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RONALD BRESLOW

Transcript of an Interview
Conducted by

Leon Gortler

at

Columbia University, New York City

on

19 March and 9 April 1999

(With Subsequent Corrections and Additions)

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RONALD C. BRESLOW

1931 Born in Rahway, New Jersey on 14 March

Education

1952 A.B., chemistry, Harvard University
1953 M.A., medical sciences, Harvard University
1955 Ph.D., chemistry, Harvard University

Professional Experience

1955-1956 National Research Council Fellow, Cambridge University

Columbia University
1956-1959 Instructor, Department of Chemistry
1959-1962 Associate Professor of Chemistry
1962-1967 Professor of Chemistry
1967-present Samuel Latham Mitchell Professor of Chemistry
1992-present University Professor

Honors

1966 Award in Pure Chemistry, American Chemical Society
1966 Fresenius Award, Phi Lambda Upsilon
1969 Baekeland Medal, American Chemical Society
1969 Mark van Doren Medal, Columbia University
1972 Centenary Medal, British Chemical Society
1974 Harrison Howe Award, Rochester Section, American Chemical Society
1977 Remsen Prize, Maryland Section, American Chemical Society
1978 Roussel Prize in Steroids, Roussel-UCLAF, France
1980 James Flack Norris Prize in Physical Organic Chemistry, American Chemical Society
1984 T. W. Richards Medal, Northeast Section, American Chemical Society
1987 Arthur C. Cope Award, American Chemical Society
1988 Kenner Award, University of Liverpool
1989 Nichols Medal, New York Section, American Chemical Society
1989 Award in Chemical Sciences, National Academy of Sciences
1990 Allan Day Award, Philadelphia Organic Chemists Club
1990 Paracelsus Award and Medal, Swiss Chemical Society
1991 National Medal of Science
1999 Priestley Medal, American Chemical Society

ABSTRACT

Ronald Breslow begins the interview with a discussion of his family life and background. He grew up in Rahway, New Jersey, the son of a physician. Max Tishler, a family friend, helped to pique Breslow's interest in chemistry. In high school, Breslow entered the Westinghouse Science Contest, which enabled him to meet like-minded teenagers. Breslow entered Harvard University, graduating with his A.B. in chemistry in 1952. He discusses chemistry courses taught by Louis Fieser and Paul Bartlett, and his research with Gilbert Stork on the structure of cedrene. Breslow received a master's degree in medical science from Harvard in 1953, and he discusses the uniqueness of the program. He continued his graduate studies with R. B. Woodward, earning his Ph.D. in chemistry in 1955 for his work on magnamycin. He discusses his graduate school colleagues and his post-doc with Alexander Todd. In 1956, Breslow joined the faculty of Columbia University, where he has worked on a variety of subjects, including thiamine, cyclopropenyl cation, cyclodextrins, and electron transfer. He discusses his colleagues, his collaborations, and his cancer research. Breslow further addresses changes at Columbia, Columbia's chemistry department, and his involvement in the American Chemical Society. He concludes with a discussion of his consulting activities and reflections on his family and career.

INTERVIEWER

Leon Gortler is Professor of Chemistry at Brooklyn College of the City University of New York. He holds AB and MS degrees from the University of Chicago and a Ph.D. from Harvard University where he worked with Paul Bartlett. He has long been interested in the history of chemistry, in particular the development of physical organic chemistry, and has conducted over fifty oral and videotaped interviews with major American chemists.

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INTERVIEWER: **Leon Gortler**

LOCATION: **Columbia University, New York City**

DATE: **19 March 1999**

GORTLER: I know you were born in Rahway, New Jersey, on March 14, 1931. You just turned sixty-eight last week.

BRESLOW: Exactly right.

GORTLER: Tell me a little about growing up in Rahway. What was your family situation like?

BRESLOW: Well, my father was a physician. Before the Second World War, he did general practice. But he volunteered for the Army, even though he was old enough that he wouldn't have had to go. He went off and ended up doing a lot of surgery. He was in what's called a portable surgical unit, which is the thing that—well, if you ever see "M*A*S*H," that's not a portable surgical. The guys up in the front are the portable surgical people—getting the wounded people, saving them, and then sending them back to something like a M*A*S*H unit. So he was doing that stuff, and then when he came back, he had done enough surgery that he decided that's what he wanted to do.

So he came back and became a general surgeon, and eventually became a Fellow of the International College of Surgeons, that sort of thing. Then he stayed on until age sixty-five—he was Chief of Surgery in this hospital in Rahway, then retired. He then was not very happy just being retired, but the problem with practicing medicine, especially surgery, is that you need to have huge insurance, and he couldn't see how he could do it part time and still pay the insurance. So what he did instead was to join Project HOPE, and he went to things like Indian reservations and on boats sailing around among Eskimo colonies and that sort of thing, doing surgery for those people, just to keep himself intellectually alive. So that's what he did.

One of his patients—his practice was in Rahway—was Max Tishler, who was at that time director of chemistry at Merck [& Co.]. So Max became a family friend. I was diddling around doing various experiments in the basement when I was in grammar school, and Max gave me a copy of [James Bryant] Conant and [Albert Harold] Blatt (1) when I think I was in the sixth or seventh grade, and this was a very good organic chemistry book. So it really got me excited about the stuff.

GORTLER: Max had actually rewritten the book. Didn't he work on the book with Conant at one time?

BRESLOW: Well, he may have, but the one he gave me was just Conant and Blatt. Also, I had friends at school whose fathers were chemists, so I knew that there was such a thing as a chemist. Obviously, Max was a chemist, too. So that was one of the nice things about growing up in that town. While I had a father who was a physician—and he was, of course, convinced his son was going to be a doctor—I also had plenty of other people around who were scientists and I thought, well, that was pretty exciting, too. So I had a basement lab and I did various experiments down there. We had a hot air heating system and my father had his office in the building, sort of attached to the side of our house, and every once in a while, something I made in the basement would get into the hot air system [laughter], get into the office, and all the patients would go screaming out onto the street. But he was pretty good about it.

GORTLER: Your father was Alexander?

BRESLOW: Alexander, that's right.

GORTLER: And your mother [Gladys (Fellows) Breslow]—what role did she play in the family?

BRESLOW: Well, my mother had been a nurse when she met my father, and she was not working except during the war. When my father went off to the Army, she actually became an aircraft inspector [laughter] for Grumman aircraft. A pretty spunky character. So she went off and did that, was crawling around inside airplanes to make sure that the welds were correct or whatever, you know.

GORTLER: My goodness!

BRESLOW: Well, during the war, everybody did things like that. So she was an interesting person. They were very supportive people, I must say. They were always cheering me on. It was a very good thing. So I was very interested in science as a kid, but I also was somewhat of a politician. I mean, I was always the president of the class, the president of the student council, that kind of stuff. In fact, I remember one election—I really thought of doing this even for the ACS [American Chemical Society] but decided it wouldn't work. My sister and my mother

made a bunch of badges that said "Bres for Pres." I thought, gee, that's a great motto. I've got to keep that one going. We never used that for the ACS, of course. [laughter]

GORTLER: [laughter] Chemists are stodgy!

BRESLOW: Yes, they would have thought that was a bit too flashy.

GORTLER: Yes, too much. Right. You mentioned you had a sister?

BRESLOW: My sister Diane. She was a younger sister. A lovely person, I must say. Very, very bright, a very pretty person also. She was a cheerleader at school, a very popular sort of person. I think I was a little bit of a problem because she would come into, say, a math class and not be able to do something and the teacher would say, "I can't believe you're Ronnie's sister!" [laughter] It must have been not much fun. But she took it in pretty good grace.

GORTLER: She did not go into science?

BRESLOW: No. She really fundamentally went into English for a while, but she was working for an advertising agency in New York. Now she's married, but she is working for one of the small newspapers in Stonybrook, which is where they live.

GORTLER: Aside from your family and these other chemists that were surrounding you, were there other teachers who were particularly influential during those years?

BRESLOW: Well, it was a very strange thing. The answer was yes, but in a funny way. I had a chemistry teacher who really didn't know any chemistry. I knew more than he did, and he was really stuck. He didn't enjoy that. But it obviously convinced me, "Gee, if this guy can be a chemistry teacher and I know so much more, maybe I can do this, too." So in that sense it was more influence because it just convinced me that I could actually do this stuff. Yes, he was a very strange man. For any chemist who hears this, for instance, once I was trying to explain to him what the actual structure of sulfuric acid was, which he didn't know. He said, "That can't be right because it has an O and then an H, and OH groups make things into bases, not acids." So this is the kind of guy I was dealing with! [laughter]

GORTLER: Yes, I've heard this story before, about people running into teachers who have just not been—

BRESLOW: Not so bad. Could be worse, I mean.

GORTLER: But in fact, it forced you to kind of learn a lot of things on your own.

BRESLOW: Yes, you learn a lot of stuff on your own. Of course.

GORTLER: I assume that, considering your father was a professional man, you were expected to go to college eventually?

BRESLOW: Oh, yes. Actually, I don't know if this is of any great importance, but in high school, I did enter the Westinghouse Science Contest and was one of the Washington finalists. That was also a very good influence, frankly, because at that point, I met all the other finalists, many of whom were from New York, many of whom were seriously interested in science, and so I got to the point where I sort of became part of that group and came into New York from Rahway a lot, and then did various things with them. They had a thing called the Young Astronomers Club at the Museum of Natural History. So I began to bum around with these people, and that was very nice. I mean, that also gave me the sense that there is another thing one can do besides practice medicine.

But you're right. I certainly was going to go to college. I had no great interest in going anywhere but Harvard [University]. I'm not sure exactly why. But some other people convinced me. I applied to maybe two or three other places. Not many, because among other things, I was convinced that with the Westinghouse thing, I would get into Harvard, which in fact was true, of course.

GORTLER: Your experience at Harvard: influential courses, influential people? As an undergraduate, first.

BRESLOW: Well, as an undergraduate, sure. I came in and did not take freshman chemistry because by then I was so hooked on organic chemistry I wanted to take it directly. So I didn't do anything much about it. I just registered as a freshman for the organic course. Nobody bothered to check and see whether that was all right. Then in my senior year, I petitioned to be excused from the freshman requirement so I could graduate. I guess they didn't know what to do about it because by then I had done a lot of the graduate courses. So I started with the organic course, which I really loved, I must say, and that was great.

GORTLER: This must have been with Louis [Frederick] Fieser.

BRESLOW: Yes, Louis. Obviously not a very mechanistic sort of person, but still a good, effective teacher, I thought. A lot of interesting things, and it was clear he was interested in what he was talking about. The class was a good class, but essentially none of my class was in there, none of the freshman class was in this course. So that also got me in touch with various people a year or so ahead of me, and some of them were juniors, actually. So that was nice, too. That sort of gave me a little bit of contact with people further along in the place. So I did organic in the freshman year. I did physical chemistry in the sophomore year, and in my junior year I started taking graduate courses. Because I really thought I was going to end up in biochemistry or medical school or some such thing, I figured my only chance to get all these chemistry courses was then, when I was an undergraduate. So I just did as much as I could, really. So when I eventually came back to graduate school, the reason I could get a Ph.D. in two years from [Robert Burns] Woodward was that I had already done all the chemistry courses. I just came back and did research for a couple of years.

GORTLER: Okay, so you came back. Did you take [Paul D.] Bartlett's [advanced organic chemistry] course in that senior year?

BRESLOW: I took Bartlett's course in my junior year, as far as I remember. Then I took, I don't know, statistical mechanics and all kinds of wild things in my senior year.

GORTLER: Obviously, Fieser had some effect on you. Other people who were influential? We're going to get around to [Gilbert] Stork in a minute.

BRESLOW: Yes, it's hard to know what to say about that. At some point, I did go talk to Paul Bartlett about what I should take. I don't know why I did, but he urged me to get into research because he said that was the whole reason they had that undergraduate research program. So this was, I think, in my junior year when I started doing research with Stork. I just looked around for somebody to do it with and frankly, I have no idea how I ended up with Stork, but I did, and that was a very good experience, too.

We worked on a problem—there was a compound called "cedrene," which is a terpene, and nobody could figure out the structure based on the data in the literature. But he was convinced that there must be something fancy going on, so he asked me to take a dicarboxylic acid one gets from oxidizing it, and to see whether in the infrared, I could figure whether it was a five-membered or a six-membered ring anhydride when it closed. By the classical ideas it should have been five, and he thought maybe it wasn't. So this was one of the first things that one did with infrared. I mean, I made some authentic five- and six-membered anhydrides and saw where they were, and they were in different places. Then I made this stuff and it was

clearly a six-membered anhydride. It was from that, I think, that we had two publications—one was the structure of the norcedrene dicarboxylic acid anhydride (2) and the other was, then, what the structure of cedrene must be as a result of that (3). I must say, there, I was pretty much a passenger. I mean, I understood what was going on, but Gilbert was clearly the one who figured out the structure.

GORTLER: I happened to look at those papers yesterday, and one did, in fact, follow the other one. Of course, as a physical organic chemist, I was more impressed by your rearrangement work—

BRESLOW: Yes, the bromonorcedrene dicarboxylic acid. Well, it was simply that if the thing was a six-membered anhydride and yet with what it became, this product, it had to be doing that rearrangement. But that was not a thing I figured out. I mean, I was just a kid. What did I know? [laughter]

GORTLER: Right. Has this structure stood the test of time?

BRESLOW: Oh, yes. There's absolutely no question it's the correct structure. It has been synthesized authentically. In fact, it turns out that if you think about biosynthesis—it's a sesquiterpene, so if you ask how you cyclize a linear sesquiterpene, farnesol, this is the structure you ought to get. It is correct.

GORTLER: So then you graduated from Harvard and you entered the medical science program at Harvard's medical school.

BRESLOW: Yes. I had applied to medical school at one point and been accepted to Harvard Medical School and then I just decided I really didn't want to do this, and I think I talked to Paul [M.] Doty at some point, who told me I should do what I thought was interesting. My father, a perfectly nice man, but a fairly strong figure, of course had this dream that his son was going to follow in his footsteps, so that was a tough one to shake off. But I finally just decided that was ridiculous and I was not interested in doing that stuff. But because I had taken all these chemistry courses at Harvard, I had taken almost nothing in the other area because I figured I would get all that in medical school, so I decided, "Well, I'll go off and take this medical science program."

It was the first year they did it. They started a program in which students came in and studied in all areas. I mean, we would take up the liver and with the liver we would do the biochemistry of the liver, the physiology of the liver, pathology of liver disease and all that. Everything in the world. It was a great course. But it was tremendously consuming of faculty

time and I don't think it was ever as good as the first year. I had some very good people there. In fact, people who are still friends of mine. A guy named Fred [Frederic Middlebrook] Richards, who's a professor at Yale [University], was one of the instructors there. Fred and I have been friends for a long time since that point. So that was really quite nice. It was a good course, and in the course of it, I got quite interested in trying to understand the chemistry that was going on in some of the biochemistry I was learning. The one that really was obviously a problem was thiamine pyrophosphate, because no one made any sense out of the chemistry. By then I'd had Bartlett's course in physical organic chemistry as a junior, and as a senior I was participating in the Woodward seminar and things of that kind, where a lot of mechanistic stuff was done. So I could see that there was a serious problem there. So I was really quite interested in that, and eventually, of course, I carried this off and worked on it on my own. That was after I got my degree. But that medical science thing, I thought it was a good experience. I mean, I did a lot of things that were worth doing.

GORTLER: You didn't take an anatomy course at that time?

BRESLOW: No, we didn't dissect anybody. This was not the medical school course. It was simply a course in the basic sciences for people who then went on—many of them went on into pharmacology. We had a good pharmacologist teaching the course. Or biochemistry. Several of the people in the course went on to biochemistry. It was a pretty good course. I would say there were some pretty good people who were in that course, although frankly, if I think about it, I'm not convinced that any of them are, let's say, in the Academy now. So I think, you know, they did well up to a certain point, but still, they were good kids and interested in a lot of interesting things.

GORTLER: But then after that year, you decided to go to graduate school.

BRESLOW: Well, that was a graduate school, but I decided not to do that. I decided that I was sufficiently interested in chemistry that I didn't find even the biochemistry part that they were doing there sufficiently chemical. They might know the structure of something, but they were not thinking about what its chemistry could be. So it just didn't seem to me chemical enough.

GORTLER: Did you consider any other graduate schools in chemistry besides Harvard?

BRESLOW: No, I didn't, and this was just because of fundamental impatience. I more or less went to Woodward and said, "If I come here, how long will it take me to get out?" He said he couldn't see any reason why I couldn't be out in two years. I thought, well, gee, that sounds pretty good, because I had already taken all these courses, and I was just itching to get out. I had also, in my senior year—I forgot this. I really should mention Frank because it was

important. In my senior year, I sat in on a course that Frank [H.] Westheimer taught in bio-organic chemistry, mechanisms. I didn't take the course for credit, but I sat in on it, and my—

GORTLER: Was that his kinetics course?

