time were watching the clock, if you were pregnant. But they had all kinds of troubles with it, and the man who headed their research was a real bastard with the people who worked for him. But he thought I was a god figure, because I understood antibodies, immunology, and chemistry at the molecular level, so he offered me a huge consulting fee to come out there and just talk to the people once a month for a couple of hours. The people loved it. I enjoyed it.

COHEN: Where was this place?

DREYER: This was over in Burbank, or that general area. And furthermore, he said, "If you come up with a better test, I'll give you five percent of the gross sales," which is kind of a neat thing. He can do that, because the cost of materials for making these is five cents or less, and

they sell them for one, two, or three dollars per test. So I promptly dreamed up a better invention for how to do that, including fluorescence and stuff, and got to the point where it was almost ready to patent. I don't like to do patents myself. And then, somehow or other, the whole place fell apart. Oh, yes. I wound up with some patents, in fact, in there on fluorescent particles that someone else, [name unclear], took an interest in. Then that led to me talking about those at some of these medical meetings. One of the things that happened was that someone from Robert S. Frost— What he did for a living was to get people who had imagination and who clearly could see the future and the way things were going in these medical areas of immunology and all that stuff [to go on tour]. He'd go on tours on three continents: US, Europe—to somewhere like Brussels—and Tokyo. He would charge companies for having their research directors attend these meetings, at which we would give talks and then they'd ask questions and pick our brains and all that. I enjoyed that. It was really fun. You felt you were doing something. I don't think he paid very much, but it was a pleasant thing to be doing. So I did that. I began to use a way to get people to open their brains to innovation. I said, "Suppose I'm ET from the planet Extraterrestrial—ask me how they do things there." For example, there were people who'd do these endoscopy things [using] rigid kinds of glass, fiberglass rounds. But [if you] used chips or CCDs—very small, tiny—all you'd need was a very flexible device. And that's the way to do it. They even had these [tiny devices] you'd swallow and they'd transmit as they went through the gastrointestinal tract. So that was a commercial [outcome]. During one of those [sessions], a guy who was [helping to start] a company called Hybritech was there, too—Tom [Thomas H.] Adams. And he heard me talk about nonisotopic assays and how you'd use fluorescence for nanoparticles and things like that. And he really got interested. At that time, most of these [pregnancy] tests were done with radioisotopes, which were nasty things and expensive and all that. So he asked me if I wanted to be an advisor to Hybritech. And I said, "Sure, I'd enjoy that." [Then he said,] "We're going to give you stock." This is not the kind of stock that I got from Applied Biosystems, but it was enough to buy an airplane with.

COHEN: Where do you keep your airplane?

DREYER: Burbank. Actually, that's where I keep my archives of old notebooks and stuff, because the hangar's got lots of space for bookcases, and I can put instruments there. And I used

to pay for storage. There are walls of notebooks. If I die and someone wants them, that's where they are—in the hangar at Burbank. I don't want them. I do tend to save old things. The reason for that is not necessarily to keep them forever, but it's my answer for how to deal with old files: rather than to go through with what I should keep or not, I just throw them in dark storage. Once in a while, you do need something. If I needed to file a lawsuit for a patent, I would have to go back through twenty-five years or something of stuff.

You were asking me about other companies. What happened there was great fun. And partly because of my experience with Hybritech, I had an appreciation of how profitable pregnancy tests could be. So I told [Adams] about that. And they in fact took on, as one of their first projects, developing a non-isotopic, simple, almost over-the-counter pregnancy test. And of course I contributed as an agitator with some ideas, but they had very good people there. I mean, I didn't invent that. But it was a nice relationship I was very proud of. I really helped them. They called me Buck Rogers, because I had said, "Look, I hate business and spreadsheets and all of that, but if you want me to do this, and you want fantasies and dreams and inventions, I'm your man, because that's what I like to do." So the bottom line is that that succeeded—the thing was a hit. There were hundreds of thousands of per-unit sales. Eli Lilly bought them.

COHEN: And you have an airplane.

DREYER: Yes. Well, I didn't need it then. But it was fun. And we're still good friends. They were getting very wealthy. And they didn't just retire to yachts there; they've been very active in San Diego, starting more companies. Surprisingly, the people who went there just loved it. I had lots of fun starting companies. Another one was called DNAX. And that happened because I had known a man named Alex [Alejandro] Zaffaroni. I met him somehow on these travels. We talked about what could be done and that you could really do great new things with antibodies—make them to order, and all of that. But basically to build your own antibodies is theoretically impractical. The company got started with that general direction, with the dream that I shared. And I had stock in that. But they were bought by Schering-Plough Corporation, in which case I got stock [words unclear]. And Schering-Plough wanted the talent, which is considerable.

COHEN: How much of your time does all this take? Because you're running a lab here, too, of course.

DREYER: Oh, not much time. I mean, you go up there and have the best scientific meetings. Paul Berg was in DNAX. There are people like Paul Berg that I got to go and talk with and interact with once every few months. And I'd pay them for that. The best science around was at those meetings.

COHEN: At these start-up companies.

DREYER: Yes. And that's an example of one that had amazing talent. My old friend Ed Haber [name unverified], whom I mentioned [words unclear], was on there. So I got to see him from Boston, and so forth. It didn't take much time and it was great fun.

COHEN: Do you see real innovative scientists coming out of these companies?

DREYER: [Yes.] Which was far more important, as I look back, [compared to] what people normally think academics do when they publish their papers. Most of the papers aren't worth a damn in terms of how they affect the history of mankind. They are of things that are forgotten. It's a pile of junk, and things go on above it. But when you develop new pregnancy tests or machines that change the world of medicine, it's just mind-boggling what the effect is. So there, again, the attitude that you're shirking your duties in doing research is—

COHEN: Well, that is an attitude.

DREYER: Bullshit. If you have a chance to invent things that— And that's, again, a capitalist thing. Some people really don't like the idea of capitalism. I'm apolitical—I mean, I'm sort of a militant independent. The practical fact is, if you want to have anything you're doing impact the world of medicine or anything else, somebody's got to deliver it. And the way to do it is sell it. That means companies. That means patents. So I did that, and with pleasure. One was a start-up in gene engineering for plants, agriculture. They got bought, and I refused to work on what

they wanted to do, because they wanted to take healthy fats, made by seeds, and engineer those seeds so they'd make unhealthy fats. I thought that was a bad thing for a big oil company; I sort of phased out of that one. But the area's exciting. There were a couple more. I once counted five or six, and they were all successful, with the exception of the plant thing.

COHEN: Are you doing any of them now?

DREYER: Am I doing anything now? No. But I am working with Caltech on possibly patenting [words unclear] results of this [theory?], and some stuff that right now I won't discuss with anyone. [Laughter] [Tape turned off]

WILLIAM J. DREYER

SESSION 5

March 2, 1999

Begin Tape 5, Side 1

COHEN: You had some other thoughts after last week's session that you wanted to mention.

DREYER: I told you that things were coming together in a very interesting way—things that started long ago. One thing I [want to emphasize] is that in January 1999 there was a paper that's a minireview in *Neuron*, which is a major journal. [Jerold Chun and D. G. Schatz, "Rearranging Views on Neurogenesis: Neuronal Death in the Absence of DNA End-joining Proteins"] What the authors talk about is experiments that have been done in more than one lab now, where they delete genes involved in the DNA alterations that occur in the immune system. This is the editing—the cutting and splicing machinery you would use if you were editing a film—that's known to occur in the immune system. That's what I saw ten or twelve years before the general scientific community understood it. And I did bring a bunch of papers, six or seven, that make it so clear to anyone who looks at it today that we really knew all this. It was very clear. And yet, in the discussion at Cold Spring Harbor in 1967 led by [Francis] Crick, they didn't get it—including Crick and a bunch of others who won Nobel Prizes. And I've mentioned several times throughout this [interview that] I couldn't understand why [they didn't get it]. And I still can't. Part of it is this difference in brains. But what I wanted to mention is that to me it's quite fun, because I told you that I knew that I was going way out on a limb in 1967 by saying what I really believed was true, including Roger Sperry's work, because I knew people didn't believe him, either. And I also told you that I think the reason I saw it so easily is that I think the same way Roger did. He was another one of these people who saw things with a kind of an image chip in his brain that many others don't have.

COHEN: He was a very good sculptor, too.

DREYER: Yes, that's right. And I tried sculpting once and it was incredibly realistic and easy for me. So I have that ability, no question. What's going on right now in 1999 in this article, this review, is that when they "knock out" those end-joining genes in the [mouse] immune system, the embryos can't make neurons. It is assumed that the reason is that to make neurons you also need to splice the genes and add them or change them as you generate the diversity—

COHEN: Now, let me just [ask this] for my own understanding.

DREYER: Sure.

COHEN: If [the embryos] have no neurons, they can't be alive, can they?

DREYER: They aren't. They make it through, up to a point, but they're really in deep trouble. So this [idea is] really valid. There has been lots of evidence that neurons change and have more DNA than the normal diploid amount. In Purkinje cells—all kinds of evidence, which, by the way, David Baltimore understood but most people don't. But this article makes it really clear that people can't escape that. What's fun is that this is one of the first times I have seen this old 1967 paper referred to, in which I said I thought the way you turned them on and controlled them was to wire up the arrays of cell surface molecules with addresses with the same kind of editing machinery. So at long last, [the authors of the January 1999 *Neuron* article] refer back to that and make comments—like even for the immune system it was ten years before it was accepted, not to mention the brain.

COHEN: Well, that's good. OK. Shall we go back to discussing what we were going to do today, which was the Biology Imaging Center [in Beckman Institute]? Let's go back to its roots.

DREYER: Well, I'm going to review. In order to do that, I pretty much have to give you a little rerun on the way I've operated at Caltech in my teaching. You've heard more than you'd want to know about my convictions and the tools that allow science to progress. And I happen to be good at toolmaking. I see the potential in all that. So, from the time I came here, I had an

advanced course—Advanced Topics in Molecular Biology. Sometimes it's a lab. Sometimes it's reading papers that are seeing where the future's going.

COHEN: And you do that every term?

DREYER: No, once a year. Typically it's one term. And for that I've always done something different. I really don't like to redo the same thing. I've tried a few lectures. Some profs can handle students nodding off and not getting excited and all that, but I see too much. I watch faces and I see what's going on. It's very, very hard to get students on the edge of their seats in lectures—although I have done that, as an aside. When my oldest daughter was at [John] Muir [High School], I was asked to come and give a talk on DNA and phage and genes and life and all of that to her science class. It turned out they had all the science classes there; they had about a hundred students there. I had really worked hard to prepare it. I had some models of the phage with a string representing DNA, and I had some movies, and I had all sorts of stuff. And that was a roaring success. There was only one student who wasn't really on the edge of her seat, and she was drugged. [Laughter] Literally!

COHEN: I believe it. I believe it.

DREYER: But that took an amazing amount of work. I can do it, but it's hard. It was harder then for me. It's hard for anyone to do that; not everyone can, in fact. So I know I can do it, but not every day—no way.

COHEN: I was a teacher myself. I understand that perfectly well.

DREYER: As another aside on that topic of why I teach the way I do, one of the things I did to communicate some of these things was I was asked to do a Watson lecture on some of the things we discussed at Cold Spring Harbor, and with a budget. And there was a student here who was obviously very much into imaging and movies. His name was Cary Lu. On his own, as a graduate student in computer sciences, he set up a series of films about biology and related

science matters; and they were attended pretty well; once a week, or something like that, he had a film. I really enjoyed that, naturally.