BRESLOW: No. I'm wrong about that. That was not my senior year. That was when I was a first year graduate student. I was sitting in on that course while I was doing research. That's right. When I was back with Woodward. That's where I met my wife [Esther Greenberg], actually. She had come up to Harvard to do biochemistry and she came over to take the Westheimer course. Yes, I guess it was a course really on kinetics more than—there was not a lot of biology in it. You're right. He was giving lectures in various places about enzyme mechanisms and that sort of thing, but that course was a kinetic course. So I got reasonably friendly with Frank, too, and I had some ideas about what might be the cause of the cooperative behavior of hemoglobin when it binds oxygen, which I bounced off him and he was really excited. It didn't turn out to be right, but they were interesting ideas. So in one way or another, I got to be reasonably friendly with Frank, and he also was urging me to get out as soon as possible to get on my own. So I had a backer there who was saying I shouldn't take any serious amount of time getting a degree. I should get out and start working on some of the things I was interested in.

So anyhow, I have to give Woodward a lot of credit for it. When I think about what's in the thesis, it isn't much, you know (4)? I mean, I was working on a tough problem. It was a structure problem, and I realized some aspects of the structure that we hadn't figured out.

GORTLER: What was particularly interesting about magnamycin?

BRESLOW: It was just a structure elucidation. I had done that essentially with Stork. It was a macrolide. None of them had been solved, and so it was one of the earliest of these macrolide antibiotics, and it had a couple of sugars hanging on it, and then it had this large lactone structure, and the question is: What on earth was the structure of the thing? There was a lot of data around, and that part was quite interesting because we spent a lot of time—I mean, I must say, I got a lot of time with Woodward because we'd spend a lot of time hashing over, "Well, did we now know enough to figure out what this thing was?" If we didn't, we'd design another experiment right off. So I had a lot of good contact with him.

GORTLER: Did you get to meet with him during the day?

BRESLOW: I saw him all the time. In fact, what he would do was really something of a scandal, I must say. I was working in a lab with a guy who was a very good friend of mine, Ted

[Edwin F.] Ullman, who turned out to be a marvelous scientist. But anyhow, Ted was there working on a synthesis problem, and I was there working on magnamycin. Woodward would come into the lab and talk to me about what was going on and then leave, and never even say hello to Ted. You know, it was really bad. But I got huge amounts of contact with Woodward, to the point where it was almost uncontrollable. I remember one day I was going to go skiing that weekend, and he went in and hid my skis! [laughter] But then he told me where they were, so it was okay.

GORTLER: Now, that work was never published?

BRESLOW: Well, it was published in a way. It was published without my name on it, and that's probably just as well because he published a chapter in a book by Alex [Alexander Robertus] Todd, which was, I don't know, *Progress in Organic Chemistry*, or some such thing, in which Woodward had a chapter, and his chapter was on the structure of magnamycin. He thanked me at the end, and there were a couple post-docs on it also. I think he thanked us at the end, but since the structure that he proposed was wrong, it's probably just as well [laughter] that we didn't get on as authors.

GORTLER: When I was looking around for your thesis, I ran across the fact that a graduate student at Columbia [University] by the name of Dorothy Gilner had written a thesis called "Studies on the Biosynthesis of Magnamycin" (5). Was this one of your students?

BRESLOW: No, it was not one of my students. She was in the biochemistry department and she worked with a guy named [P. R.] Srinivasan. Magnamycin is a polyacetate, but not exactly, because it's got some extra methyl groups, so the question is, do those methyl groups come from propionic acid, or do they come by sticking a methyl group on after you've made the macrocycle? At that time, people didn't know. Now, they usually turn out to be mixed acetate propionate compounds, and erythromycin is almost entirely propionate. That is now understood, but at the time it wasn't. I had nothing to do with that.

The other person who worked on magnamycin was a guy named Martin Kuhne, who was at [University of] Vermont. He worked on this afterwards, from which it became clear to him that the Woodward structure was wrong. [laughter] But the part I had figured out was not wrong. It's just that it was only a piece of it.

GORTLER: Actually, there was another student who wrote a thesis in 1969, probably one of Woodward's last graduate students, by the name of Lawrence [Stanley] Weiler, who did a thesis called, "Further Studies on Magnamycin" (6).

BRESLOW: Gee, that's interesting. I didn't realize Larry Weiler had done this. I think Larry Weiler is now chairman of the McGill [University] chemistry department. I knew he had worked there. I'd forgotten that he'd worked on magnamycin.

GORTLER: Yes.

BRESLOW: It was not an earth-shaking piece of work, in my opinion, but at the time—see, Woodward, of course, is famous for his synthesis, but as a structure elucidator, he was really brilliant because he just squeezed every piece of information, you know? This one happened to be not quite right because he went a little further than the information really took him. But that was very interesting for me because I was in contact, in that case, with a tremendous analytical intellect. I mean, he loved to do it. He loved to treat it as a puzzle and to try to see whether he could figure it out. I thought he was just great at that. But his synthesis work was good too, obviously.

GORTLER: Are there other graduate students or post-docs whom you got particularly close to at the time that you've stayed in contact—

BRESLOW: Yes, well, there were people that I was fairly friendly with. One of them was Steve [R. Stephen] Berry, who's now at the University of Chicago. He and I have been friends for a long time. We first met in the Westinghouse science talent search in Washington. He was one of the other finalists. I met him there when I was in high school. Then he was a Harvard undergraduate, and we were quite friendly pretty much throughout. In my sophomore year, we teamed up with two other guys and the four of us went to Europe, got bicycles, and bicycled all around Europe for a summer. Steve and I sort of put this together and then he had these other people who wanted to do it. So I was quite friendly with him, and then I was friendly with him in graduate school. He, of course, moved very much into physical chemistry and he was even doing theory for a while with Bill [William] Moffett, as well as doing experimental work.

Then I was quite friendly also with Andy [Andrew S.] Kende. Andrew Kende was also in the Westinghouse contest. In fact, I think he was the big winner in our year. He and I have remained good friends. So those early connections, one does tend to retain. Among post-docs there, an awful lot of Woodward post-docs were Swiss, and I was perfectly friendly with them at the time, but you don't see them very much, you know, normally. So I didn't have too much contact further with them.

I'd say mostly it would be the other graduate students and Ted Ullman, my lab partner there. I met him there, of course. Eventually, Syntex and Varian [Medical Systems] started up a company which they called Synvar, until they discovered that some outfit in Baltimore called Synthetic Varnish was using the word "Synvar," so then they became Syva, Syntex and Varian. Carl Djerassi, whom I knew because he was always around here because he was a friend of

Gilbert Stork's, called me up and asked me to be a consultant to this company and help them find a director of research. We got Ted Ullman, who was then working at Lederle [Laboratories, Inc.]. So Ted and I have stayed good friends for years, and I was a consultant with Syva the whole time until Ted finally retired from it last year, and then I decided I was not interested anymore. But for a long time I was a consultant with that company.

So that was a very close relationship, and we've gone to each other's children's weddings, you know, that kind of thing. We've been very, very friendly. Ted's a great chemist. I must say, he's a marvelous man who probably should have been an academic. He was very good at what he did, but I think he really enjoyed the intellectual part of chemistry and was not all that fascinated by the amount of money you could make from it. So perhaps he should have gone into academia and not industry. There were a lot of good people at Harvard. Paul [von Rague] Schleyer I knew at Harvard. Of course, Paul was in P. D. Bartlett's group. Martin Saunders was a very good friend of mine. Martin and I have been friends throughout, and still are.

GORTLER: Oh, and Ed Wasserman.

BRESLOW: And Ed Wasserman. Now, Ed I knew in part because of Harvard, but interestingly, the main connection I had with Ed was that he and my now wife, Esther, had both been Cornell [University] undergraduates and had both been sort of competing with each other in the same class in chemistry where, from time to time, she beat him. So that was the earliest connection I had with Ed—because of my wife Esther. But of course I didn't know her then.

[END OF TAPE, SIDE 1]

GORTLER: When you finished at Harvard, you went to England?

BRESLOW: Yes. I went with Alex Todd. Todd was, at that time, visiting at MIT [Massachusetts Institute of Technology]. He was giving lectures at MIT, which I went down to, and he was also a good friend of Woodward, so I met him there. I was very interested in him because he was very different, in many respects, from Woodward, and in an important way. If I could sort of simplify the thing, I would say that Woodward worked on very intellectually challenging problems that were not always terribly important. They were more very interesting puzzles, some particular structure. It didn't open up things to the extent that perhaps one could. Whereas Todd was very different. He was not the puzzle-solving intellect that Woodward was, but he had exquisite taste in working on projects that really would make a difference, like figuring out the structure of Vitamin B_{12}, this complicated molecule, and figuring out how to make nucleic acids, which really made a huge difference. So that appealed to me a lot, to see

that part of chemistry also, and so I did that. So I went with him as a post-doc for a year with some fellowship.

There was another reason to do it. At that time, I forget which war we were fighting—probably the Korean War. God knows what! But anyhow, they were drafting people unless they really looked as if they were still continuing their studies, and if you took a post-doctoral out of the country, everybody realized that was not a job; that was a study thing. So I thought it was very desirable to take a post-doc out of the United States because I didn't feel like ending up shooting Koreans. The fact that my father was such a patriot, I suppose that was a bad reaction on my part. But I really didn't feel I wanted to do this. So I thought if I took a post-doctoral out of the country, that would make a difference. There were fellowships available to do that, and so I did.

At that point, when I was going to leave for England, my wife and I, my now-wife, decided we should get married because I didn't want to leave her behind. In those days, no one would dream of traveling with a woman who was not his wife. That was considered to be extremely immoral. In fact, it was funny. Even after we were married, she had a passport in her maiden name, so when we would check into hotels, sometimes these hotels would list us as being in separate rooms so there would be no scandal about people with different names in the same room. [laughter] It was a different world.

GORTLER: What type of work did you do with Todd?

BRESLOW: Well, there I did two things. I worked on the nucleic acid problem, trying to devise a new methodology for making DNA [deoxyribonucleic acid]. In fact, I made pretty good progress with it and eventually one of the post-docs in that lab went off on his own and developed my procedure further, and it's one of the ways you can make DNA. Nitrophenyl phosphate ester exchange was what I dreamed up that would work. It did. But the other thing I did is I started my own independent work—I mean, one of the reasons I went with Todd also was that he had worked on determining the structure of thiamine way back and had done a lot of work in his lab on thiamine, and I knew I wanted to solve this puzzle of how on earth this thing worked, and I thought having access to these compounds would save me a lot of time. You know, just going to a place where they have a shelf full of all kinds of thiazole derivatives and would let me work on this project. So since I came with my own money, he was pretty good about it, and he didn't worry too much that I was working on his project with one hand, but working on my own project with the other, which is what I did. So I started working on the thiamine business there, and it was helpful to have some of his compounds, frankly.

GORTLER: You've already told me how you met your wife. Since you brought her up, what influence has she had on your career? Did she continue to work in science?

BRESLOW: Oh, yes. She went with me to England. She started off to get a Ph.D. in biochemistry at Harvard, but of course, obviously, we got married and she came with me to England, where she sort of did a post-doc without benefit of Ph.D. She found a lab where she could work and she did really some nice work there, I must say. It was very good. Then when we came back to New York, it was pretty clear that there were a lot of choices where to go, and she actually went back to New York University [NYU] where she had been, I guess, an undergrad. No, she'd been an undergraduate at Cornell. She must have started something at NYU and then transferred to Harvard. Anyway, she went back to NYU and finished her Ph.D. and then she went to Cornell Medical College. Her Ph.D. thesis (7)—unpublished, which is absolutely criminal, but it was not her fault—was the first demonstration of poly-A/poly-U binding. I mean, the whole thing that was so critical to understanding base pairing—she was the one who showed that, because at that point, [Severo] Ochoa had just developed methods for making things like poly-A and poly-U when Ochoa was at NYU. Ochoa had just developed this methodology for making these compounds, and she started doing the physical studies on them and showed this binding association that was getting between these materials. The A-U recognition. Never got published. Absolutely nuts.

Anyhow, then she went off as a post-doc at Cornell Medical College, where she worked with a protein chemist. He left but she stayed on there and inherited his lab and inherited the grant more or less, and eventually was put on the faculty there not too long after that, and is now a full professor there, and was in fact acting chairman of the biochemistry department a few years ago. So she's still actively working as a professor of biochemistry. Still working on proteins. She's a protein chemist and very interested in small molecule binding to proteins. So that has been a very good interaction. I mean, certainly, I've learned a lot of things from her, and I think she has learned things from me, so it's worked very well.

GORTLER: You have two children.

BRESLOW: We have two children, yes. Both attorneys. Well, one of them went to Harvard and thought she might be a scientist. She was completely turned off by freshman chemistry. Like me. As I told you, I never took that course. So it didn't do me in. I should have told her not to take it. [laughter] But anyhow, she was completely turned off by freshman chemistry, and decided she couldn't believe the kind of thing that people were teaching was so repellent. So she switched and instead became a history major, went to law school here at Columbia. At that time, and it's still true I think, Columbia kids get free tuition in the graduate schools, professional schools, and everything. She went to Columbia law school, and she's now a partner in one of the good, small boutique New York law firms and has had a lot of offers from the big, not-so-boutique places, to move, which she's turned down. So she's here in New York as an attorney. Then the younger girl, she never had any great interest in science.

GORTLER: The older one is—

BRESLOW: Stephanie. Then the young one, Karen, she never had any great interest in science and she went to Cornell. So Stephanie went to Harvard, which is where I had been an undergraduate, and Karen went to Cornell, and that was a sort of an interesting thing in a way because she went there as a faculty child since my wife was on the faculty of Cornell here in New York. So two hundred miles away, you're still a faculty kid, with completely free tuition. That was very nice. Cornell was a very good place for her, because you can do everything there. She started off thinking she wanted to go into business, and so she sat in on some courses, started to take some courses and various things about business and found them really repellent, and then eventually found that there was a course in the philosophy of law taught by the law school people there for undergraduates. She took that and she thought that was terrific.

She decided she'd just go to law school, but then she'd use that as a way to get into business because she still thought she wanted to do that. Then when she was here at Columbia Law School, she was taking a course in litigation, and at one point the instructor called her in and said, "Well, my partner and I have discussed this"—it was taught by two people—"and we've agreed that you are the greatest natural litigator we've ever seen." [laughter] So at that point, needless to say, her head got completely turned and she went into litigation, where she's absolutely sensational and for a long time was litigating with Paul, Weiss [Rifkind, Wharton & Garrison] here in New York. They hated to see her go, but she really wanted to do entertainment litigation. She said she didn't care which bank won, so how can you throw yourself into a thing like that? Who cares who wins?

She was really interested in entertainment law because she also had a very good voice and she had sung with small groups, so she figured she'd put her hobby and her business together. So she went into entertainment law in California. She had Clint Eastwood as a client, she was really doing good stuff. But she discovered that while the clients were interesting, the law was stupid. It was people arguing about whose dog bit whom, things of that kind. It was just not interesting law. So then she left that and went into regular litigation and at some point she married and decided she really needed time. Litigators can end up sitting in Las Vegas for six months. They never know what's going to happen to them, and it's just no life. So she went in-house and she became an attorney with Sony Pictures, and she's now vice president for litigation. She shot right up over everybody in the place. [laughter]

GORTLER: Terrific!

BRESLOW: She's a young kid and she's still running the place now. Not bad. So I feel pretty good about my kids. She's about to produce my first grandchild in a little less than a month now!

GORTLER: Oh, both of us are going to be first grandfathers in about a month's time!

BRESLOW: Yes, it's about time, isn't it?

GORTLER: When and how did you receive the call to Columbia?

BRESLOW: Well, I was sitting in Cambridge, England as a post-doc and I was applying to various places, and I asked Gilbert Stork, because I had worked with him as an undergraduate, if he would write letters for me. So at some point, I got a telegram from him. I had an offer from Bill [William] Johnson at [University of] Wisconsin, which was at the time a very strong place. So I had an offer from Wisconsin, and I asked Stork to write something, and back came a telegram saying, "Do nothing until you hear from us" or whatever. Back came an offer to Columbia. Now, it turned out—I think they offered me a job that didn't exist. I mean, I think this was a strictly Storkian kind of operation.

GORTLER: This is the same story I got from Louis [Planck] Hammett about you.

BRESLOW: Right. I think this job didn't exist. But somehow or other they had some money from somewhere. I think they had some money from a DuPont [E. I. du Pont de Nemours & Co.] gift or whatever, and they offered me this job nonetheless. I had no great interest, but I had spent some time at Columbia one summer. I'd worked with Stork when I was still an undergraduate, when he already had moved here. I think it was the summer after my senior year I worked down here. But anyhow, I had no great interest in it, but I thought about it. I thought, "Well, okay, at least it's not a bad place to start."

What I didn't appreciate was that it would be rather nice to be close to family. As it turns out, it was. My parents were nearby, and my sister was nearby, and my wife's family was here. So Thanksgiving was a huge thing. That was really pretty good. So I ended up here, into this non-existent job. I guess, maybe I was in my third year—I was an instructor—when the people at Cornell offered me an associate professor job. So I just told the chairman about this, and they had an emergency meeting here, and they popped me up. So I never was an assistant professor. I went from instructor to associate professor with tenure. Of course, nobody starts as an instructor now, so it's perhaps less of a consideration. They offered me tenure, so I got tenure after three years here.

From time to time, I certainly have considered moving to other places, because at one point, various people were convinced that nobody in their right mind would stay in New York, and therefore clearly, you know, you could steal people away. So I got various offers, and there were always factors against it. Some of the factors were that by then my wife's job was pretty good, that we had all this nice family contact was pretty nice, and frankly, New York is an interesting place, and the faculty here are pretty interesting. I mean, Stork is a kick-and-a-half to have as a colleague. He's always doing crazy things, but they're amusingly crazy things, and

obviously he's a brilliant scientist. So that was not bad. So one thing led to another, and I just decided to stay here. But the so-called "call" was pretty peculiar. Louis Hammett mentioned this at some point, did he?