COHEN: So did you give this Watson lecture? Do you remember what year that was?

DREYER: Oh, of course. That was in ’73. So with the budget, Cary Lu and I—I got him to help—made a movie.

COHEN: Do we have a copy of it here in the Archives?

DREYER: Well, it’s pretty crummy. No. I have a copy, but it’s pretty impossible to reproduce it now, because we had three movie projectors and two slide projectors. So I could show what I just described as a marvel of various kinds of life forms. And I could show the sculpture of Gustav Vigeland, a Norwegian guy who showed identical twins from birth, basically, all changing form [as they developed]. These are identical twins, male and female, at puberty and on through life—even in old age—in sculpture. If you had an identical twin, he’d be the same as you. He’d have very much the same shape and form that changes from pre-puberty on. And it’s sort of frightening. With two double projectors we’d see twins and all that sort of thing. That grabbed so many people that I got tons of letters, and people saw different things, like a Rorschach. The religious saw religion. The not-religious saw secrets of how everything works. And I was asked to repeat it. I could have gone on a lecture tour for a year. But I did do it for the OB-GYNs. They saw it as help—how their field worked, how you develop an embryo and whatnot. There’s a segment in the movie of a chick embryo developing from the egg, but I didn’t do that part of the movie. I had others [i.e. segments] that showed DNA. But [the chick embryo segment] was set to Beethoven’s Egmont Overture—*Egg-mont*.

COHEN: [Laughter] Did you talk at all?

DREYER: Not a lot. I did. But if I were going to do a book on that, I would love to do it with the ability to show these movies, images, and everything else.

COHEN: So let's go back to your—

DREYER: Well, I'll get to it. So that's my answer. If I teach, that's the kind of teaching I love to do, and I do it very well. When I'm asked to do a biochemistry course, if I find it boring and it's something I was interested in ten, twenty, or thirty years ago, I'm not going to be able to put it together three times a week and make students excited.

COHEN: So you are, in some sense, fortunate that you are at a school that can take this in.

DREYER: That's the only reason I came here. I had worked that out with Bob Sinsheimer, and Ray Owen to a degree. I was just reading work by Sarah Elgin, one of the people I helped stimulate to be interested in chromosomes. She's doing that now. That's the kind of thing I was trying to do.

COHEN: She was a graduate student and now she's—

DREYER: She took that course here. And quite a number of them got hooked through that course.

COHEN: How many people would you have? It probably varied.

DREYER: They ranged from fifteen to almost fifty.

COHEN: Oh, so that's a lot. That's big.

DREYER: Yes, most of the time it was twelve to fifteen. If you're going to have a discussion course, which I did, they'd read in advance whatever it was. Or if you were going to have a lab course—either way, it's awfully hard to do it well. The kinds of things I took up on the tool side of it—which was different from discussing how chromosomes work and all of that, which I did do—were things like learning to do molecular separations of DNA, protein, and so forth by gel electrophoresis. Nobody here was doing that. And this particular method, called gel

electrophoresis, was obviously very, very powerful. It did things that ultracentrifuges couldn't do. So I introduced that.

COHEN: This was going on somewhere else?

DREYER: Yes. I typically would find someplace in the world where something new was happening and was obviously revolutionary in its potential as a method, and then bring it here and introduce the students to it. Typically, the last person to be interested would be the chairman. The second to the last would be the professors. The ones who were really interested were the postdocs and the graduate students. Another example of the kinds of things that I tried to bring in would be monoclonal antibodies, which we've talked about. The techniques were revolutionary, and there were only two people in the world who were doing it at the time. I knew the Milstein group.

COHEN: César Milstein. You mentioned him last time.

DREYER: Yes. He developed that [technique], trying to prove me wrong. He was a good friend. I enjoyed him a lot. But I knew that this technique was powerful—really powerful—so I introduced that. We now have a facility to do that. There are methods to make proteins from a DNA culture—proteins to get the sequence [here]. We now have a facility for that. What I'm saying is not that I invented these things but that I stimulated the students to in turn stimulate the faculty to then, eventually— Another example that's more to the point is the scanning electron microscope. They had one at JPL. So I did that—just part of it for one of these courses—and took students up to JPL with material from their labs to actually get data, get pictures. So, for example, a student from Seymour Benzer's lab—Seymour wouldn't have been very interested and wouldn't have known about it—took a fly up there and came back with awesome pictures of the eyes of *Drosophila* and that whole thing. And Seymour immediately wanted one of these machines, and got it. So that's imaging. Many of the things in biology that I wanted to do involve generating not words or numbers, but images. And I had known Scott Fraser and had him come up and join me, not to teach, but for discussion.

COHEN: Now, was Scott here already?

DREYER: This is when Scott was at Irvine. We're going back into, I guess, the late seventies. I'm not sure; I can't date it exactly. But I had him up here discussing. He was interested in developmental biology, embryology, and whatnot—and also about what tools to use and theory. He is a theoretician as well. I asked him if he would come up, and he enjoyed the whole idea of doing this kind of course, and he joined me.

So some years later, the Beckman Institute was built [1989], and there was a call for pre-proposals as to things that could be done there, including research projects but also centers. And so I thought, "Boy, what could be finer?" The mission of the Beckman Institute was essentially to invent the tools of the future. I thought that was fabulous. In fact, it was really tough [to carry out] that mission.

COHEN: The Biology Imaging Center? Whom did you have to sell it to?

DREYER: Well, what I did was get together with people who I now know have this image thing: Al [Alan Howard] Barr [professor of computer science] was at that time in computer science and developing software that has helped revolutionize computer imaging. They call it SIGGRAPH. I knew him and I thought he would be a great person to get involved in this. John Allman was involved in trying to understand the brain, imaging the brain. So I did a rough draft of a pre-proposal and went over this with them and invited Scott Fraser to join us. And Jean-Paul Revel [Albert Billings Ruddock Professor of Biology], who was doing—

COHEN: He did electron microscopy.

DREYER: He did the only thing close to the Imaging Center. And there were tools coming up. It wasn't hard to get him interested in the scanning scope, for example, when there was a possibility of getting funding for it here; I never had resistance to these things from him. So I asked him to join. We wrote a proposal—a short one. It was a pre-proposal. And it essentially was summarily trashed. There was a scientist in neurosciences here who John Allman says has never had an original idea in his life. That scientist was trying to put together slices of the brain

by slicing it like a salami, but it was sloppy to store it and move it around. And you distort it by slicing. He had a quarter of a million dollars a year in funding to develop computer programs to try to put it back in the shape it was before it was cut. One part of [this pre-proposal] was to take images of the brain after you cut it—and save some slices, but mostly don't worry about them. You get high-quality images with a variety of optical techniques that still haven't been [implemented?] all together. It's really exciting stuff—before you cut it. Then you cut it again and throw the sloppy slice away and take an image of the cut surface, which is not going to be disturbed. And you do that for hundreds of slices. With [some] new graduate students I've come to know through my course, we did a prototype study with the chick embryo to show that this was totally feasible. Still, it didn't get through the committee. The committee included the [division] chairman and the guy whose name I didn't mention. And it appeared [that] they just couldn't understand the whole concept, which I'm sure you got immediately. There, again, I wind up being totally baffled by what can't be immediately perceived. As an aside, [the idea] that was turned down was picked up by the National Library of Medicine. The head of it did that with humans. You may have read about it in the newspaper a long time ago. They had a male and a female, and froze them as soon as [the people] were dead. It was kind of ghoulish, really. Then they went all the way through their bodies to collect digital data—gigabytes and gigabytes of data—until they had the whole anatomy in 3-D of humans, which is a major, major task. That's like what we had proposed.

COHEN: Did you call [what you were proposing] an imaging center?

DREYER: Oh, yes. But what happened was that we were persistent. And also, I formed a committee. We started small and started inviting more and more people—maybe [met] once a month or something like that, maybe it was once every two weeks—those of us who wanted to do this, whom I've mentioned already. I didn't get Scott out here for a time, but he was definitely enthusiastic. So we'd bring in more and more people who would see how important it was, including the guy who I'm pretty sure was responsible for trashing it in the first place. And after a year of committee meetings, we finally got it. [But] this didn't go through easily. I, in effect, wound up seducing about half of the division into seeing how important this whole thing was for what they were doing, and what things like confocal microscopes could do and what new

things Scott was interested in. I'm sure one reason it was [originally] turned down was because I know that I am not a good person to be in an administrative position. But I didn't want to be.

COHEN: So you think people said, "Oh, he'll want this and he won't be able to run it," or something like that?

DREYER: Right. But I made sure we found another person to run it who didn't have the visual abilities but was recognized as a very good administrator. That's what he liked to do. He was a disaster as far as the imaging, but that's not important. So he wound up, after a lot of manipulation and whatnot, agreeing to chair [the Biology Imaging Center]—to be the administrator. So, at that point, it basically started to happen, with Harry Gray as the head of [Beckman Institute]. I don't have any feel for whether [Harry Gray] was for or against it. And finally we recruited Scott Fraser. He's doing awesome things.

COHEN: So what year did all this happen?

DREYER: It's been going at least ten years. When did [Scott Fraser] come here? I'm not sure of the date. [Scott Fraser joined the Caltech faculty in 1991—ed.] So now everyone, especially Harry Gray, thinks this is just exactly what the Beckman Institute was intended to do. And I'm really pleased with [the Imaging Center], because [Scott] has dreamed up some new tools. He's got a lot of ability; Scott's highly respected. So is the facility. And it does, indeed, get used by lots and lots of people.

COHEN: Now, his wife [Marianne Bronner-Fraser, professor of biology], who came a couple of years ago [1996], doesn't do the same work.

DREYER: She's not a toolmaker. He worked hard to get her here, because they have children and he was commuting an hour a day each way. She works in an area that's related—of how cells assemble—the neural crest cells that help assemble hearts. And Scott gave me two words when I showed them both the data last time. He said that he knows everything and where it's going. "Neural crest," he said. That means that he thinks that these molecules are what we're

talking about there—how these cells migrate to form the heart. So that's how the Imaging Center got going.

COHEN: And it's very successful.

DREYER: Very, yes, it's going strong. It's well funded and appreciated by everyone.

COHEN: Do you have a berth there now?

DREYER: I've moved over [from Church]. My office is two floors up.

COHEN: On the second floor.

DREYER: Yes. [Room] 272 is on the west side. That's when I had to have a temper fit for our chairman to make good on his promise. That's what I was after. I mean, I didn't give up the wet chemistry without expecting that at least I could have a lab—to get over where I wanted to be, as opposed to being stuck in the Church lab.

COHEN: So, how many people are there in the Imaging Center?

DREYER: That's a hard question to answer. If you ask, "How many people are there that are associated one way or the other?" it would probably be ten or twenty in various ways. It's a big group of people, but [Scott] runs it loosely, by letting people have the reins. He has one person working and heading up a group to do NMR [nuclear magnetic resonance] imaging—which is the hottest brain-imaging method now—but doing it on mice and smaller creatures. They're working to do it on humans. I think it would be an awesome thing for the next century—a $100,000,000 program to carry on with the imaging. John Allman would love it. It would be an extension [of what's] already starting. And one person is working on the machinery—big magnets and all that. Another one is working on chemistry. These are semi-independent people.