GORTLER: Yes, one of the things he said was, "Stork tipped us off to Breslow," and then he vaguely remembered using some company's money—

BRESLOW: Yes, that was DuPont.

GORTLER: —earmarked for research to put you in a research position for a year until you could be appointed to a faculty line.

BRESLOW: That's right. That's what actually happened.

GORTLER: Yes. So your first publications were on the thiamine problem, and you've already told me how you got interested in it. Somehow or other I didn't get a chance to look at the first paper, which was in *Chemistry & Industry* (8), and apparently you put in a mechanism and it may not have been the right mechanism.

BRESLOW: No, it wasn't the right mechanism. I put in a mechanism based on essentially the activities—I mean, I tested a lot of different compounds that might act as catalysts. It turns out, it had been discovered in Japan during the war, published in Japanese, that thiazolium salts would catalyze the benzoin condensation. So I knew this reaction existed. I found somebody who could read Japanese and got the thing translated—this is when I was a post-doc in England—so I could see what these characters had actually done. Then I just set to work trying to see which compounds were catalysts and which were not. Based on that, I concluded that the reaction must be at the methylene group that sits on the nitrogen of the thiazolium ring because without that methylene, it was never a catalyst. It turns out that the reason for that is that anything other than the methylene there either is not electron-withdrawing enough—it was sort of a benzyl group—or it blocks the active site. I came up with a perfectly good mechanism by which the methylene could be a catalyst, and to some extent, there was precedent in the literature for acidities of the methylenes on benzyl pyridinium compounds and things of that kind. That CH_2 can be ionized. A guy named Langenbeck was the one that did that. Anyway, it was a pretty reasonable mechanism, but of course it did not have the critical evidence in its favor, and then Frank Westheimer, a much more sophisticated mechanistic chemist than I was at that point, realized you had to test this with deuterium and he discovered that methylene didn't exchange, so he published something saying, well, this was baloney. Obviously it can't be going on there because that methylene is not, in fact, acidic enough to handle the mechanism.

So then I came back here to work on the thing seriously and tried various things again, and eventually concluded that the hydrogen in the thiazolium ring must be acidic even though there was no previous real evidence for any such thing. We had an infrared spectrometer here. I put the thiazolium salt into D_2O, and discovered that what was a fairly strong CH band seemed to shift into the carbon deuterium region. So I said, "Well, that's pretty good." Then Ben [Benjamin] Daley had a homemade 30 MHz NMR [nuclear magnetic resonance] machine here that you tuned by inserting a screwdriver into a hole in the back and fishing around until you found something that it would engage with and then turning it. [laughter] A typical physical chemist's idea of a machine. You know, no labels on anything. You have to be a mechanic to run the damn thing. Anyhow, this thing existed up there and so we put the thiazolium salts into D_2O and there was a CH hydrogen that disappeared and I was able to show that that was the one. So that's how the thiamine business got started. Yes, so the first paper published by me alone, out of England, in *Chemistry & Industry* (8) was certainly not right, but I think from then on, the rest of it seems to have been correct.

GORTLER: Now, this approach was more physical organic than would be expected from somebody who came out of Stork and Woodward—

BRESLOW: Right. You've got it!

GORTLER: You've already said that you had these courses with Westheimer and—

BRESLOW: I had courses but I never actually worked with any of the physical organic people. I mean, it was very strange in a way. You know, every once in a while, you see stuff like this. There are people out there in the world who are doing things so close to the kind of stuff I do that everybody assumes they must have worked with me, but they didn't. I mean, sometimes people just go into a new thing. I really didn't want to do this structure business. It was very tough stuff, and you can bang away at it, and you can end up with nothing much. It didn't seem to me to be the best place to do things. But anyhow, I was just interested in understanding how that thing worked. That obviously was a big influence.

GORTLER: So you were more interested in the problem as opposed to—

BRESLOW: Yes. I was not so much saying, "Let's do a physical organic problem. What shall we do?" What I did was to say, "How on earth does this thing work?" There is a reaction that catalyzes in solution a process that has the electronic characteristics of what it does biochemically, and if we can understand the solution reaction, we'll understand the rest of it. That wasn't clear either. It took a while before I realized, after I'd sort of eliminated other possibilities, that it must be that that hydrogen on the carbon between the nitrogen and the sulfur

on the thiazolium ring must be acidic. If you ever made that anion, of course it would look like a cyanide ion and it would do the benzoin-type chemistry, you know? So that was pretty clear that if that were acidic enough, then it would be able to do it. So after we saw that, then we made various intermediates and showed that they were active, that kind of stuff. Normal things one does.

GORTLER: It's interesting, because you also mentioned that Westheimer was looking at the thiamine action in 1956 and he was looking for proton exchange, just as you said—

BRESLOW: Well, he was just checking our thing.

GORTLER: Yes. But he was convinced that it was somewhere else, perhaps in the other ring.

BRESLOW: Yes, the pyrimidine ring.

GORTLER: Yes. Here's a quote from an interview that I did with him in 1979 (9). I'm going to leave it with you. You'll look at it. Because he just felt he was so stupid because apparently a graduate student had said to him, "I think it's at the 2 position," or "The data looks like that," and Frank just ignored it.

BRESLOW: Oh, that's interesting.

GORTLER: Afterwards [laughter] he felt really terrible about it—

BRESLOW: Yes, well, I don't think it was his fault. See, the thing about it, which was of course an important thing that one should notice: nature doesn't do things for completely bizarre reasons. There were almost no thiazoles around.

Actually at almost the same time, though, we did this cyclopropenyl cation business.

GORTLER: Yes, that was the next thing I was going to ask about. Actually, someone called to my attention the fact that exchange in the thiazolium ring was done in 1937 by a guy at Fordham [University]. Did you know that?

BRESLOW: Who had shown that that hydrogen exchanged?

GORTLER: No. He had studied the hydrogen exchange. If you go back and look at his data, apparently it really meshes with your data.

BRESLOW: Oh. Well, that's interesting. That's surprising. At the time, what was relevant to it, there was a decarboxylation of pyridine 2-carboxylic acid, you know, which put a proton in the pyridine and then a carboxylate ion flew off, and so then obviously the anion in the pyridinium ring sort of had to be an intermediate in that. That decarboxylation we found when we saw the thing about this thing. We looked back and we said, "Oh, my God, there's this reaction." But I didn't know about the deuterium exchange into thiazolium. When was it?

GORTLER: This was in 1937 that he published it (10).

BRESLOW: Well, that's astonishing. I mean, deuterium wasn't around that long.

GORTLER: Yes, it was. I mean, he had—

BRESLOW: He must have gotten some from [Harold Clayton] Urey.

GORTLER: That's what I was thinking.

BRESLOW: Yes, he must have gotten the D_2O from Urey, and looked at it and discovered there was some exchange. That's amazing. Well, there were a lot of places where things could exchange. It depends on what he had. If it was a simple thiazolium ring, I agree that that was—

GORTLER: He did it with Vitamin B_1. He did it with both synthetic and—because I guess he had access to synthetic Vitamin B_1 at the time.

BRESLOW: That's interesting. I certainly didn't know that and that's interesting. But every once in a while you can find stuff like that. I think the Diels-Alder business that we did in water, which everybody thinks we discovered; somewhere you can find some case where somebody else did it. I certainly wasn't aware of that 1937 paper, and I don't think anybody else was either.

GORTLER: The 1958 publication on thiamine (11)—you thank Edward [J.] McNelis and Rudi [Rudolph Ernst Karl] Winter for assistance.

BRESLOW: Ed McNelis was a graduate student who had not done enough of it that he could really be part of a full paper. Rudi Winter was an undergraduate who worked with me. McNelis is now at NYU in chemistry. He was my first Ph.D. student. Rudi Winter went on to get a Ph.D. and is now at the University of Missouri in St. Louis, in the chemistry department also. So they both went on.

GORTLER: Now, you mentioned just a minute ago your first paper, 1957, on cyclopropenyl cation (12). This was obviously something also you'd been thinking about. How did you happen to get into the business of non-benzenoid aromatics?

BRESLOW: What happened is, I was reading something or other—I don't know what, something by [Sir Christopher] Ingold—at some point in the library in England, and he was proposing a mechanism in which a cyclopropenyl anion had to be an intermediate. By then, I was aware of various things that had been done on Hückel and non-Hückel compounds, and thought that it was pretty unlikely that this 4π electron system would be formed as readily as Ingold suggested. For some reason, and I really don't remember why I did this, when I came back here, I started to work on the question of the cyclopropenyl anion, which we did with a student—Merle [A.] Battiste, actually—but then I also started working with a couple of undergraduates and decided to go after the cation. By then I knew—Jack [John D.] Roberts had published a lot of molecular orbital calculations on non-benzenoid things—the cyclopropenyl cation was important, and I thought that we could come up with a decent way to make it. So that, of course, was more just a synthetic challenge, how to make this crazy thing. I don't know how one gets interested in these things, except that they seem to be areas where one doesn't understand enough, and I got so used to the idea with Woodward that everything could be understood. I mean, he was such a rational person and [laughter] obviously I was not prepared to tolerate situations where one didn't exactly know what the properties would be of a thing of that kind.

By then I think one knew about the tropylium ion that existed. I guess I hadn't appreciated sufficiently at that point—well, maybe I did—but were no other examples except 6π electron cases for single rings. I mean, naphthalene is ten, but it's two rings so it doesn't really count, you know. But in terms of the Hückel business, the Hückel rule for monocyclic compounds, only six had actually existed at that point. Cyclooctatetraene dianion, for instance, came later. So we went after this. Originally, I went after the triphenylcyclopropenium cation and I think that was an interesting case because, as I remember, the first ACS meeting I went to—maybe it was a year after I got here, maybe even less, I don't know—I had a tremendous mob of people listening to the talk of this kid. The rumor had gone around that we had made some derivative of this fundamental cation, and so Don [Donald J.] Cram, I remember, was there, congratulating me. I mean, it was really quite a heady experience.

GORTLER: Then it really turned into an entire program.

BRESLOW: Well, sure, and in fact, it's a program that's still not stopped. I'm still really quite interested in making decent isolable derivatives of anti-aromatic systems with ground triplet states so that we can really look at the properties of these ground triplets, especially the solid state properties, the materials properties. There are some theories that electron exchange involving a singlet and a triplet can be used to organize a firm magnetic domain. So we're really quite interested in that, still.

GORTLER: These things have very short half-lives now—

BRESLOW: No, they don't.

GORTLER: You can make things that are somewhat longer-lived now?

BRESLOW: Oh, yes. Oh, they'll live forever.

GORTLER: I mean the anti-aromatics.

BRESLOW: The anti-aromatics. Oh, sure. Depends on what you make. Cyclobutadiene doesn't last because it dimerizes, and cyclopropenyl anions, they have not been made as long-lived species; benzene di-cations—we have a hexaminobenzene di-cation that lives forever, and it's a triplet. A cyclopentadienyl cation—these things are okay at very low temperature, frozen temperatures. There's not a good room-temperature one yet, but we're bloody close to one, frankly. So they don't, in principle, just disappear—see, they're not going to dimerize if they have a charge. They don't just fragment or explode or whatever. They're not very stable, but—compared to what? So if you put substituents on, you can stabilize them.

GORTLER: You collaborated in a number of instances, first with Willie [William H.] Reinmuth, and then Ed Wasserman and Martin Saunders, and I didn't realize that you knew these people from before.

BRESLOW: Well, Willie Reinmuth I knew because he was here. At some point we were interested in the possibility of using electrochemistry as a way to determine the energies of, as

you say, very unstable species like cyclopropenyl anions, and of course all you have to do is pump two electrons into a cation to get an anion, so the question is, were there electrochemical techniques that could be used to get thermodynamic information on that? Willie was an expert. I mean, the fundamental thing we wanted to do was ours, but Reinmuth was an expert in electrochemistry so of course he was a great help, and so we did collaborate with him on how to get this stuff going. At one point, he had a student who had worked here—I knew about this work—on a technique called second harmonic AC voltammetry, which was, at that time, the best way to do really fast sweeps and get reversible potentials on unstable species. So we adopted that technique and used that to characterize these things. I think we may have published with Willie Reinmuth only once or so (13). I don't know how much we published with him. At that time, already, I think he was in some trouble and partly I was interested in trying to keep him going. You know, his science had sort of faded away to some extent. He eventually quit doing anything. We had projects where it was clear that his expertise would be helpful. But it was also partly, frankly, just to keep him engaged in things, and that sort of stuff.

Ed Wasserman. Of course, no such thing was required with Ed. In the case of Ed, what happened was that we were convinced we had a triplet species, pentaphenylcyclopentadienyl cation, because the NMR suddenly disappeared when you made the cation, and so we said, "We must have a triplet here," and so then the question is: where can one find that out? By then, Ed at Bell Labs was already doing triplet ESR [electron spin resonance] on carbenes and things of that kind. So I called him up and just said, "Look, we have this thing," and so we arranged it, and we went down there and did these experiments there. So that was good.

And Martin Saunders, the only thing we did with Saunders was when we went for the parent cyclopentadienyl cation itself. We had, by then, developed a way to make monohalocyclopentadienes like monochloro, monobromo, on the saturated carbon. So it was clear we could pull halogens off somehow and get the parent cation. But all the simple mixing experiments didn't work. But then Martin was, at that point, doing things where he was shooting a Lewis acid and a substrate in and getting reactions on a cold surface. So we decided to ask him to get involved in this thing, and so we did that with him. Mike [Michael] McBride, at Yale, was also doing this sort of work.

[END OF TAPE, SIDE 2]

BRESLOW: So anyway, Martin was firing our halocyclopentadiene and antimonylpentafluoride from two different jets, and condensing them on a cold finger somewhere, and Mike McBride was set up to do ESR spectroscopy and so we collaborated with him because he was right at Yale. So the three of us were essentially on that paper for the parent cation (14).

Ed Wasserman then went on and did some other things that were related. He took hexachlorobenzene and managed to get a di-cation out of it and show that it was a triplet and that was also one of these 4π systems. Then after that, we eventually made a benzene di-cation

with six amino groups, sort of a big flat thing, which we called HOC [hexaazaoctadecahydrocoronene]. But anyhow, it was six amino groups, six nitrogens sitting on a benzene, and that went to its di-cation. That was also a triplet. It was things of that kind. By then we were interested in looking at whether we could get some ferromagnetic domains out of these things, and so we did some of that stuff. We actually kept it up for quite a while, this approach to ferromagnetic materials. The most recent thing that happened in that area is that I had a very good post-doc, William [S.] Jenks, who's now at [University of] Iowa. It's not Dr. Bill [William] Jencks of Brandeis [University], it's the other physical organic guy. Anyhow, William Jenks was working with me as a post-doc and we made some materials that had the potential for being ferromagnetically organized. I had a colleague in the physics department named [Yasutomo J.] Uemura, who was very interested in solid state properties of organic materials, and especially magnetic properties, and so we got involved with him. He took our materials out to a place in Vancouver, where they were generating muons, and he did muon spin resonance studies of our material and showed that we had what was called a spin glass, sort of an organized spin thing. We didn't have ferromagnetic materials, but we had some other kind of organized magnetic stuff, and this is published in a journal that nobody—no friend of mine has ever heard of (15). [laughter] It's a physics resonance journal. But the interesting thing is that the muon would pick up magnetic alignments. If you send a muon through magnetic material, it gets aligned as a result of interacting with the magnetic material, and you pick up muon alignment because when muons decay, they do the low energy decay that is the kind of thing that had been studied by T. D. [Tsung-Dao] Lee having to do with non-conservation of parity. Muons normally would decay in such a way as to send out particles sort of isotropically in all directions, but if you have aligned them with a magnetic spin, then they don't. Then there's more forward particles than reverse or whatever; that kind of thing. You pick this up with sort of a quadropole arrangement of detectors. Anyhow, that was kind of gratifying because it never occurred to me that I would ever have any actual contact as a chemist with non-conservation of parity that my friend [Lee] over here in physics won his Nobel Prize for. But that's what's involved in that case. So that was sort of fun.

We're still after it. It's not clear whether we can make ferromagnetic materials with our high-spin things, but one of the things that's interesting about anti-aromatic compounds is if they have at least 3C symmetry, then they will be high spin. They'll be triplets. If you can make triplets and have them stable and do spin exchange, there are various theories that all argue that you might be able to organize a ferromagnetic domain, and ferromagnetism is an important useful property so it would be a good thing to be able to do it. So we're still after that. But maybe in another twenty or thirty years we'll succeed.

GORTLER: For a short period, you worked on a project of cyclizing squalene-like molecules, using free radical catalysis.

BRESLOW: Right.

GORTLER: Again, was this just a hot topic of the time?

BRESLOW: No. It was by then clear that squalene was the precursor of steroids, and it seemed to me that various cationic cyclizations had a problem—you're always going to be losing protons, but free radicals don't do that kind of thing. So I thought there was a real chance that you could do this thing with the free radical addition to the double bond and get the thing to cyclize. It turned out to be true. I mean, it did actually work. But at that point then, further evidence came out about the biochemistry that indicated that squalene first goes to the epoxide and then that opens and there really is a cation cyclization, and so then I was less interested in it. What was to me interesting was the possibility that this might actually be the biochemical way it happened. It turns out it was probably a mistake to stop that soon because really it doesn't matter whether nature does it that way or not. Free radical cyclization turned out to be a good way to make molecules. So we just did a little bit with it, not a lot.