COHEN: Now, these are postdoctoral people who are doing this?

DREYER: No.

COHEN: Professors?

DREYER: No, not professors. They're—

COHEN: Senior research types?

DREYER: They have some position as a member of the Beckman Institute.

COHEN: A member of the professional staff?

DREYER: Yes.

COHEN: These are all soft positions that have to be made by contracts.

DREYER: They have a little better title, and they're probably partly supported by—this particular kind of position is an actual research position in the Beckman Institute.

COHEN: So the Beckman Institute supports those positions; Caltech doesn't support those positions.

DREYER: No, the Beckman Institute [has to have] people who know how to design and use these big magnets and things of that sort.

COHEN: And they have to be here; they can't come and go.

DREYER: Yes. I don't know the details [of how they are supported]. Again, I don't like to get into the spreadsheet side. But the Beckman Institute does have—

COHEN: Money for these positions?

DREYER: To develop these instruments and tools. And to do that, as in astronomy, you need people who work on the big telescopes, and you can't do that with temporary positions. People have to feel important and all that stuff. Well, Russ [Russell E.] Jacobs has a position like that [member of the Beckman Institute]. And there's a chemistry group, too. These are under the umbrella of the Imaging Center, under Scott Fraser. You need those positions. You've just got to have them. If you want to make Caltech as I would like to see it and you want Caltech to become a world center of understanding how the brain works using various techniques, you need to bring in physicists, you need to bring in chemists, you need to do what Scott's doing, only more so. And you need big money—a significant [amount], like $100,000,000 or more. Typically, chairmen are not toolmakers, and typically [they] jump on me when I talk about the importance of toolmaking.

COHEN: Now, let's go back to your course a bit. You've continued to teach this.

DREYER: I am taking a sabbatical, which I told the chairman I was going to do.

COHEN: This year?

DREYER: Well, the course that I wanted to teach—let me back up. This is my general course [Advanced Topics in Molecular Biology], in which I keep doing different things. Something like six or seven years ago, it was apparent that digital stuff in many ways which relate to imaging, and digital information for the library, could be and would be stored on the then-very-primitive Internet in the future. So I took that as the topic for my course: that you could expand the electronic availability of information. [Electronic] information was already available through NIH with a great search system, where you could get abstracts but not whole journal articles and whatnot. And Kim [Kimberly] Douglas, a [Caltech] librarian, who was very helpful and sympathetic, [took the course]. So did Daniel Taylor [library staff] and quite a few others. Four or five of the librarians participated; they showed up for this course, they were interested. What I was aiming to do was to get information digitally and to encourage Caltech [to go in that

direction]. They were already good at starting to build the Internet and whatnot, but I encouraged them to do much more through teaching, being able to do research on-line, and all those things. The librarians participated even though part of what I was lobbying for was that whenever you can get scientific journals on-line, digitally, [then you can] cut down on the number of paper journals you have that aren't considered very important and invest in the digital side. And I gave that course for several years. We called it a course, but it was a workshop. [Then] the whole Internet exploded, and most people who participated [in my course] were involved in that. Part of the aim was to get access to information in profoundly better ways. A concrete example: Before, when you wanted to look up who referenced a paper that you were interested in, you had to go to the library and leaf through these books. They [the indexes] started to become available on-line but you had to pay fifty cents or a dollar [per search]. It would quickly break anybody's bank to do it digitally. And then you'd have to go in there and write down by hand, typically, the various references. You might get fifty references out of this. It was an unbelievable pain. I knew, and the librarians knew, that this could be done digitally. That's called citation indexing. What's happened is we now have it, and it's awesome and it's powerful for everyone, not just biologists. Without that, I never would have been able to [write up this paper] that was published in August of last year. That was made incredibly easy by having this digital information. Mining the genome databases—that's all digital stuff. I wanted to have a session showing how valuable the computer could be for teaching, especially in those areas like the brain, where you can teach more with images, by rotating and moving them, about the structure of the brain—more than you could ever do with chalk and a blackboard. There was pressure from on high—even in our faculty [presentations]—not to use any slides or visual stuff. [We were supposed] to use chalk and a blackboard, or a whiteboard. And that has to do with people who don't use the imaging technology. [But] in fact when we do this, people just refuse to obey the rules. If you want to show the stuff that Scott's doing, you have to. But I could not get the equipment we needed [in order] to show [computer images] in a classroom. I tried. I made presentations to the faculty, and now it's slowly happening—even having classrooms that will allow you to show movies with a VCR. Old-fashioned projectors—which no one uses—you could always do that. But if you wanted to show a tape, in [the Biology Division], we only had a TV set, a small one, in front of a big lecture room. It was just crazy. [Tape ends]

Begin Tape 5, Side 2

DREYER: And I had spent my own money to get—actually an expensive laptop that was capable of showing students how to teach this way, how to use it for teaching. Exciting stuff was being done with great success all over the world—not here, not in the real way that it is starting to happen with Web sites.

COHEN: Now, I've certainly seen people lecture with their laptop computers projecting the pictures. I've certainly seen that.

DREYER: Yes, but not in the Biology Division, I don't think. Now there are two places you can—that's true. One is, of course, the Beckman Institute, thanks to Al Barr.

COHEN: The auditorium here, upstairs?

DREYER: Yes. At least it has the ability to do that and to have conferences with centers throughout the world that way. You can now see their images and see *them*, which is really nice. So I became very frustrated with trying to do some of these things, and with the [division] chairman. I basically decided that that wasn't going to fly anymore. This year, I don't know. I haven't decided yet [whether or not to teach]. [My course is] set up so that it will be taught by the staff.