GORTLER: Yes. Then in the late 1960s, you began a program of mimicking biological systems that carry out reactions on substrates at centers away from the functional group.

BRESLOW: Yes, this so-called "remote oxidation." That type of thing. Right. So, in other words, we started off with the idea that, if you look at what nature can do that we can't, it would be very desirable to take a molecule related to cholesterol, let's say, and figure out how to get an oxygen into Ring C so you could be in the corticosteroid series. So the question is: how do you do stuff like that? It seemed to us that it was clear that nature was doing it with geometric control, so could we do something as simple as hang a rigid substituent way down off the hydroxyl in Ring A, and reach up into Ring C, and carry out some chemistry there, just because we know the thing would reach that far? It actually had not been done. I mean, what had been done was the kind of thing that [Sir] Derek [H. R.] Barton did *in extenso*, which is to use functional groups to bite nearby centers, five or six atoms away. All that intra-molecular stuff over short distances was well known. But nobody had done these big jumps, and yet it had to work, it seemed to me, if you had a rigid spacer so that it couldn't curl back and bite some nearby spot, but it would have to bite further away.

So we started off that, and the first question was: what would be a good way to do this? By then I knew something about photochemistry, because I had my colleague Nick [Nicholas J.] Turro around here doing photochemistry, so I knew what he was doing, what people in the field did. It seemed to me that with something like benzophenone, photochemistry had the big advantage that if, for some reason, it didn't bite something right away, it would just relax to a starting material and you could do it again. In other words, you didn't have a reagent go off and do something else. So we just hung benzophenone derivatives onto steroids in various ways and saw that we sure enough could pick off hydrogens quite far away. In fact, we could hang something off Ring A and pull off the hydrogens off Ring D, about as far away as you could go. I had a post-doc working on that who had some background in photochemistry. That was very helpful. In addition to that, other people came in who had this kind of expertise, and we got a

little bit into some of the physical photochemistry of it, looking at rates of quenching. Sometimes we would take a swipe at a remote position, but we wouldn't produce a permanent transformation, but we would nonetheless quench the excited state, and so that was interesting. We got a little bit into trying to figure out how to calculate this, and one of the early graduate students on it was a guy named Mitch [Mitchell A.] Winnick. Mitchell Winnick then went on to be very interested in polymer chemistry and rates of reactions and that sort of thing, which really derived out of the work he had done here. He's actually a very well known polymer chemist now who does calculations about polymer conformations and that sort of stuff.

But anyhow, we did start that. Then we got into the business about well, it's one thing to do it as a synthetic tool, but it's another thing to use it also to find out about conformations of molecules; that is, what do you bite when you have flexibility and you can bite various places? So we did some of that. Then we even went into micelles and membranes and discovered something that I thought was rather interesting, which is that the further into a membrane we went with one of these things that could bite, the further we went away from the end of the material that was going into the membrane. In other words, the material that made up the membrane went down and then curled back up, so that the methyl group, let's say, at the end of a long chain was actually up near the surface. So when we went deeper, we bit away from the methyl group, and when we went for a short distance, we went up next to the methyl group. So you learned a lot of very interesting things out of just using this as a probe for conformation. So we did some of that. Of course, the other direction we went was to try to develop better chemistry for this remote functionalization business, which we did, including this so-called "radical relay" chlorination that we developed.

GORTLER: You could, in fact, selectively halogenate and some of the positions were important positions as far as pharmaceutical transformations were concerned.

BRESLOW: That's right. We learned how to selectively chlorinate carbon-9 and put in a 9-11 double-bond, and that let you put an oxygen at eleven, a fluorine at nine, and that's what the good corticosteroids are. So that was good. In fact, I also had by then a post-doc with me named Barry [B.] Snider, who's now a very good synthetic organic chemist at Brandeis, and Barry had been a [Elias James] Corey Ph.D., so he was really a very good synthetic chemist. So Barry took this stuff and carried it on to a real synthesis of cortisone, which we did, using this technique. We got some patents on it (17), and some companies were even looking at it for a while. But the problem with it is you hang a functionalizing group on a molecule, and then you use it to direct the chemistry, then you take it off. It's a little awkward compared to an enzyme turnover catalyst. Every once in a while, somebody uses it for something. I think a lot of research people use it, this remote functionalization business. But nobody manufactures with it that I'm aware of. If they do, they're violating our patent. [laughter] But I don't think they do.

GORTLER: The next major program that you've been working on for almost thirty years involved the use of modified cyclodextrins as enzyme models. Again, how did this program begin? Why cyclodextrins?

BRESLOW: When I was in England as a post-doc, I came across a book by man named Friedrich Cramer. Friedrich Cramer had been a post-doc with Todd some time before that, but he wrote a book called *Einschlussverbindungen* (18)—essentially it's "inclusion compounds" in German, so this book was in German. But luckily I had, at one point in my education, learned enough German that I could read the thing. So anyhow, it was mostly focused on cyclodextrins, and I decided, since I was, for a while, quite interested in the idea of learning how to do the chemistry that nature did, not just understand it, but learn how to do that kind of stuff. It seemed to me that there was a big advantage to starting with a molecule that would make a well-defined complex with something, and then try to see what kind of chemistry one could achieve within that complex. So that's how we got started.

Then at about the time that I came back from England, I think Myron [L.] Bender published the first example where he put some sort of a meta-nitrophenylacetate into a cyclodextrin and found that the geometry promoted attack on the hydroxyl (19). Of course, this was not a catalytic reaction, but still it was a geometrically controlled thing. So I thought that was pretty interesting. So then we, at the same time, pretty much had decided to try to take a look at the possibility of using cyclodextrins to direct an aromatic substitution. But I knew that a molecule like anisole would bind into the cavity because it was pretty clear from the literature that things like that went in, and so it seemed to me that if we took a molecule like anisole, which would normally chlorinate ortho and para, if it went into the cavity, there was a good chance that the para would be peeking out and the ortho would be hidden and therefore you'd get only para-chlorination. So we tried this, and sure enough it turned out to be true, but not for those reasons. When we did a serious kinetic and mechanistic study, it became clear that the reason we were hitting the para position was because a hydroxyl group of the cyclodextrin was picking up a chlorine by exchange and delivering it to the para position. It was not just that we were hiding the ortho position. We were actively catalyzing para-chlorination. So then we pursued that for a bit and we eventually made even a polymeric material where we could run substrates down the thing and out the bottom would come selectively chlorinated material.

By then, I had come across a man named Lowell [P.] Hager, because the early work on thiamine had gotten Fritz Lippman very excited and so they had me come down to Rockefeller [University] and talk about that research, and Lowell Hager, I think, was maybe a post-doc at that point. Anyhow, I had met Lowell there, although he eventually became a professor at the University of Illinois. But at some point, I came across his work and he was studying an enzyme, chlorinase, that would take anisole and chlorinate it, but it gave a random mixture of products, ortho and para. So I thought, well, that was quite interesting that we had a molecule that was better than the enzyme at doing this, but it was still only using simple cyclodextrin. But then I decided we should really hang on functional groups, and of course we've been doing that ever since. You know, hang functional groups onto cyclodextrin, and try to put on co-enzymes. The first example of that was done by hanging pyridoxamine onto ß-cyclodextrin and

seeing that we could get amino acid formation with selectivity for substrate, and as it turned out, even some chiral selectivity for product. Then we did other co-enzymes, and then we did other catalytic groups. We did metal ions—one of the earliest, the first compound that in the literature is called a "synthetic enzyme." I mean, maybe it was just arrogance on my part to call it a synthetic enzyme, but it was done with Larry [E.] Overman, who was my post-doc, and now of course is an extremely well known synthetic organic chemist. Larry Overman was a post-doc with me, and we assembled the molecule with a metal binding group in the cyclodextrin. The idea there was that were a number of examples in which metals catalyze reactions very effectively, but always with substrates that they bound to; you've got the binding and you've got the catalysis. So the idea was that maybe we could separate it and use the cyclodextrin as the binding group and use the metal just as a catalytic group and do things on substrates that wouldn't otherwise be touched by metals. That turned out to work. So that got started. We're still doing such things now. We have some cases with two metals cooperating or with metals and bases cooperating. That line has still been carried forth.

We've done a lot of things in the cyclodextrin area, both putting catalytic groups on and most recently making cyclodextrin dimers; these turn out to have very interesting properties, in unpublished work. We find they will dissociate certain enzymes that only work as dimers. Some enzymes come together and dimerize. We've done two so far: lactic dehydrogenase, which is a tetramer when it works, so four proteins have to come together, and citrate synthase, which is a dimer. The enzyme only works when two enzyme molecules come together, and in general, those binding groups where they come together are pretty hydrophobic patches. There are a lot of hydrocarbon side chains there, and we knew by then that our dimers would bind to amino acids on polypeptides. We had published that already (20). So we've looked at that, and it turns out that works. That is, it takes these dimers apart, and the excitement there is that some of the most interesting proteins around include things like HIV protease, which is a dimer, and if we can take that apart, then that could be a very interesting approach. There's another enzyme called HIV integrase, which also is a dimeric material. But the whole business about protein-protein interaction—which, you know, to some extent, maybe I've gotten this, as I said, by osmosis by my wife's interest in this area—is something that we think has tremendous potential and so making molecules that will bind to a hydrophobic side chain of polypeptides and block the dimerization seems like a very good thing to do. I've got three students working on it here. One is just about finishing up and two others, who are M.D./Ph.D. students who have taken two years of medical school, are coming down here now doing Ph.D. work on making these molecules and seeing whether they can't get this kind of behavior. Because these things have tremendous medical potential. I don't know how selective they'll be. That's the most serious question. But other than that, blocking aggregation of proteins is going to have huge effects on lots of things, as I say, including HIV protease, perhaps. So it's an interesting general challenge.

GORTLER: The word "biomimetic"—you're proud of that word.

BRESLOW: I like that word.

GORTLER: It seems like a natural word.

BRESLOW: Well, it is a natural word, but it was a natural word that didn't exist before, actually. For that matter, anti-aromatic didn't exist either, it turns out, and it's really strange when you think of it. Well, anti-aromatic, if we could go back to that one for a minute, came out because nobody really knew that these non-Hückel things were going to be bad. They just knew they weren't going to be good. We were able to argue, from the data, that the wrong number of electrons made the thing actually worse than a normal molecule. The theory at that time did not accommodate it. Simple Hückel theory doesn't really handle that, because in simple Hückel theory, these damn things turn out to have essentially no delocalization energy. But that's because it doesn't include electron correlation. If you put that thing in, if you do a calculation with any kind of decent regard for electron repulsions essentially, then it turns out, they're worse. So anyhow, anti-aromatic—that word seemed to be fairly sensible.

Biomimetic—well, I don't know. I mean, we were just interested in building molecules that would mimic what it is that nature does, and it seemed as if perhaps one ought to give that field a name. It seemed the sensible thing to do. I don't know why it hadn't been done before. People were trying to mimic nature for a long time. They just happened to not use that name. Everybody uses the name now. I haven't seen any royalties for the name. I don't think they give me anything special for it. [laughter]

GORTLER: The work on the cyclodextrins has led to your more recent work on mimics for cytrochrome P450.

BRESLOW: Yes, that's still going hot and heavy.

GORTLER: Do you have any more recent results than those you published (21)?

BRESLOW: No, probably not. We have some, but since they're not published, they're probably not yet publishable. We are able to move the position of attack around some. We still haven't developed a great catalyst. See, the best we have now is a catalyst with, I guess, four hundred turnovers or whatever before the catalyst dies. We'd like to be in the thousands, you know. We really would like to be up there. But four hundred turnovers before the catalyst dies, and the product comes out and the starting material goes back in and gets functionalized. It's really quite selective, but we have not yet been able to send it to the spots on a steroid we really care about, and so we're still doing that. There are two people working on it right now and perhaps another one will join that. We can change the geometry some and we have evidence that we can attack a saturated carbon and leave a double-bond alone, for instance, and we know

that we can attack a saturated carbon and leave a hydroxyl group alone because the product is an alcohol and yet the product is never oxidized to the ketone. You can't reach the hydrogen you'd have to reach in order to oxidize it further. So we do have part of what was fascinating about enzymatic chemistry, that is, the ability to ignore the intrinsic reactivity of the substrate and just let geometry govern the whole thing. We have some of that, but we don't have as much as I'd like to see. So we're still banging away.

GORTLER: In these cases, you have to build the substrates so that—

BRESLOW: So that they'll bind.

GORTLER: —they contain anchors.

BRESLOW: Yes, right. In the ones we did there. So you have to wonder, where are we with that? I mean, it seems a little bit much. Nature does a little bit of that, not too much. I mean, it might put a sulfate on a hydroxyl, but it doesn't do anything as fancy as what we have done. That's why I would say this is, at best, a beginning. We have some examples of substrates that bind directly without being functionalized in that way, and most of that stuff is still going on. So I really can't talk about it much yet. But we do have cases that will bind where you just put the material in; things like lithocholic acid, for instance, goes in and gets oxidized. You don't have to do anything to it. So there are real cases where we don't do anything to the substrate. In the case we did, we just wanted to see whether we could steer and get a turnover and all the rest. So we did that as a starter, but that's not the ultimate goal. The ultimate goal is to bind an ordinary molecule and do something to it, and spit it out. We're just not there yet. We'll have to do that some time in the next thirty years or so.

GORTLER: Last question, which goes to this. What methods do you use to determine the best fits or the catalyst's substrate? Do you have models? Do you have computer programs?

BRESLOW: We do both. That is, we generally will build a solid model because you learn a lot from playing with it, turning it around. But then we will also do computer programs for this because they, in principle, also give you energies, let you minimize energies, and get the best conformations and that sort of thing. So we do both things. Then, frankly, we also try things, and not everything that we try works well because you don't really know enough about the geometries. You don't know enough about how things bind into the cavity. The cyclodextrin cavity is somewhat open-ended. We've made things that aren't. We've made things that are cup-shaped, but with the simple cyclodextrins, you don't know exactly how far in you go, and so that leaves you some ambiguity about what's going to happen. So to some extent, we still have to do experiments to find out. Luckily, it's not that hard to do. One reason to work with

steroids is that the whole steroid structural chemistry has been worked out so well that, for instance, one knows what will happen to the NMR of the angular methyls if you put an oxygen in a particular place. So you can use that as a way to tell what you've done. That's very helpful. Also, you know that methyls will be in different places, so if you get mixtures, you're not going to get nice clean signals. Probably at some point, maybe in the future, we can talk about the cancer research I mentioned because that's been very exciting.

GORTLER: Yes, it was absolutely fascinating. I take it you can buy cyclodextrins.

BRESLOW: Yes, you can buy alpha, beta, and gamma cyclodextrin. The price keeps coming down. We mostly get it free from companies that are interested in having us just do things with it. So I really haven't paid for cyclodextrin in a long time. But it's cheap. It's very cheap.

GORTLER: How do you do the chemistry on it?

BRESLOW: It's a little tough.

GORTLER: There are a lot of—

BRESLOW: Lot of hydroxyl groups. Beta-cyclodextrin—twenty-one hydroxyl groups. How do you do it selectively? Some of it you do with geometry. For instance, if you want to hit one hydroxyl here and another one over there, then you use a rigid reagent that can span—you know, you make a disulfonylchloride and you hit one hydroxyl and then the other one goes over there. So some of it's done with geometry, and that's how we can make particular geometries of catalysts, which we do. Some of it is simply that there are some selectivities built in. If you take cyclodextrin and treat it with tosylchloride, the first tosyl goes on faster than anything else because I think once it's on there, it's sitting in the cavity and to some extent blocking other tosyl molecules from doing the same thing. So you can do selective reactions. A certain amount of it had to be worked out, but much of it is understood now.

That's what you lose. What you gain is, you don't have to make the cavity. You know, you have this stuff, this free stuff. We start with that, because that you can easily do, and learn what we can achieve, and then we try other things. We've done some of that. In the transamination, for instance, we then made a synthetic cavity binder. Instead of cyclodextrin, we hung the pyridoxamine on the synthetic cavity and saw how it worked. Some of the dimer stuff we've done also with synthetic cavities. So we've done some of that just to make sure what happens, and sometimes the synthetic cavity is better. They're often more hydrophobic than the cyclodextrins. It's got some oxygens inside. So sometimes they're a little better, but

they're an awful lot more work to make, and so as a pioneering part, it doesn't make a lot of sense to do it. Maybe that's just my position.

GORTLER: All right. We'll finish off the last questions at another time.

BRESLOW: Good. And the cancer thing is going very well. The National Cancer Institute [NCI] is now going to put these things into clinical trial this summer.

[END OF TAPE, SIDE 3]

[END OF INTERVIEW]

INTERVIEWEE: **Ronald C. Breslow**

INTERVIEWER: **Leon Gortler**

LOCATION: **Columbia University, New York City**

DATE: **9 April 1999**

GORTLER: I had gotten up to hydrophobicity. In 1980, you began publishing material on the reactions of organic molecules in water where there were significant rate increases (22), that is, overreactions in organic solvents. One of the earliest findings concerned the rate enhancement for the Diels-Alder reaction, and the question is how the research began. In my own mind, I thought, "Gee, somebody dropped this stuff in water accidentally!"

BRESLOW: No. We had, of course, been studying reactions that occurred in cyclodextrins, and for things to bind into a cyclodextrin, you have to be in water because that's a hydrophobic binding. So I asked one of my new graduate students to see if we could make a Diels-Alder reaction occur inside the cavity, because I thought that there was a good chance the diene and the dienophile would both pack together inside the cavity and that reaction would be accelerated as a result, and possibly even directed in terms of geometry. All of that was actually true. It did happen. But we also found that in the control reaction, when we omitted the cyclodextrin, we also got big rate effects. They weren't as big. The cyclodextrin was better, but that's a special situation. But the thing that we found in the control was that the water reaction also was much faster than any other solvent. So we realized that water produces a cage, as well. It just happens to be a spontaneous cage, and the reactions were going on inside a water cage, and that was an interesting thing to pursue.

We're still pursuing hydrophobic effects to this day. The Diels-Alder story is largely finished, I think. We started that and showed both that we got great accelerations and that we also got very big increases in selectivity. That is, the molecules came together so as to minimize the exposed surface area, so we got, for instance, in the high 90 percents of endo-product, where things are very compact, whereas in other solvents you generally get a mixture of some kind. So that, actually, has been picked up and studied by a number of other people. Paul [A.] Grieco then picked that up and used this water effect to direct some Diels-Alder reactions that were of interest in terms of natural product synthesis, and a man named Engberts in Holland, who has always been quite interested in the properties of water and reactions in water, he picked up our stuff and ran with it, too. So there have been other people looking at this.

Even then, we realized that it's one thing to say that reactions are faster in water, and it's another thing to know that it has to do with the hydrophobic effect. It turns out that protein chemists knew that there were materials that would decrease the hydrophobic effect. They knew for a long time that there were materials that would denature proteins, and they began to

realize that this was because the hydrocarbons that are normally in the interior of a protein get exposed to the water as a result of diminishing the hydrophobic effect with the so-called "denaturants," but some of the fundamental work on it—there was a man named Arnold Wishnia at [State University of New York at] Stonybrook who did some studies of the solubility of hydrocarbons in water, and as they were affected by these denaturants, and he showed that the hydrocarbon solubility increased with these denaturants. A protein is a complicated thing; you could be changing hydrogen bonds and who-knows-what. He showed that the hydrophobic effect was a major factor for these denaturants, that they did in fact increase solubility of hydrocarbons, which meant it didn't cost you as much energy to put a hydrocarbon next to water, you know, which is what that effect was.

At that time, they were called denaturants; sometimes they were called water structure breakers. But that involved the idea that we knew how it happened. So with one of my students, we looked into the question of whether one really knew why it was that this solubility increased. At the same time, it was known that things like lithium chloride and sodium chloride would decrease hydrocarbon solubility. That's a well-known salting-out effect, and people use that even in the laboratory to make things extract better. So that was known, and what was known about that was that you get so-called "electrostriction," a decrease in volume of the solvent. As you put sodium chloride in the water, the volume goes down and therefore, in a sense, you squeeze out the empty spaces, or putting it another way, if you want to dissolve something in that water, you've got to create a space and now you have to fight against this salt effect that's pulling it in the other direction.

So that was electrostriction, and so a lot of people assumed that the denaturants just worked in the other direction. That is, they made it easier to make a hole in the water rather than harder. We looked at that. If that were true, then the denaturants should actually decrease the surface tension because when you make a hole, you're creating more surface. So if it's easier to make a hole, the surface tension should go down. But, in fact, these denaturants increased the surface tension, and so as a result of that, we concluded that it wasn't because you made water open up more easily, but it was because things like urea, which is a denaturant, would be able to sit on the hydrocarbon and help solvate it, because it's a better solvater than water is, and also bridge to the water. So they [the denaturants] simply intervene between the water and the hydrocarbon, and it was a solvation effect and not a water-breaking structure effect. So we decided we don't want to call them only denaturants because that's too narrow a term, because it has to do with the idea that you're denaturing something, but after all, you're really solubilizing even hydrocarbons, so denaturant doesn't seem like a good word for that. We didn't want to call them water structure breakers because that's not how they work, and so that didn't seem sensible. So we termed them anti-hydrophobic agents because they, in fact, decreased the hydrophobic effect. It's sort of just a description of them. We've pursued that ever since and have done a lot of work with that. I don't know how much of that you want me to go on about.

GORTLER: Yes, that was my next question. In fact, many times you just used organic solvents that have been miscible with water, like ethanol.

BRESLOW: Yes, well, what happened is that we originally did a study with the benzoin condensation. We decided that in the Diels-Alder reaction, it was clear that the two components had to come together, because that was the product. But in the benzoin condensation, we thought there was a good chance that benzaldehyde and the mandelonitrile anion, the sort of cyanohydrin anion, when they came together, we thought there was a good chance that the phenyl rings would also sit on top of each other. If you think about the geometry, the stereoelectronic requirements of that—it did seem as if these phenyls should be able to get at each other. So one of my very good graduate students, I must say, a man named Eric [T.] Kool, who's now at the University of Rochester, took up this benzoin study and he studied the benzoin condensation in water with added reagents like lithium chloride. In fact, the reaction speeded up, but then he used lithium perchlorate, which is an anti-hydrophobic agent, which in fact dissolves hydrocarbons, it turns out. Lithium perchlorate makes benzene more soluble in water. It makes other hydrocarbons more soluble also. So the perchlorate anion is the point. If you have a large ion, that large ion can generally solvate a hydrocarbon and if it has some charge on it, it can bridge to the water, and so it works in this solvation mode.

Anyhow, so he looked at it, and lithium perchlorate decreased the rate, and so we saw that this contrast between a pro-hydrophobic and an anti-hydrophobic agent in the rate indicated that what was going on with benzoin condensation was not just water better solvating some charges, but was in fact some hydrocarbon packing. Then we decided that if we looked at those curves, we should be able to interpret them in terms of how much each benzene covers the other one. In other words, have they fully eclipsed, or is there some partial covering or whatever? We should be able to do that in principle, but I didn't like using the salts for that because I was afraid that ionic strength effects could be something that we wouldn't really understand well enough. So we went to ethanol because ethanol will also do this, and in fact, I don't think anybody has any doubt that the way ethanol solubilizes a hydrocarbon is to have the ethyl group sit against the hydrocarbon and the OH in the water. I mean, that's pretty clear. Although in fact, as it turns out, ethanol does decrease surface tension, so if you argued about water cavitation, ethanol does actually decrease the surface tension of water, and so maybe that's a factor, too. It's hard to know. But the major thing, obviously, is that bridging business.

Anyway, we looked at ethanol for that, and the first thing that we established was that there was a quantitative relationship between the effect of ethanol on dissolving a hydrocarbon and the amount of exposed hydrocarbon surface. It's a critical thing to show because we wanted to make something quantitative out of this whole business. So we showed that compounds with one phenyl ring, no matter what they had on them, might have grossly different solubilities in water, depending on the polar group it was hanging on, like an amide group or whatever. But then when you added ethanol, say 10 percent or 20 percent ethanol, a volume percent—when you added ethanol to the water, what you found is that there was an increase in solubility which was the same when you translated it into free energy terms. That is, in other words, the change in free energy that one got as a result of solvating the benzene ring was the same regardless of what was hanging on it. So in fact, that other piece determined the original solubility, but the solubility change turns out to be because of the way equilibrium constants and free energies go;

you know, there's a logarithm you have to do. I mean, there's a well-defined relationship. But when we did that, we found that it was always the same amount so that, first of all, a simple phenyl ring with a certain amount of ethanol is solubilized by a change in free energy, $\delta\Delta G$, which is always the same, so that was helpful. Then we looked at cases in which we had two phenyls in the molecule, held apart so they couldn't interact in any way. We had three different cases of that. The simplest one was an oxirane, ethylene oxide with a phenyl up and a phenyl down, trans, so the phenyls were clearly held apart. We found that that one had twice the free energy change, with the same amount of ethanol, as things with only one benzene ring. In other words, if you doubled up the amount of hydrophobic surface, then the $\delta\Delta G$, the free energy change, was twice as big. You know, it's not an unreasonable result, but you had to know that it's true.

So we showed that, and we had a number of cases showing that relationship. We've also showed, as an aside I could mention, that a benzene ring and a cyclohexane have about the same $\delta\Delta G$. That is, cyclohexyl compounds and phenyl compounds are increased in solubility by an amount, when translated into free energy change, that's the same. But then we also showed that if the phenyls could get near each other, we didn't necessarily get doubling because the phenyls could cover up to some extent; the first case was actually the molecule benzoin. Benzoin has two phenyls sitting on a two-carbon linker that does not force the phenyls to be apart. In that case, we saw there only seemed to be only one and a half benzene rings in the molecule, and so half of a benzene ring had disappeared from solvent contact, and that was sensible because part of each benzene ring covers the other one, and so fair enough. But it's important to know that kind of stuff because of things that have developed later.

Then we also took the oxirane, the ethylene oxide, and had the two phenyls on the same side, and again, we got about a 1.6 benzene rings exposed rather than two. So we were covering, you know, maybe 40 percent total of the hydrocarbon surface area somehow. So with that kind of thing, it seemed to us that it was reasonable to start looking at reactions because once you knew that the $\delta\Delta G$ was proportional to the amount of hydrocarbon surface exposed, if you could find reactions where that was the only effect of the ethanol, which is a critical, critical point—which is not necessarily true of everything. If you found one where that was the only effect, then in principle you could figure out how much hydrocarbon's surface is exposed in the transition state, and that's the geometry of the transition state, a thing that otherwise one doesn't know.

So the first thing we did was a couple of cases where we knew for sure what the result was going to be, just to make sure that we got the right result. So we did the Diels-Alder dimerization of cyclopentadiene. Now, when these two rings come together, each one more or less covers the face of the other one because in water they give entirely endo-addition. There is no exo involved. So they come in in a very compact transition state. We thought, well, they must each be covering one face of the other, so we ought to have about one cyclopentadiene, more or less, disappearing from contact. The ambiguity is that you can cover one face of each one, but you still have the edges, so you have the other faces that are exposed, and then you have the edges. So you probably won't cover quite one whole cyclopentadiene. When we did the effect of the ethanol on the rate of the reaction—not just ethanol, but we did a whole string

of different alcohols; at that point, we were just exploring this whole area—we found that we could see what they did to the solubility of cyclopentadiene. That was a calibrator for the whole surface. Then what did they do to the rate? It was a very good correlation over a whole range of different co-solvents, that 90 percent of a cyclopentadiene was disappearing in the transition state, which is about what you'd expect for covering two surfaces. So that looked good. That looked as if maybe you could use this method and learn about transition states.

Then we also did a Diels-Alder reaction series on an anthracene compound. It was an anthracene carbinol, because we needed it to be in solution, but it was a species we had actually studied before in our early work on Diels-Alder, before we got into this quantitative stuff. So we looked at an anthracene carbinol reaction with n-methylmaleimide and it turned out there that what you find is that you are covering about 27 percent of the anthracene in the transition state, again assuming that this is only a hydrophobic parameter you're changing; you're not changing anything else. For the cyclopentadiene, it's pretty clear—there won't be any polar solvent effects. For this maleimide-anthracene carbinol, you have to wonder whether maybe there is any kind of polar effect on the dienophile, but in fact, we just checked and sure enough, we got 27 percent, which means you're covering about half of one surface of the anthracene, a little more than half, and that's what it should be for the Diels-Alder going right over the middle ring. It, in fact, will cover half of the middle ring of the anthracene and the whole benzene on the side. But then you can also look at the solubility of the Diels-Alder adduct and look at how it changes with ethanol. When you do that, that tells you how much hydrocarbon surface is now exposed in the product, and 90 percent of it was there then again. In other words, because you do a Diels-Alder like that, but then it goes like this in the product [showing overlap and opening up in product with hands], and you re-expose the hydrocarbon surface. So that all made very good sense, and so we said, "Gee, this stuff really makes a lot of sense," you know?

So then we went back to our benzoin condensation to see how that looked with this ethanol story, and that was a little trickier because, obviously, you've got a charged anion hitting a carbonyl and so will there be polar effects, and who knows, you know? So one has to worry about that. But we decided, "Let's see how it looks." So we ran that case and it turned out that from this same argument about looking at benzaldehyde $\delta\Delta G$s, you know, the free energy changes, and then looking at the rate effects, we could deduce that about one-third of a benzene had disappeared. One-third of the total hydrocarbon surface had disappeared in the transition state, whereas in the final product, benzoin, it was one-half eventually gone. That was from the early solubility studies. So that said, "Well, okay, we're on our way in, but we are not coming in with these two phenyls lying fully on top of each other, because that would give you a big effect. We're coming in at an angle." Then when you think about it, you realize, well that makes good sense because to add to the carbonyl—the carbonyl doesn't stick straight out; it sticks out at an angle—you've got to come in behind the carbonyl, and as soon as you come in behind the carbonyl you're getting only partial occlusion of the rings. So whether one-third is the precisely right number, I guess one has no other evidence for, but at least it was not an unreasonable number.

So with all of that, we decided, okay, we could afford to get into things that were a little riskier, and so we've done that. The risky part had to do with getting into things where there

were real charges being made and broken in transition states and how much can you ignore other effects of these co-solvents in changing the dielectric constant of the medium, and that kind of stuff. So we did a couple of control reactions, which actually looked pretty good, but we went back and did more extensive control reactions now and, in fact, what I've got in my computer right now is the report of that stuff because I was not happy. We had a few control reactions where we didn't seem to see any effect of adding ethanol; reactions like hydroxylamine hitting chloroacetate ion and things of that kind where you're clearly getting charged groups, and yet the rates didn't change with ethanol. But I was not satisfied that this was enough to establish the whole thing. We've now done a bunch of control reactions, and right now we're right in the middle of sorting this whole story out. There are, sure enough, small reactions, displacement reactions, where putting in, say, 10 volume percent ethanol or 20 volume percent ethanol does have an effect on the rate and has nothing to do with hydrophobicity, because there are charges that solvation changed. But we've been able to sort that out with a very interesting trick, and this also, as I say, is something that's just being written up now. If we substituted dimethylsulfoxide [DMSO] for ethanol in the water, what we found was that dimethylsulfoxide is about 50 percent better than ethanol at the same volume concentration in solubilizing hydrocarbons. So it's even more anti-hydrophobic. I mean, it's got those two methyls that it packs right against the benzene ring, and then it's got the sulfoxide sticking out into the water, and so it's a terrific solvator. On the other hand, the dielectric constant of the water doesn't go down seriously at all with DMSO as a solvent compared to ethanol. So we were able to sort out a dielectric constant effect, then, from a hydrophobic effect, and with that we were able to show that in, for instance, the nucleophilic reaction of N-methylaniline on benzyl chloride, there is, sure enough, an anti-hydrophobic effect operating as well as whatever is going on with some solvating of the developing charges. I mean, when N-methylaniline hits benzyl chloride, you generate a chloride ion, it's got to get solvated. You generate an anilinium cation that's got to get solvated, you know, with a hydrogen bond and all that. So there are polar effects there, but we were able to sort them out with this trick, and see that there, sure enough, is an anti-hydrophobic effect there.

But the situation is a little more complex than that because some of the anti-hydrophobic effect comes from a phenomenon that we found. Nobody had worried about any of this stuff, so nobody knew about this either—but it turns out that if you have a neutral compound, like a benzyl chloride, and if in the transition state you develop benzyl cation character, that charge gets delocalized into the benzene ring, and that benzene becomes less hydrophobic as a result. So you can diminish its unhappiness with contact with water by just getting charge into the ring. We showed that that was true. We also showed that that was true with, say, a phenoxide anion. If you go from a phenoxide anion to a neutral phenyl ether or something, using it as a nucleophile, it starts off not hydrophobic at all. That charge is enough to make that benzene ring perfectly compatible with water, as judged by our ethanol story. On the other hand, when you go to the neutral species, then in fact, you get a significant hydrophobic effect.

So in all these reactions, you have to worry about losing hydrophobicity in the benzyl system as you could develop some benzyl cation character, developing hydrophobicity in the phenoxides, and that in addition to whatever you get out of packing. So it's a more complicated story, which we knew it was going to be. I mean, we knew we were getting into a serious area

here, but on the other hand, people had not really worried about this stuff in ways that are really quite interesting. For instance, very early classic work by Saul Winstein, on solvolysis, said that when you look at tertiary-butyl chloride solvolysis in water, which is one of the fundamental classic organic reactions, and then you look at that in 20-volume percent ethanol and water, which happens to be what he did; I mean, he did it in the same volume we'd been looking at. It turns out the reaction is three times slower in the 20 percent ethanol than it is in straight water. He argued that that was because of the change in polarity of the medium. But ethanol will solvate the tertiary-butyl chloride strongly because it's a hydrophobic unit—it's a hydrocarbon, essentially. Ethanol will solvate the starting material strongly, and when you go to the cation, you lose that. So it's the same sort of thing as in the benzyl cation. That is, when you start putting charge into a hydrocarbon species, you will lose its hydrophobicity. In benzyl cation, I mean, there's a lot of charge actually out on the protons, even. You know, the methyl groups or t-butyl cation even carry a lot of the charge. We've done some calculations on this, and we don't have any measurements on it, but the point is that in a lot of classic work, people have not thought enough about this question of ethanol helping to solvate the neutral compound, and we started off with that being an effect we were mostly concerned with. We now have to sort that out from all these other solvation effects. The world has gotten more complicated, but that's all right. We're getting it. I think we're getting it.