As to where I'm going: I always ask, "What am I excited about?" But one of the things I see for the future—and I always do my teaching there, too—has to do with this whole area that I've been talking about so much: how the brain works, differences between people, the notions that the anatomy of the brain [is] made by these molecules—that [they] put the brain together with very great precision. And it's going to be really interesting to know about the differences in that precision—how the various kinds of people differ anatomically in terms of what real estate they use when they think or when they work. There'll be a meeting set up in May or June, probably at the National Library of Medicine, where they have done this already. They're into this imaging, the digital project, to discuss ways to carry out this kind of work. If I'm successful, [there will be] one or two people from UCLA and from San Diego. John Allman's interested in

joining, [along] with Tom West, who is not a scientist but who is so involved that he's helping catalyze the formation of [this meeting]. And that would be something that I'm willing to be drawn into, I've decided.

COHEN: So continuing what you're doing, but a new phase.

DREYER: It's not the same thing I've always done—I just keep evolving. But I'm quite pleased, as you heard last week, that at least the molecular level of understanding—that probably other molecules are involved, and the genes suggest where to go next, which makes it relatively easy to look for differences in people once you have image differences and all that. So that's where I want to go. But I'm getting old. One has to be realistic, because I'm seventy and a half, and I don't know anyone, in all the years I've been at Caltech, who still had all their marbles at seventy-five. Now, admittedly, I'm slow, but I'm in really good physical and mental shape compared with some people at this age.

COHEN: I don't think, judging by this interview, that you've ever wasted your time too much on things you were not interested in.

DREYER: No. And that makes some people angry. And that's part of why I haven't done—I mean, I'm terrible at committees. I get impatient. You were going to ask me about committees.

COHEN: Yes. Well, you said you did form one when you saw a reason for it, which was for the Biology Imaging Center.

DREYER: Right. I also was on what could be called a committee—I really did a lot to help it. This was the Milton Wexler Foundation for Hereditary Diseases.

COHEN: So how did you get into that?

DREYER: I did an interview, like the one that was in *Engineering and Science* ["A Changing Concept of Health Care," *E & S*, 32, 2-8 (1973)] and it was published in a TechniCon trade

sheet. It was distributed widely to physicians. It talked about—I reread that *Engineering and Science* article. It talks about the major changes that are going to occur in this field in the next twenty years. Well, [more than] twenty years have gone by, and those changes have more than happened. That's exciting. But then [a psychiatrist] at Creedmoor State Hospital, in New York, read the interview. He was a shrink, and he was interested in aging but also in Huntington's chorea. He had a number of patients there. What causes the brain to drop dead, or the neurons to start dying way before they should? So he called me up and offered me a high honorarium to go out there and talk to his shrinks, and I said, "No way. I don't see anything that I can say that could easily be communicated to that kind of audience." It was just so different. I had probably had a lot more psychology, because my first wife had her PhD in therapy and psychology. I was a spouse that learned a lot of great stuff, by the way, including human sexuality and group process, with a leader of the field, Virginia Satir. So I probably knew more about that than they ever did about molecules or genes. But he persisted. I finally said, "OK, if you're willing to bill it as an experiment in communication and be up there on the podium with me." So I did it, and in the audience was Marge [Marjorie] Guthrie, who was Woody Guthrie's widow—one of his wives. He died of Huntington's disease. So she was very interested in what could be done in the future with these promises—which, in fact, as I say, are coming true. I was invited to join her and some wealthy person who was helping fund that research in New York for dinner, and they set me up to meet Milt Wexler out here. He was trying to form a West Coast branch. That was the beginning of our relationship. But I really was interested. So call that a committee, if you like, but I stayed with that for maybe ten years.

COHEN: And what did you do for them?

DREYER: I helped run workshops designing the—Seymour Benzer and I—[Wexler] credits us with starting the approach that worked, which was: What do you do with, say, $200,000 a year when many laboratories had much more in their budgets than that? The amount they raised—they got more than that. And Milton, by the way, was chief therapist for a huge number—I mean, really dozens—of movie stars, as you might know. I'm not going to rattle them off. He was a manager-trained psychoanalyst and a PhD—a very strange combination. But he was very good and very much sought after. He ran groups for Shirley MacLaine, Jennifer Jones Simon—

COHEN: Now, it was Wexler's wife that had the disease. Is that correct?

DREYER: That's right. His wife died of it. Two daughters—

COHEN: Both of whom I know, by the way.

DREYER: Nancy Wexler? OK. She took it up. So he could raise this money through Jennifer Jones Simon and others too numerous to [mention]. Most of them I've met, because they'd have these parties. Norton Simon's home in Malibu had some art, by the way, that's awesome. He hung his paintings at home, so there was a Van Gogh in the children's bathroom and things like that. It was a wonderful experience, because of the art and being with all these actors.

COHEN: And you would explain to him the science?

DREYER: Yes. They loved it. I wasn't the only one. I mean, more scientists from around the world were drawn to this thing. But the key thing that Seymour and I both lobbied for—I certainly did lobby for it—was to forget about trying to fund research in the normal way, because you don't have [enough] money to do anything meaningful. But if you can get really bright, young postdoctoral fellows and seduce them into coming to the West Coast with an offer of $2,000 a year to spend on books or whatever they want and meet Hollywood stars—and the workshop, where you have the same kind of thing I do in my teaching. That's part of why I liked it. And Milton was a professional at running groups. And I was, to a degree, with my own teaching. So that's how it worked. Together with others, we had these workshops. And we did, indeed, attract postdocs from some of the best labs that were funded for $1,000,000 a year.

COHEN: So you would give them a personal stipend to work on this other stuff?