GORTLER: But then you used this anti-hydrophobic effect as a probe for single electron transfer, as well.

BRESLOW: Yes. That one is an interesting case. There, what we found was that with something like a thiophenoxide anion as a nucleophile, and let's see, our cleanest case actually is the one that we published recently in *JACS* [*Journal of the American Chemical Society*] (23), which was the cyclohexylmethyliodide. We looked at a mesylate as a leaving group, and an iodide as a leaving group, and we had there a big increase in the hydrophobicity of the thiophenoxide anion, so it started off as a delocalized ion which wasn't very hydrophobic, and when it lost that charge, then there was a big increase in hydrophobicity. We got a very large number for that, as judged from the transition state rate effects. That was provided it kicked off an iodide. Carbon iodine bond is a bond that you can cleave fairly easily with a one-electron reduction. It has a very low potential for single electron reduction, whereas the carbon mesylate, the corresponding mesylate, you can't reduce. I mean, that's one of the classic kinds of things that electro-chemists worry about—the difference between something like a weak bond, like an iodine, and a strong bond, like a carbon oxygen bond.

So anyhow, what we found is that we didn't see anything like these huge effects when we were kicking a mesylate off, but we got this big effect when we kicked an iodide off. So that was at least symptomatic of something going on. In addition to that, what we found is that when we kicked the mesylate off, having a hindering group, putting a couple of methyls on each side of the thiophenoxide sulfur, slowed the reaction—not a huge amount, but slowed it significantly, whereas in fact, it had no effect at all on the iodine case. So that said that the

sulfur is a lot further from the carbon in the transition state for the iodine case, and could be consistent with the single electron transfer.

I think at this point, our position is probably a little more moderate than what we advanced. We said that this is evidence for single electron transfer, but there are two interpretations of that, and I don't think we know which one is correct. One interpretation is that you are setting up what we think of as an SN2 transition state, with relatively long bonds in this case, and with a serious amount of single electron transfer character in the transition state. So that the thiophenoxide is somewhere between an S- and an S•; and the carbon is somewhere between a neutral and a C• or whatever, or C+ and C•. I think there's a lot of single electron transfer in there. It's the only thing that makes any sense for this, but I think that we don't really have evidence that you go all the way to a pair of radicals, which then couple. That is harder to do. You can do that kind of stuff in other cases, and people found it in other cases, so there are well-defined cases where you actually do a full single electron transfer and make a pair of radicals in a cage which then couple. But generally the evidence for that is things like, you lose stereochemistry. Well, we haven't been able to do that here. That would be an interesting thing, but we haven't done it. Or you get radical rearrangements in the course of a reaction. Well, this doesn't do anything like that. So we are missing some of the classic pieces of evidence for a bona fide free radical actual intermediate.

GORTLER: You don't see any coupling reactions or anything of that sort?

BRESLOW: No. But you see, if this is a cage recombination of a pair of radicals, you're not going to see anything. You're not even going to see inhibition. We put in radical inhibitors, chain inhibitors, but these are not chain reactions, so nothing happens there either, and it doesn't happen with any of these other classic cases. So I think at the current point, our position really would be now a little more moderate, and we'd say there's a lot of single electron transfer character; whether it's a full product all the way through a pair of caged radicals before they couple, or whether the sulfur is already beginning to bond to the carbon before the iodine is quite all the way gone, I think we wouldn't really be able to say. That's an interesting challenge that I guess we're going to have to try to figure out how to deal with. It's because I think we've become—as we've done more work—more aware of the fact that you can get a lot of increase in hydrophobicity in a thiophenoxide anion or in a phenoxide anion by simply getting most of the charge out. You don't have to get it all out. If most of the charge is gone, you're going to get a lot.

Some of this is related to calculations we've done. We've developed a calculational model for this anti-hydrophobic business, which has been very helpful and which correlates pretty well with things that we know. In the computer, we take a molecule, we put it in water, we bring an ethane up to it, let the ethane probe around the surface, and we try to see what happens to the free energy of that combination. In other words, the ethane was originally separate from the compound and then when they come together, there's a decrease in free energy—by how much? Then we know that, well, in the real system where you're in water and

you have some ethanol, you're not going to have 100 percent of the ethanol sitting on the hydrocarbon, so that we have to calibrate that in some way. So what we did is look at the calculated effect on solubilities, on the $\delta\Delta G$s for solubilizing hydrocarbons, and then the real effects, and we found that the calculation at 20 volume percent ethanol over-estimated the effect by a factor of four. Now, if we'd had more ethanol, presumably, it would over-estimate less because it would have more chance of solvating. So the factor of four is presumably some measure of the extent ethanol is there compared to just floating around in solution, because it costs you entropy to lock it on the hydrocarbon.

So then we took the factor of four, and we applied it to some of our rate effects, and it works pretty well. So we're able to account for a lot of the things that we measure by this calculational model for what the co-solvent should do. But I don't think it's perfect yet, and so obviously we're working on that too, you know, trying to see if we can't get a model to work well, because I think ultimately the direction physical organic chemistry has to go is to get to the point where we can calculate a lot of this stuff in really good detail and trust the calculations. So part of this project is not just diddling around with solvent effect, but trying to see if we can't calibrate these calculational models and come up with something that really works.

[END OF TAPE, SIDE 1]

GORTLER: Since you brought up the computer programs, which I knew nothing about, are you using developed programs? Are you developing your own programs?

BRESLOW: Well, we've developed this particular way of using the program in order to calculate the thing, but the computer program itself is one that I stole from my colleague Richard Friesner. We're lucky in this department. We have a very strong theoretical group, and Friesner is one of the developers of a program called "Jaguar," which is a good *ab initio* program, and he has ways of putting solvation in this so-called "continuum solvent." In other words, when you put water in, you put it in in terms of its bulk properties, but you don't put individual water molecules in, although you could, in principle, do that. So we've been using his program and it's very helpful. Sometimes we have to add some other parameters or whatever, and he's right here to do all that. So that's very helpful. We've not been looking at other programs. There are other ways of doing this. You know, Bill [William L.] Jorgensen at Yale has some computational things he does, and I'm sure he's not using Friesner's program. He's using something else. But most people who are doing this stuff seriously now are using *ab initio* methods, not using parameterized methods, the kind of thing that Michael [James Steuart] Dewar developed. Most people are tending not to do that, because I guess the assumption is that if you have to use parameterized methods, there's always a danger that the parameters are going to fail for the case you're interested in, and the *ab initio* programs in principle don't require that. The problem is, they don't always work. But I think it's clear where this is going to go. What has limited it largely has been computational power, but that's so much better now that it's not a big factor. So we're doing that. I have one student who's doing that, he's very good—a very

intelligent man, I must say. He's doing about half calculations and half experimental stuff. That's a very good combination. I even have him synthesizing a molecule because I don't want him to get out of this group without having made something. He's making an interesting, challenging molecule besides everything else.

GORTLER: Yes, I noticed that in one of the articles that you like to have all your students make something.

BRESLOW: They'd better, if they're going to get out. See, that's the great power that organic chemistry has that no other field has. I mean, these other guys all have to ask us, "Can you give me this molecule? Or can we buy it?" I mean, it's a fantastic power, and I think the estimate I heard—it's a very interesting estimate—is that we have made less than 1 percent, by a lot less, of all the conceivable molecules under molecular weight five hundred that have just carbon, hydrogen, nitrogen, phosphorus—you know, a few of the normal elements. We're nowhere near exploring the whole available world. That doesn't mean we want to do it, necessarily, but it does mean there's a lot of need to make new things in order to explore stuff.

GORTLER: For about twenty-five years now, you've been collaborating with colleagues at the DeWitt Wallace Research Labs. You have to tell me what those are. And [Memorial] Sloan-Kettering [Cancer Research Institute] on cyto-differentiation.

BRESLOW: All right. The DeWitt Wallace Research Labs is somebody who just came into that one paper for their particular contribution (24). The collaboration has been with the people at Sloan-Kettering. Actually, it started first when everybody was at Columbia. I started collaborating with a man who was at one point the dean of the medical school at Columbia and is now the head of Sloan-Kettering, named Paul [A.] Marks, and with Richard [A.] Rifkind, who was at that point a professor of medicine at the medical school and is now director of research at Sloan-Kettering. So that's really sort of the tripartite collaboration. From time to time, people have gotten into this who have done some particular things with our compounds.

But that research program developed very interestingly. Let me tell you that story because that's really a wonderful story.

GORTLER: Yes. That's the one I want to hear.

BRESLOW: All right. So what happened is the following. A woman named Charlotte Friend, who was at that point at Mt. Sinai Medical School, was studying what were called Friend Cells, named for her. She didn't name it that, but everybody else calls it "Friend Cells." These were so-called "pre-erythrocytes." Erythrocytes, red blood cells, as essentially every cell, are formed

from some kind of a stem cell. That is, at first you make a sort of a juvenile form, and then that form differentiates to the adult form. So the first thing that can be a red cell isn't. That is the first thing—a pre-erythrocyte is white, it has no hemoglobin in it, and it's spherical. Then eventually it becomes an erythrocyte, a red cell. It develops hemoglobin, becomes red, and it also flattens out. It looks a little bit like sort of a discus with fat edges, you know; the red cell has a very different look from a sphere. So these pre-erythrocytes normally differentiate, and they have two jobs. They have to multiply because you have to make more stem cells, and they also have to differentiate to an adult form. Adult cells normally don't proliferate at any significant rate. That is, you make new tissue by making new stem cells and multiplying them and then differentiating to the adult form. Red cells don't, for instance, make more red cells. They all come from this kind of process.

Well, what happened is this pre-erythrocyte is infected with a virus, which is called the erythroleukemia virus. Then animals that have that infection develop a condition called erythroleukemia, in which their stem cells are simply making more stem cells but are not making red cells anymore and so they don't have the erythrocytes they need. That's because you have changed the balance between proliferation and differentiation. Various biological studies made it clear that what you have done is fundamentally cut off the differentiation path. You haven't so much speeded up proliferation; you've simply cut off this differentiation path.

So what Charlotte Friend had been trying to do was to soak some of these pre-erythrocytes that were not differentiating at all—she had a whole tube full of them—soak them in aqueous DMSO to soften up the membrane so she could get something into the cells. When she came back and looked several days later, the tube had turned red, and she looked at it under the microscope and there were erythrocytes in there. So that these cells, which would never have differentiated before, differentiated as a result of having dimethylsulfoxide in the medium. Not an anti-hydrophobic effect. A different effect, it turns out.

She talked to Paul Marks about it because he was in hematological oncology, essentially; the leukemia area was one of this special areas. She talked to him about, "What could be going on here?" He decided he really had to talk to a chemist about what on earth could be going on. So he came down to talk to me because we knew each other, and said, "This is going on. What could be going on here? What, if anything, can we do about it?" The level of DMSO that was required to differentiate these cells was about 280 mM [micromolar]. So if you took a guess that you were going to use this as a technique to deal with human cancer, you'd have to titrate people up to a level that was preposterous and so nobody really thought that was a serious possibility.

Well, the first thing we did was to see whether just polar solvents in general did this, and whether it had anything special to do with methyl metabolism or things of that kind, which it could have. It didn't. It was just polar solvents. In fact, amides were better than DMSO, acetamide, things like that, dimethylacetamide—these were better than DMSO, but not a lot better. You still needed like 100 mM, so you hadn't gained much.

So then I had to guess, "Well, how can we make this whole thing better?" I said, "Well, maybe if we're lucky, the reason you need so much is that there are two pockets into which you bind, and those pockets might be nearby, and if so—"

GORTLER: This was just a guess on your part?

BRESLOW: It was a guess. We knew nothing. Now we know where these things go, but at the time, we didn't know anything. We said, "Maybe there are two pockets into which they go, and maybe these pockets are close enough that we can take advantage of the chelate effect and we can lump two of them together," so that when one goes in, the other one is sort of automatically there, and you'll get much stronger binding than you would with separate molecules. So I explained this to a post-doc—a very, very smart guy—and he said, "Well, this is all very amusing, but because we know nothing about all this. By the way, what kind of linkers should we put between these two things to [laughter] bind to these hypothetical pockets?" I said, "Well, look, the truth is, we don't know whether it will work, but it's not hard to find out. Every chemist knows that when in doubt, the number six is the magic number. So put six methylene groups between each one [laughter] and let's see what happens."

It turns out, he made the molecule. He put it in. It was about one hundred times more effective. That is, we were down to 1 mM, instead of 100 mM for simple amides, and furthermore, six was the magic number. That is, when we varied the methylenes, five was not as good, seven was not as good. We had a curve that peaked at six.

GORTLER: You started with hexamethylenediamine or something like that?

BRESLOW: Yes, hexamethylenediamine, and you just made a bis-acetamide. We started essentially with nylon, more or less. A highly available compound. That compound is called hexamethylenebisacetamide [HMBA], and that compound actually had been studied quite extensively and it turns out that it was very effective, not just against these Charlotte Friend pre-erythrocytes. I mean, it differentiated them all very well. But then it did a lot of other things, too. We looked at human cell tumors of various kinds. There was a so-called "HT29," which is a colon tumor, there was a normal human leukemia, tumor—not this funny erythro-leukemia disfunction. These cells were also differentiated so that they quit multiplying and they essentially behaved like normal adult cells. Then we looked at developed tumors with this compound and we were able to arrest the growth of those tumors.

GORTLER: Now, we're talking twenty years ago. Or fifteen years ago.

BRESLOW: Yes. Exactly. A long time ago. We were able to get some results out of that. The dose that was required was still awfully high, and we weren't really happy with that, but that's what we had. You know, 1 mM is still a lot of stuff. Hexamethylenebisacetamide has a problem that it de-acetylates and you make diamines, and you don't want all those diamines floating around at decent levels, you know. So that was a problem. We weren't happy about that.

But anyhow, the compound looked pretty good and so they filed a so-called "IND" [Investigational New Drug application] and they got permission to do clinical trials with this stuff, because they showed it wasn't a big problem in animals, and they went into dogs and there was no great toxicity of the stuff. So they went in and they had a group of patients that they studied for a particular form of leukemia, and most of those patients got a good response right away and many of them who had been sick in bed, got up and were able to walk around, et cetera, but most of them eventually succumbed. We were not ever able to get blood levels of these people up to what we thought we needed in order to do this. So in fact, eventually, the disease took over. But for a while at least we had knocked it out.

One patient, one remarkable patient of this group was for some reason—her disease was particularly susceptible to this stuff, and she's still alive. She was supposed to be dead in two months.

GORTLER: This was how long ago?

BRESLOW: This was about twelve years ago now. She's still alive. So, for her, this has been an enormous success. She had so-called "non-small cell lung cancer," which is what smokers get. She had this disease, and it was roaring along, and she'd been through every normal treatment and they couldn't control it. She went on our stuff and after a year—you know, they didn't want to biopsy the lung because that's a very invasive, so they were taking x-rays—they couldn't see any sign of the tumor. It had just essentially stopped growing and then had disappeared.

GORTLER: This is HMBA?

BRESLOW: HMBA, yes. After a year or so, we convinced her that she didn't have to continue to take the stuff because our studies had shown that if we exposed tissue culture for a significant length of time, then the transformation was permanent. If we took the stuff away early, then the cells reverted. But if they were exposed for a significant length of time, then the transformation was permanent. So that seems to be true with her anyway. She's not on the drug.

But for most people, obviously, the doses required were not appealing, and so we knew that this hexamethylenebisacetamide was one way of making a bis-amide, but you could also turn the amide group around and have the nitrogen on the outside, and that also was effective. And just about equal. But not any better. But then I decided that if we thought about this seriously, you have to ask, "Well, what are we binding to?" I mean, amides either make hydrogen bonds or they bind to metals; there's really nothing else you can do with an amide. In either case, a hydroxamic acid is going to be a better ligand; it's going to make more hydrogen bonds and if it's a metal that you're targeting, which in fact we now know is true, then the hydroxamic acid is going to be a better group. So we made a bis-hydroxamic acid, and we got another 10^2 [one hundred fold] efficacy. So now we were talking about things down in the sort of middle micromolar region—20-30 mM, that kind of thing. So that was pretty good. We made a number of compounds like that with different spacers. You know, we weren't just putting six methylenes in there. We had all kinds of benzene rings and that sort. Some of these things were really quite interesting. We put some rigidification into those spacers, and some of that was helpful. But you know, not hugely. We never really made a big breakthrough there.

But then I decided that we had no evidence at all that both ends had to be hydroxamic acids and it seemed unlikely in a way that both ends were doing the same thing. Why would that be true? So we decided, "Well let's at least find out whether there may be a hydrophobic group on one end that would do something if you're doing any protein binding off in the pockets into which things bind." So we made a compound with a hydroxamic acid at one end, and a benzene amide at the other end, and made various versions of that. That gave us another factor, I guess a little more than a factor of ten. So we got down to the region of relatively low mM, but still not into the nanomolar region. We were at about 1 or 2 mM for the differentiation induction. That compound is the compound that we call SAHA, an acronym for suberoyl anilide hydroxamate. The base was suberic acid, a dicarboxylic acid. We had an anilide at one end and at the other end was a hydroxamic acid. That was SAHA.