DREYER: Not to pay for research—just to get them here. Get them curious. Get them involved by discussions. I was among those who would give out a bunch of theories. I'd write on the board, and someone would take notes. We'd think about it and work it out and challenge them

to get involved and come up with their own ideas. If they'd want to test them, especially their ideas, they could go back and use their million-dollar facility. And then, again, as I said before, you'd get the young guys, the postdocs, going and talking to their bosses. And they'd start using the bosses' funds and interest and whatnot.

COHEN: Now, you said you did that for only about ten years. You don't do that anymore?

DREYER: No. I burned out on it. Plus, by then it had really taken hold. There were very good people. And some of these young people had grown up and started their own laboratories, doing this work, finding the genes.

COHEN: They have found the genes, but they don't have a cure.

DREYER: No. But the procedures and the ways of going about it were started by this foundation. They have been used for many things. One reason that this particular disease was appealing to me is that the genetics are so clean cut. If you have one copy of the gene, you die. It's dominant. [The disease] typically comes on at age forty-five, with high variation. We don't know exactly why. [Milton Wexler is] almost ninety. He's still hanging in there. So that's a committee that I'm very proud of being involved in.

COHEN: And the patent committee here at Caltech?

DREYER: It can be so frustrating. What I proposed is that they set up a separate entity so that, specifically, they could get Carver Mead [Gordon and Betty Moore Professor of Engineering and Applied Science], Dick Feynman, and myself, together on a retreat for just a few days to tackle some major important problems. And [they should] set it up such that everybody would benefit, through patents and royalties, including Caltech. And that would have been an amazing thing to see happen, because you'd combine the different perceptions of three good inventors.

COHEN: But it didn't happen?

DREYER: It couldn't happen, because of the bureaucracy. This would have been twenty years ago. That's when it was unpopular to be an inventor. And I was trying to change that.

COHEN: And that has not changed?

DREYER: Now it's changed. And, again, I would like to think that nibbling away at it, which I've continued to do, slowly helped. But I don't have the patience to be on committees like that.

COHEN: Have you ever been in on any of the governance of Caltech? Things like tenure committees?

DREYER: No. I'm just not interested in that, and people have the good sense not to ask me. You always have the chance, if you want to, to suggest that they consider you—and I just don't. Many of [the committees that interest me] have been elsewhere, including, as I said, half a dozen new start-up companies, where you do something useful for people. They've all been successful and have been bought by others. Of course, I wind up getting stock in each of these but that wasn't why I was interested.

COHEN: Are you unique at Caltech in sponsoring your own research? How does that work? Do you have any trouble doing that? Do they charge you overhead?

DREYER: No. Right now, the main funding for research [comes] as long as they keep paying me. I do have resources. I can't help fund multimillion-dollar stuff, but I can buy computers. For example, the laptop that I bought wanting to teach people how to use these in teaching. That's $6,000-plus. With software it could easily get into $10,000 just to be able to teach that way or to use them for mining the database. And I have another one—a desktop. And a big MacIntosh, that does graphics and all sorts of things. Janet's now doing that. And we have the scanners. We can make CDs. We can do all the things that, if I want, document what we've talked about properly. It would all be done with equipment you don't even have here, but we do. That I can pay for. But I'm not paying to hire a technician. I do get help from people. And I'm

thinking about hiring someone to help me do this business of entering things in the computer—this image stuff.

COHEN: Do you have page charges and things like that? Maybe you don't have that in biology.

DREYER: Oh, yes. I had to pay $2,000 to publish the [August 1998] paper in *PNAS*. [It was] a four-page chart and color paper stuff. And I've ordered an exciting new computer from [word unclear] that does a new thing in silicon graphics. So, stuff like that. Nobody else is going to do that for me. As I told you, I couldn't get a grant to do this work, to support buying these computers to do the [words unclear]. But fortunately, things I most need in my research are these very, very expensive instruments—the computers—that are already in this building. As soon as we're done today, I'm going to go use the two-photon confocal microscope that Scott [Fraser] helped cause to happen.

COHEN: You wanted to talk about your family, and I'd like to hear about your family.

DREYER: I just thought it was appropriate to mention them. I did tell you that I was married just as I was getting out of Reed College. And Mary Dreyer was a great person, a nurse, whom I met through being an orderly. I told you I had always worked in the summer. I worked as an orderly at the hospitals locally, and I always enjoyed her. She had a great sense of humor. She sort of followed me through Reed. We were together for some time. She worked while I was in grad school, and I'd take care of the oldest daughter, Brynn. We had two more daughters, Susan and Kari. All three have master's degrees, and all three are generally in the area of technology and therapy. The youngest, Kari, really had trouble with dyslexia in school. All three of them see images in their heads—this basic dyslexia pattern. Kari's dyslexia was so bad that she was refusing to go to school in the sixth grade, and finally we figured out that it was because she kept getting negative stuff thrown at her: fail, fail, fail. And she just couldn't handle that—and her reading. I can hardly believe the school systems aren't better at identifying people like me or like Kari, because there are ways to teach very differently and understand that. So we found this place down in South Pasadena, or San Marino—on Huntington Drive—that specialized in treating dyslexic kids. It was just an office, where they worked one-on-one with a computer.

And there was lots of positive reinforcement and all kinds of neat stuff. They dealt with it. And after just a few months of that, she jumped three grades on her testing. And that could have been done in school. By the way, that's part of what I think the positive side would be of where I said I wanted to go in the future—understanding these huge differences in people and their abilities.

COHEN: I think that's being recognized more and more.

DREYER: OK. So that's just an example. And it has to do with the chips in the brain and all that sort of thing. She now is an executive with a very high income. She's in great demand, negotiating contracts to do with health maintenance organizations, doctors and whatnot. So those are my three daughters. Mary Dreyer had something strange psychologically; she'd get hysterical, and this was really hard to take. When she was good, she was very, very good. But when she was bad, she was horrid—like the old nursery rhyme.

COHEN: Was this something that came on later?