That compound turned out to be very interesting, and that has been through a lot of studies, and a compound closely related to that is the one that's going to go into the clinic, as far as we know, this summer. There are two exciting things that were done with SAHA. For one thing, it was put into mice that have so-called "xenografts," that is, that have foreign tumors in them, so-called "nude mice." You know, these are mice that don't reject things that easily, so you can put a human tumor into a mouse and the mouse will not reject it automatically. So some of that was done, and we got regression of those tumors. But then more seriously, two things were done, and a collection of our best compounds were sent down to the National Cancer Institute. They have a library, I think, of close to seventy human tumor cell lines, and they looked at these with our compounds, including SAHA, and they all stopped growing. Some of them simply stopped growing and were still viable. Some of them went into what's called "programmed death," apoptosis. But apoptosis is a state that cells can go into, which is essentially—if you're screwing up what it is they would like to do, they decide, "To hell with this," and they stop. But it's not anything that happens to normal cells. So the cancer cells were doing this. So that was fine. We were killing them selectively because they went into this programmed cell death, and then some of them simply stopped growing.

So then what was also done was to take these human cancers—this was done at the National Cancer Institute now—and put them into porous tubes that were implanted in the peritoneum of rats and then you don't have to worry about doing it in mice or anything like that, because the rats can't interfere with those human tumor cells because they're not in contact because they're inside a porous tube, but drugs can diffuse into the implant. So then the drugs were administered to the animals, and so they were processed—whatever the animal did to them—and then at some point diffused into the peritoneal tubes. We got tremendous response. I mean, the National Cancer Institute said they had never seen such a collection of highly effective compounds, and so we had to zero in on which were the best. So we went in and picked out two of them that looked great, and one of them was closely related to SAHA, but the difference from SAHA is that instead of having a benzene ring, we had a pyridine ring. It's about as hydrophobic, but it gives a little better water solubility and a little better ability, therefore, to be used as a drug in various ways. So the one that's actually going to fly, I think, is the one that is SAHA except that instead of an anilide, it's an amino pyridine that one has in there. It's almost the same compound, but as I say, it's better soluble, and it turns out that was important for some of the toxicity studies.

Anyhow, feeding studies were also done—and that may be the group that you were mentioning, this other operation—with SAHA, and that was put into the feed of rats and then a control group just ate their normal feed. The bunch that ate the food that had SAHA in it didn't mind it. I mean, they ate the feed perfectly well, no funny things happened. You look for the drug to do bad things to rats; for example, they start losing their hair—these didn't lose any. Or they start doing funny things, if there's any neurological effects—there were none. The rats behaved normally, and then they were all injected with nitrosomethylurea. The control group all got massive mammary tumors, and ours got many fewer, and they were small and didn't seem to be much of a problem. You know, little lumps. So it's not as if nothing happened to them with nitrosomethylurea, but whatever happened to them didn't seem to be a big problem compared to the control group. So the guy who does this work has done a lot of feeding experiments trying to look at the so-called "chemopreventive agents," and he said he's never seen anything as good as that. That was good. He's talking about the results plus his own experience.

GORTLER: This is here or at the National Institute?

BRESLOW: This is at that Institute somewhere. We didn't do any feeding. This is the guy who does this stuff for a living, a guy named Cohen. So that, plus their own experience, convinced the National Cancer Institute that they had something really good, and so they then started a serious study on the pre-clinical toxicology, and they did rats and they did dogs. They didn't see any big problems. The closest to any problem at all was when dogs were on a seven-day infusion of the compound—you know, infusing it directly into their veins. At first, white cell counts went down a bit, but then they came back, even though the drug was still being administered. They said they'd never seen that either, because most things knocked down white cells because they're tremendously sensitive, and any kind of toxic compound knocks them

down, but either we knocked them down and for some reason they recovered, or we were just temporarily shunting them into some kind of a reservoir somewhere. We don't know what happened. We don't know why this happened.

But anyhow, the white cells came back to normal, even though the drug was being administered, and so they're very excited about that, and so they are now doing the last part of the toxicology that you really have to do before you can go to the FDA [Food and Drug Administration], which is another set of studies with animals, using now drugs manufactured by what are called "Good Manufacturing Processes," that is where they have a contractor who can make this stuff in bulk. It's an easy compound to make. We gave them the procedure, but it's an easy compound to make. He's made this stuff in bulk, and he's made it carefully in such a way that it's an absolutely reproducible lot so that whatever we learn with animals, we're going to be able to take the same kind of material and put it in humans. You have to do that. So that's going on right now. It's going into the animals, and the animals are not only being looked at for gross symptoms, but they're being looked at very carefully by pathologists, looking at all the tissues to see that no funny things have happened of any kind. You don't know until the thing is over that it's all right, but I think it's awfully unlikely there's a problem because we've never seen any symptoms or anything before.

So, assuming that this pre-clinical tox works all right, we should go into Phase I some time in the summer. They're talking about July or August at the latest for this stage. So we'll go into Phase I clinical trials and see what happens with humans with this stuff.

GORTLER: That's very exciting.

BRESLOW: It has tremendous potential.

GORTLER: Are they looking at specific types of cancer patients now?

BRESLOW: Well, they're not in human trials yet.

GORTLER: I mean when they—

BRESLOW: But when they do, yes, you generally have to do that. Your Phase I trials, in principle what you're trying to find out is whether the drug is tolerated by humans. Are there any adverse effects that you hadn't thought of? Of course, it's hard to imagine adverse effects worse than the disease itself, so you have to be a little bit careful about saying, "Well, suppose it caused a brittleness of your hair?" or something. I mean, who would worry about crap like that, you know? This is a serious disease we're dealing with here. So the chances that there'll be a

problem I think are small, and people are already talking about when they finish Phase I, how we're going to do Phase II. In Phase II you go after serious business, where you're supposed to be trying to demonstrate that you're actually curing disease. Phase I you're supposed to be looking for serious side effects, but in real life, what you always do, is you do it in cancer patients—because after all, people have to have a reason to volunteer, and so besides everything else, you also say, "And, oh, by the way, did it help?" So that's what goes on in Phase I. Then Phase II, it's a serious effort to do that. Double blind studies, that kind of thing. Then Phase III, and then you're out into the world.

I think it's tremendously exciting. I think that the only ambiguity is: will somebody come up with something better? But that's fine. You know, what kind of a downside is that? But, if nobody comes up with something better than this, I think this has really interesting potential, and it's rather broad. That is, we have not found any cell types in tissue culture that don't respond to this stuff. I mean, it does so-called "neuroblastomas," which means you're going to go after brain tumors, and yet it does also leukemia. Some things are better responsive than others, and some compounds are better at some things than others in the NCI tests. That was part of the criteria we used in picking compounds. We picked the compound that looked like, among other things, the best broad-spectrum material, which is what this SAHA is. Some of the other compounds were a little better at some things, but they weren't quite as good at something else, so this is the best broad-spectrum drug.

I think it's very exciting, and we'll have to see how it all works out. We've been talking to drug companies. We've been talking to an outfit that acts as agents between academic discoveries and companies. We've got to find ourselves a good industrial partner, because we're not interested in setting up a company. You know, we are not interested in making money out of this. We just want to get it out. So our best bet is to find a company that will really push it out and has the resources to finance the clinical trials and all the rest and get it going.

If it really works, it's a crime in a way that it has taken so long to get to this point. But part of it, honestly, has been that we keep getting better compounds and we're still working on it. I have three people now working in the lab. They're interesting people. One is an M.D./Ph.D. student. He spent two years in medical school and now he's getting four years here for a Ph.D. and then one year in medical school again. He'll get an M.D. and a Ph.D., and he's an excellent chemist. He was a Dartmouth [College] chemistry major undergraduate and really did a lot of research at Dartmouth. So he's excellent and he's knocking this stuff out. Then I've got another graduate student, a very good graduate student, who's also working, just a straight organic graduate student. Then there's a woman from Japan who's come over, who's a medicinal chemist, and she's going to be working in my lab for not quite half a year—on their expense—just to sort of find out what we do over here, and she's knocking out compounds. So we think, one way or the other, we can probably get better compounds. That's always what you want.

But the NCI's position is interesting. They say, "Look, this compound is not toxic. It's effective. It's chemically stable, and it's easy to make. You put that all together, and you don't

necessarily need a better compound." I mean, the estimate for a human dose would be on the order of an aspirin tablet of a fairly easily available compound. So suppose we could make it one hundred times more effective? Do we know that we wouldn't bring in toxicity? So who knows? Their position is, "Look, this is what we want to do, and let's make sure that this type of thing really is effective in humans. Then we can always worry about better compounds later."

Anyhow, so we're in the better compound game, because I think that's what we need to do. We're trying to make back-ups so in case something funny happens with this one, we'll have something behind it. We have four or five compounds already that are comparable to it. That's why we had to choose at the NCI which one to go with. No, it's pretty good stuff, there's no question about it. It's not very physical organic. But it started with a physical organic idea. The chelate effect. [laughter] After that, it took off.

GORTLER: Yes. I think I've finished most of the chemical work. But you've been here at Columbia for almost forty-four years. What major changes have you seen take place?

BRESLOW: Let's see. I came here in 1956. Yes, you're right. I didn't realize it was that long. Well, there have been huge changes in the place, thank God! It was, when I came here, a rather parochial place. They were a little frightened because at one point, they knew they had been a great institution and they couldn't figure out quite what had happened, you know. They were slipping. Part of the problem was that they did not have a very effective fund-raising operation, and part of the problem was that they were horribly inbred. A good fraction of the faculty did both their undergraduate and their graduate degrees here and then stayed on. I mean, it's ridiculous. Everybody has some of that. Harvard, frankly, has more of it than they'll admit to, but still, it was horribly inbred. But not in the chemistry department. The chemistry department was pretty good. But that also extended to the administration, so they knew the Columbia way of doing things, and you didn't change it. It was really paralyzed.

So a number of things changed, and some of them actually I had some role in. The one that I think was probably the most important for the Columbia undergraduate population was that I became chairman of the committee to make the place co-ed, because we were a male college.

GORTLER: Except the females were across the street.

BRESLOW: Well, I know. We had Barnard College, but Barnard College is not truly part of Columbia. It has an affiliate arrangement. They have their own endowment. They have their own president, their own board of trustees, their own faculty. They really are a separate small college, which happens to have a very close connection. So everybody figured that the way for us to become co-ed was to somehow arrange a thing where we would absorb Barnard. They

said that Barnard would be to Columbia as Radcliffe [College] is to Harvard. Sort of a name but not a real separate—well, Radcliffe is not a separate institution. But Barnard is. They said, "Well, we have to do that because if we went co-ed on our own, that would kill Barnard," and that was always the argument: that an all-female Barnard couldn't possibly survive a co-ed Columbia next to it. I was convinced that I had to deal with that question because there was no other way of dealing with this. At one point, the president said to me that they were afraid if we went co-ed, that we would have a corpse as a partner, and so they were frightened of it.

[END OF TAPE, SIDE 2]

BRESLOW: All right. So the question is: would it really do Barnard in? Because if it would do Barnard in, then we would have to press on with trying to absorb them somehow, which was certainly a tough fight. The faculty were totally uninterested in being absorbed, and they correctly figured that whatever we said about how we would all be co-equals, that they probably wouldn't be treated in the same way because they were a small college faculty, different from a research university faculty. Anyhow, what I did was I decided to just survey the country to find all the places where a male college had gone co-ed and had had a female coordinate college that had stayed female. There turned out to be a remarkable number of them. I mean, one of the well-known ones, for instance, was [University of] Notre Dame, which went co-ed and left Saint Mary's [College], which is right across the street from them, as a female college. Notre Dame originally was going to try to absorb Saint Mary's and become a single co-ed college, and the people at Saint Mary's resisted being absorbed, and so finally Notre Dame went co-ed, and everybody said, "That's the end of Saint Mary's." So I contacted the people involved and did it happen? The answer was that everybody knew they would be dead, but they weren't. This happened in place after place. Goucher [College] was a coordinate college of Johns Hopkins [University] and Johns Hopkins went co-ed, and everybody said, "That'll be the end of Goucher." It had no effect at all on them. When Amherst [College] went co-ed, everybody said, "That's going to be the end of Mount Holyoke [College]," and of course it had no effect at all on it. So I found about seven or eight places that had gone through this nonsense with the same pattern. Everybody said, "That's going to be the end of them." It wasn't. So I put all that stuff together, and I also put together an analysis of who were the women who went to Barnard and who were the women we were likely to attract. There was a small overlap. The girls who wanted the best place they could go to in New York—maybe they had husbands who were lawyers in New York or whatever—all went to Barnard and many of them would, in fact, go here, and I think that has turned out to be true. But really, other than that, the population was rather different. There's a serious, interesting population of girls who like to go to an all-female college where they will be—first of all, it's a small college; they'll have much better contact with their faculty; they will be the heads of all the organizations; they won't have to sit around and try to look pretty for the men in the class. There's a serious group of people who want to do that, and so we went co-ed. I convinced the president and the president convinced the trustees that this was not going to kill Barnard, and in fact, it did not.

GORTLER: Did Barnard College students take courses at Columbia?

BRESLOW: They have always done that. They've always taken courses here, and we actually allow Columbia people to take courses there. There are courses they give there that we don't; there are courses at a different time, spring versus fall, that kind of thing. There's always been back and forth. We even shared dormitories with them at one point. So it wasn't such a drastic change. The main change was we suddenly brought women into the place. The first year that we were co-ed, our incoming class was 45 percent female. There was this tremendous pool of people waiting to come here if they could [laughter], and we now have a percentage of that order, and frankly, if you look at the prize winners in the place, I don't want to insult the men, but the women win more prizes than the men do here. I mean, we get very good women here. Yet Barnard is doing extremely well, because Barnard finally had to pull up its socks. They also knew that there was the Barnard way of doing things. I mean, to give you an example of the idiocy that had to be changed, freshman had the lowest priority for dormitory rooms. The seniors had the highest priority, and the freshmen got them if there were any left. Well, that's completely mindless. Now they changed it. Now at least the freshmen all get dorm rooms and the seniors can go off and rent an apartment if they have to, and any sensible person would know that's what you do [laughter], but they didn't do it.

So anyhow, various things of that kind went on, and the place got better and better here, I think, as a result of various forces. This happened to be one in which I was heavily involved. But a lot of very good things went on. One of the biggest things that went on, frankly, was the increasingly better presidents. I was the chairman, actually, of a committee to get Bill [William J.] McGill at the time when the place had really gone through this tremendous uproar. I was the chairman of the Faculty Committee, and then the Faculty and the Student Committee joined, so then I was the chairman of that. There was also a Trustees' Committee. But Bill had been a former faculty member at Columbia, and he fundamentally wanted—you know, he talked to both groups, but I was the one he really talked to, and so at a certain point, when we offered him the job, he called me up and asked me to go out and convince him that he should come.

GORTLER: He was where at the time?

BRESLOW: He was at the University of California, San Diego. So I went out there in February. You know what New York weather is like in February. I got out there. Whales were spouting. People were swimming on the beach. [laughter] My job was to convince him to leave all that and come to New York.

GORTLER: It's hard to go from La Jolla to— [laughter]

BRESLOW: Well, but it was possible. What I said to him, in so many words, is, "Look, you're too young to retire. This is a great place for retirement, but if you're in the middle of New York, you're going to be in the middle of the action, and you're going to really have a chance to make a difference," and whatever. For whatever reason, he came. I think he was a big help. Then after Bill McGill, Mike [Michael I.] Sovern took over, and he was probably the best of the potential internal Columbia people. He really knew the place very well, and had been dean of the law school. He was a brilliant person, and he really got an awful lot of stuff going. He was really very helpful. Then after Mike, we got the current person, George Rupp, and George Rupp had been the president at Rice University in Houston. For various reasons, his disagreement with the board down there—he was looking for another job. He wanted to run a big fund drive at Rice and they didn't want to do it because they knew they'd be tapped, and you know, that's just the kind of guy you want. A guy who's unhappy with a place because they're not willing to let him raise money.

So he came here and he has been wonderfully effective and he's been the first president that Columbia's had, at least in living memory—maybe forever—that has not started out as a Columbia person already. So he came in with a fresh view and looked at the place and said, "There are things here that make no sense." He's a quiet, nice man, but things have changed here in very important ways. He's expanded the undergraduate body. At one point, Columbia was sort of a special place with a very strong graduate school and not very many undergraduates. Way back, not so far back in its history, but somewhat back in its history, we were churning out a large fraction of the Ph.D.'s in the country because not everybody was doing that. But everybody's doing that stuff now. So we weren't unique in that area, and therefore we were increasingly in a situation where—how many English Ph.D.'s do you need? Meanwhile, the college is awfully small and we don't have that many college alumni, and we don't have that much tuition coming in from the kids. So he's changed all that, and he has re-balanced the place in an important way. Sensible people have been brought in from the outside who know how the real world operates, so that suddenly money is available for research in ways that it never was before because people understand that that's what you have to do if you're going to keep the place strong. Very good hires are being made. It doesn't hurt any that New York has come back enormously. The reputation of New York is terrific. So we've hired a number of very good people away from Harvard that they didn't want to lose. I mean, it's a very different world now from the way it was, because I know Jeremy [R.] Knowles, who's the dean at Harvard, very well, and he's quite unhappy about some of the people we've managed to steal from them, and we've managed to hold people here against Harvard offers that might well have left before, but have not left now. So I mean, I think in general, we're doing pretty well.