DREYER: No. It was always there, and it would get worse. Then we had therapy. That's probably part of why she went ahead and got a PhD in psychology, because there's a theory that if you're a wounded person, you can be a better healer.

COHEN: So Mary went off and did her own thing, I gather.

DREYER: We separated.

COHEN: Your girls were grown by then?

DREYER: Yes, that's part of why I hung in there. I was single for a couple years, or whatever. Southern California in the seventies—

COHEN: Fun?

DREYER: As a guy who was sought after by some—whatever. But I've never been one to want to prove anything. But my mating activities, my deep relationships, have been serial—close to monogamy.

COHEN: So you met your present wife [Janet]—?

DREYER: She gave a talk at the Hereditary Disease Foundation, and we immediately got together.

COHEN: Where was she working then?

DREYER: She was at UCLA, sort of a senior postdoc. We have not had children, mostly because I— It's really hard bringing up children, in case you haven't noticed. And my daughters are great—not without problems themselves, but they are working on them. We see Kari every two weeks. She and her husband, Eric, get along great with us; they're probably our best friends for this kind of thing. So that's kind of nice—I do have a nice family. And Janet is awesome—a PhD who's also gone to the Art Center and gotten her degree there.

COHEN: And she continues to work with you on these various problems?

DREYER: She's an enormously great enthusiast. So that's that. What else do you want to ask?

COHEN: I was going to say, "What do you see in the future of Caltech?" but I think you've done that. Good and bad.

DREYER: The biggest problem I have with the recruiting going on now—

COHEN: Oh, you mentioned something about that.

DREYER: This has always been true about recruiting: People who are already here tend to want another person like themselves. "We've got to have another like me." Caltech is a very, very

small place in the scheme of things today. It was small to begin with, but nowhere near what it is now compared to the rest of the world. So, for example, if you try and do now in immunology what was relatively easy when I came—with Lee [Hood] and so forth—we led the world as a center of great excellence. We led the world. These are major, major things, that don't mean one more person who studies synaptic connections or something that is basically pretty well understood already. I think that the provost [Steven E. Koonin, professor of theoretical physics], and probably the president, will be very receptive to the idea that if Caltech's going to remain something like Mount Olympus—a major, major center of something—it's going to have to be something more or less comparable to what happened in astronomy starting with Mount Wilson. It's going to depend on tools. Sure, I'm prejudiced. But that is a fact. And there are probably a number of areas where those tools could be developed. Or, better yet, the provost, who I think is much in favor, and the president can overrule whatever other powers might be to put up serious money and positions—and non-professorial positions to, say, build a brain-imaging center that many people would really like to see. In neurobiology—to lead the way in the world.

COHEN: I see. That's your analogy with the telescopes. That would be many people coming together.

DREYER: Oh, yes, not individuals. That's the point. It wouldn't be just more of us already here. That's disastrous.

COHEN: There's the LIGO project.

DREYER: Well, LIGO I don't want to touch. I don't know anything about that. But I do know about some other things that require a major commitment of faculty and space—for equipment and instrumentation and whatever else—in the new building [Broad Center for the Biological Sciences]. It initially was a no-no, but I think it might happen. My prejudice is that's the only way Caltech's going to continue more or less—

COHEN: Why do they say the building will have room for ten professors to set up ten labs? That's not what you're talking about.

DREYER: No. Not unless there's some kind of major thrust. If you read the history of Caltech—and I haven't really studied it—but on a number of occasions they would have real questions about where they would go as a major effort, like when biology got started. There were big discussions concluding that this was the one place in the world where you could apply the rules of chemistry and physics—and the knowledge—to understanding how biology works. There wasn't any other place [that did that], so they decided to really invest seriously in that, and that would be the thrust. And that's not happening. I must say the president and provost are working on it.

COHEN: It's not happening now, you're saying? But you're very encouraged by this new administration?

DREYER: Very, yes. I think that many of the things that the existing leaders in biology would like to see happen are in the areas that will be all over, in terms of the major new advances. Not all over—it never is. But they'll be putting in the final pieces of the jigsaw puzzle. That's not where I think Caltech should be going. You already know most of the answers, and that's not my style.

COHEN: OK. Well, let me ask you just one final question. Could you have done what you did anywhere else? Or did you find that Caltech's really been a unique place for you, and *the* place for you? I end up here, and mostly I get accolades. But go ahead. You may have fought, but you did what you wanted to do.

DREYER: I ask myself that. It's been such a struggle, as you can see, to get support and funding for innovation. By the way, Maxine Singer said she never could have done what she has done in her life at a place like this or anywhere else. I'm not sure about NIH. Had I stayed there, it's hard to say. Because if you didn't have to worry about funding…. I was always—just like my mother let me go, that's what Anfinsen did. I took up phage genetics without him. He didn't even know about it or what the deal was, but he allowed me the freedom to do that. If I had continued at NIH…. I can't tell you.

COHEN: So you're not convinced that this is the only place you could have managed to do what you did. That's not a feeling you have.

DREYER: I can't answer that question. I mean, let's face it, I benefit enormously from Caltech. But I don't have a clear answer, because at institutions where they provide real encouragement for the things that I like to do—I don't know. If you look at what actually in fact happened, despite the struggle, I'm very pleased. And, of course, [having] students like Lee Hood…. Well, I had those at NIH—the best, brightest: Claude Bennett, who wrote this antibody [paper] with me. So I can't answer the question.

I think [Caltech] could be better. And it certainly could be better for others in the future if they'd focus more support—probably in astronomy, too—on high-quality staff that's non-professorial. In this era, if you want to be number one in the world, you'd damned well better have mechanisms to make people feel important without having to be a damned professor. It's just crazy. So that's that.

COHEN: Well, that's a good observation. Thank you. [Tape turned off]