The place is looking good, but it's tied to the fortunes of New York. I would say if New York takes a dive, goes into some of the kinds of problems we had with previous mayors, we could have troubles again.

GORTLER: You were chairman of the chemistry department from 1976 to 1979.

BRESLOW: Yes. We do that here. We have a rule that you can only be a chairman for three years. You cannot succeed yourself. That was done for special reasons at one point, but I think we're all happy with it, because it means that at the end of the three years, instead of people saying, "Oh, maybe we could talk him into staying on," they have to face seriously the issue of whom they can get. Most people have, let's say, at least one good thing they will do as chairman. So if you can get a good thing every three years, it's better than a good thing every six years. So I was chairman for three years.

GORTLER: Do you remember your good thing?

BRESLOW: Well, I would say the best of the good things I did was to start the move to improve the facilities here, because they really stunk. At one point, I produced a document for the trustees that demonstrated that for six million dollars, they could really do wonderful, wonderful things and bring the chemistry department up to the kind of space they needed. Well, eventually they approved it, and it came in at more or less the same number. I don't remember if it was actually sixty million, not six million. [laughter] But it was only off by a factor of ten. Part of that was because it took them so long to do it, but I don't think inflation took the whole factor of ten there. Part of it was that there were many things that needed to be done. An addition was put on the building and a huge renovation was done of the 1898 Havemeyer Building, so now it's absolutely first class. This one [Chandler Laboratory], in a way now, is a poor relation. My labs they redid because a very nice man who was on the visiting committee to this department at one point wrote a report saying that my labs were a disgrace, worse than anything he's seen in the third world and a menace to the students! At that point, my star was very high because I think they had just made me University Professor or whatever, and so they forked over some money and redid my labs. My labs are nice. So now the rest of this building is going to be done, and that's this architect's meeting this afternoon.

So I would say getting the facilities going well, and then there were a certain number of academic hiring things I did, and holding onto people. But, you know, the university has been pretty good. We had one faculty member who had an offer from a very good place for a 50 percent increase in his salary, and I just went to the administration and they forked over the 50 percent increase. They said, "Whatever it takes, we do." That's pretty good. So we held onto an extremely good person that way. A certain amount of that day-to-day stuff you do. You hire people, you try to keep your faculty happy, keep them from quitting, stuff like that. But in terms of initiatives, that was mine. Koji Nakanishi was the chairman a few years ago and he started an industrial affiliates program that's been very effective with a lot of companies now affiliated with us, and a lot of meetings with them, and money coming in from them, you know. So everybody has their thing that they do, and that's been very good so far.

GORTLER: So the department has also changed in ways. Has it gotten a lot bigger?

BRESLOW: It's not gotten a lot bigger. It is growing in a good way. See, the problem is, to some extent, you get a certain amount of turnover—you know, some people leave. I mean, we certainly have lost some extremely good people. Mostly the inorganic area has been somewhat unstable. If you take a look at the people who've left this department in inorganic chemistry, you'd put together the best inorganic chemistry department in the world. I mean, you've got Harry Gray, you've got Jackie [Jacqueline K.] Barton, you've got Walter [G.] Klemperer. There were others. I mean, I'm probably ignoring one of the other very good people, but some very good—Steve [Steven] Lippard, of course. Yes. So very good people left over time, and so we keep hiring. But you have to hire at a decent rate to stay even with people retiring, and occasional deaths. I mean, Brian [E.] Bent, a young man, died. That was a real loss. He was a brilliant guy. So you have to do a certain amount just to stay even. But we're pulling ahead now. Our goal is to get up to some number like twenty-three or twenty-four. I think we can do that. We're probably around twenty now, I think, or something like that. So we're creeping up there slowly but surely, but we're hiring very good people, I think. The place has proven to be fairly attractive. We've hired good people against some very good outside offers. A lot of people like the idea of living in New York. I mean, for grown-ups it's a playland, you know. It's a great place. [laughter]

GORTLER: In addition to running a major research program, you've been very much involved in teaching of undergraduate and graduate students.

BRESLOW: Yes.

GORTLER: Tell me a little about how important teaching's been in terms of your life and also your research programs.

BRESLOW: Yes. Well, I like it. I must say, I know there are people who are very good research people who don't like to teach, but I think it's mainly because they're not convinced that they do it well. I think most people, if they're at all excited about their field, would like to get other people excited. But if they find that classroom experience, the kids always hate it, or whatever, you can imagine that people wouldn't enjoy it after a while. I don't think we have anybody in that category now, frankly, here. We have had, in the past, some people who were outstanding research people but, let's say, just not awfully good at teaching. One shocking example is Louis Hammett.

GORTLER: Yes.

BRESLOW: Louis Hammett was a brilliant research person, but his classes were generally considered to be paralyzingly bad by the kids. So I don't know that he enjoyed it. Probably not.

It's hard to say how you enjoy that kind of thing. But I enjoy it. It makes you think about things you don't always think about, which is the real thing. You can't just spend the whole term teaching your research. I mean, there's no way to do that. So you've got to think about things you don't otherwise think about. I think that broadens your horizons. There certainly are research ideas that have come out of thinking about things as a result of teaching. There's no question that it does that. Also, frankly, the kids are fun. Part of our business is producing research; part of our business is producing educated people, and that part is fun, too. We get very good students here. When I first came here—I think I probably mentioned this somewhere, probably in that Priestley address—one of the first undergraduates I ran into was Roald Hoffmann. When you get people like that, it gives you a pretty good sense of what the place could be. So we get very good people. But Roald Hoffmann is not the only one. I mean, there are a lot of people out there who've done extremely well, who were undergraduates with me. There always are good undergraduates, and even frankly, the people who do well in the course, go on, become physicians, maybe very successful physicians, but not necessarily names in the world of science. Those kids are still fun, because you run into them and they all tell you how great it was and all that. I won the two teaching awards that they have here, so that's a help. It makes you feel, "Well, gee, maybe it's working." So that makes you feel good. Frankly, research doesn't always go well every day and so it's not bad to say, "Well, I don't know how this project is going but at least I gave a pretty good lecture today and it really turned some people on." So that part is good. I think teaching is an important part of chemistry and it's part of our job, but I think it is very important that it be in the correct proportion. When I came here, I think the teaching load was about twice what it is now, and it was too much. Especially if you were starting. There was one semester when I was teaching two different courses and trying to get a research program going. Maybe that doesn't sound like a lot, but if you're really trying to do other things, it was too much. But now I think the teaching load is right. It's competitive with that of our best competitors. I mean, some people on the quarter system, they do it differently, but fundamentally we are like MIT, we're probably like Harvard pretty much, we're probably like Stanford [University]—

GORTLER: What do you teach? One course a semester, or one course a year?

BRESLOW: No. We teach one-and-a-half a year. So we'll teach one course one semester and then we'll have a shared course one other semester, and that's what our number is. That's a number that I more or less instituted at one point because it became clear to me when I analyzed the thing that we could do that, and I knew what was going on at MIT and it was less than what we were doing, and I thought we really can't afford to be non-competitive if we want to hire people. You know, young people looking at it will say, "Gee, I'll go there where you have more chance to do research."

I think that works out all right. I mean, I'm right now giving my full course. I'm giving a full course in bio-organic chemistry. It's got a bunch of seniors and even one junior in it, and it's got a bunch of graduate students, and it's got a big pile of post-docs auditing the course because it's a special course. Then in the fall, Tommy [Thomas J.] Katz and I shared an

advanced organic course, which was, again, undergraduates and first year graduate students. It was a physical organic course, and he taught the first half and I taught the second half. The advantage of that kind of plan is that then I have a half a semester when I don't have a teaching commitment. It doesn't mean I'm not here, but it does mean that if I have to go off and give some lecture series somewhere or whatever, I put it into that time. If somebody wants me to go to Japan, I do it then, rather than have to deal with missing classes. So there's no question, the teaching's enjoyable. I like it a lot. Well, you have to be somewhat of a performer to do well in this business, and you get up in front of this class and you do this stuff, and it's fun.

GORTLER: Yes, I understand. You've also written a couple of books. The one I'm most familiar with is *Organic Reaction Mechanisms* (25). It's been pretty widely used. How did that happen?

BRESLOW: Yes. Well, what happened there—there was a man, a Greek tragic figure. His name was Bill [William] Benjamin, who started the Benjamin Publishing Company, and for a while, he wanted to do small books. His idea was supplementary books, not the big textbooks, but the idea that it would publish things that people could use as supplements. I guess he asked me and Martin Karplus to be co-editors on this project, and Martin was to do the physical part and I was to do the organic part. Eventually I concluded that really the place we should go after was probably the senior level. That is, if you looked at undergraduate education, there were good books for freshmen, there were good books for sophomores. Some people take physical chemistry, there were good books for that. But in the senior year, you could make a good case for a special topics course where they did a certain amount of something—that kind of thing. It was an ideal thing to do in the senior year. In small colleges and places of that sort, where people didn't necessarily have graduate courses that they could feed into. So I decided to do that and I started and got a number of people involved in it and decided that I myself would do the mechanisms book. So that's how it got started. That was fun. That was an interesting thing to do. But, you know, it takes time. So I upgraded it once only for the—I guess we had a second edition. That was upgraded a little bit, and then people keep asking me to upgrade it again, and I did this for a German translation. The German translation was done rather later than some of the others. The thing is in about—I don't know—I've got all the different versions of it up there. It's eight or ten languages. I don't remember which one. But it's been translated in a lot of places and heavily used in a lot of countries. Everywhere I go in the world, people say, "Oh, I used your book," you know, that kind of stuff.

GORTLER: What happened to Benjamin Publishing? Were they just taken over by somebody else?

BRESLOW: Well, Bill himself, as I say, was a tragic figure. He was a person who couldn't live with success. As long as he was struggling his way up, he was terrific. As soon as he was reasonably successful, he became kind of wild. He would bring his girlfriends into the office,

where his wife was working. I mean, just crazy stuff. Just absolutely wild. You know? He just couldn't handle that situation. So he sort of fell apart. The company then fell apart as a result and it became Benjamin-Cummings. It was sold to somebody, et cetera, and it sort of exists now, I guess, in some form or other. Somebody told me they'd seen him recently in Florida or something. He's still around, but it was a shame. He was absolutely brilliant at getting these things started, and he had wonderful ideas. For instance, he got a place on Martha's Vineyard and got authors to stay on this place and they would work away during the day and then they'd do who-knows-what, but the point is, he got them really beavering away because there they were, you know, sitting in his place while he was around. He had a number of really great things he did. Jack Roberts was very heavily involved with Bill Benjamin. You know, Jack still has kept up with Bill. I haven't kept up with him much. I mean, I eventually got really irritated with his behavior because I thought it was preposterous. He had a lovely wife and he really treated her brutally and eventually that fell apart. So in various ways I just did not admire Benjamin, the person, as distinguished from Benjamin, the book publisher, who was very effective.

GORTLER: You've recently published a book with ACS called *Chemistry Today and Tomorrow* (26). I'm not familiar with that one so—

BRESLOW: I'll give you a copy if you want. I've got a box of them over here.

GORTLER: How did that project start? What was the intent?

BRESLOW: Well, the intent was the following. At that point, I was president-elect of the ACS, and I asked, "What can I do with the presidency that would be helpful?" I decided that one of the things that the presidency of the ACS would do would: a) give me credibility for a book aimed at the general public about what's so great about chemistry; and b) give me, probably, financial support for getting that book distributed so that you didn't have to just sell it on the street and hope people bought it. I really was very unhappy about the general image of chemistry and the extent to which people didn't know: a) what we had done; and b) what were the prospects in the future that chemistry would contribute. So I decided to write the book and take advantage of this ACS connection, particularly being president, in order to get it out. So I wrote it, and I wrote it actually pretty fast, I must say. I think I started in June and it was ready by December or whatever, because it was easy to do, and I took advantage of a lot of my contacts. I contacted an awful lot of smart people in the country, and even some not in the country, and said, "Look, I'm writing a book on the past and the future of chemistry, and the past I think I can do, but do you have any ideas yourself about what you think chemistry is going to contribute in the future?" I acknowledge all those people in the book. I got some pretty good ideas from some of these people. There are people like George [M.] Whitesides, a very thoughtful guy. You know, George has a lot of good ideas. So George was very helpful. A lot of people had very interesting ideas. Bob [Robert G.] Bergman, my former post-doc, had

really some very nice ideas. I don't want to just single them out, but I just remember those two in particular as having made very good contributions in terms of, "Well, here are some of the things I think we're all going to do."

So anyhow, I used those ideas, and obviously my own—I acknowledged them, but I didn't just copy what they wrote—to put this thing together. Then what we've used it for, which has been very effective, is in all the dealings with the Congress. I've always found ways of using this book because it is written at a level at which you don't have to be a chemist in order to read it. At the end of the book, I do a little about how chemists actually make a new molecule, and I might show a few structures, but even there I explain what they are and they're not too complicated. But the early part, you really don't have to know any chemistry to do, and I bounced it off people; I have a very good friend of mine, a neighbor, who's a literate person but no scientific background at all, and she was one of my major readers and she said, "I don't understand this section," so then I'd go back and try to figure out what to do about it. Margaret, my secretary, read a lot of it and was very helpful, too, and Madeleine Jacobs, the editor of *C&E News* [*Chemical and Engineering News*], was very helpful. She read the thing. She's used to communicating. There were a lot of people who were very helpful with this book, and so we got it written and put out and the ACS did a beautiful job of it and partly, as I say, because I had significant funds available as president for a special initiative and I decided this would be it, and then we've given it to Congresspeople and said, "Look, maybe your staff can use it. There's material in there they can work into speeches because we have some numbers there that are useful." People gave it to their high school kids. A lot of chemists have bought it and given it to their families so their families have some idea of what it is that daddy does and why should they care. So that has been helpful. I still have it around.

Now, it turns out in the meantime, the books division of ACS had a problem, because fundamentally, they published perfectly nice books, but they had no distribution mechanism that amounted to anything. I mean, they had nobody going around visiting bookstores and saying, "You should carry this book," or any of that kind of stuff. So I think they were fairly ineffective at that, so I said that I really wanted this co-published with a commercial publisher who would do a good job, and so we did go with Jones & Bartlett as a co-publisher. Jones & Bartlett at least were able to place it into colleges and universities, which is what they're fairly good at, and people have adopted this for these "Science for the Citizen" kind of courses, to some extent. I know places that have been using it in that kind of class, where kids are reading about science rather than doing science. So it's been used for that, and we also got it distributed—and this is one of the things I really cared about, and it was done through the ACS—we gave it away free to a huge number of high school chemistry teachers. One copy to all these people. The idea being that they could look at it themselves and they could also make it available to the kids, make it available in the libraries so that kids could see this thing. Because frankly, it's a very thinly disguised, but not false, depiction of what a great field chemistry is. It's what the whole thing is about, how great it is. What chemists are doing now to deal with things like the environmental problems that occurred in the past because people didn't pay enough attention. So things of that kind. I don't really gloss it over. I don't say, "Don't worry about that smoke." I mean, it's, "Don't do that." So it's had that effect.

I use it for all kinds of odd things. I just got a note from Rita [R.] Colwell, who's now the new head of NSF [National Science Foundation], congratulating me for the Priestley Medal, so I dropped a note saying, "I didn't realize you read *C&E News*, but since you do, perhaps you'll be interested in this." I sent her a copy of the book, you know. I mean, I'm pretty shamelessly tossing this thing around. I sent one to Pete [V.] Domenici. Pete Domenici, a very important senator, head of the Senate Finance Committee, was a high school chemistry teacher. Nobody knew this, but at one point, I was in Washington making some speech, and Pete Domenici was there and we were chatting afterwards, and he told me he taught chemistry in high school, and I said, "Oh, my God, this is a resource beyond belief!" So we've been trying to keep him as part of our family if we can, you know, the chemistry family, because he's an important figure. So I use it for that.

I even sent one to [President William Jefferson] Clinton's daughter [Chelsea Clinton]. Because she was, at that point, heading off to college, thinking about being a pre-med, and I said, "I thought if you were going to be interested in science, you might want to take a look at this, and the worst thing you do, you give it to your chemistry teacher in school." I have no idea what happened. I sent one to [Vice President] Al [Albert Arnold] Gore [Jr.] because he was supposedly interested in the environment. I said, "Well, you have a whole chapter here on chemistry approaches to the environment so you might find this useful. There's material in there your staff could use." I got back a letter that was purportedly from Gore. I have no idea whether it was. You can't tell this. I know I got a letter from Domenici, which was from Pete. I know that was because he talked about things that nobody else would have said. But Gore, a lovely letter back from him about the book. So I don't know. You know, it's possible that it makes a difference. You just have to keep plugging away.

GORTLER: Well, that's great.

BRESLOW: Well, you have to do this now. I mean, we all have to do it. We are the great invisible science. It's absolutely bizarre, and nobody knows what the contributions are. I mean, when I was president, I spent a lot of time working on this. I visited *The New York Times*, for instance, and talked to Malcolm [W.] Browne who was, after all, even a chemist by training and he's one of the science writers at *The New York Times*. Every Tuesday, a science section in *The New York Times* comes out. I said I was going to file a complaint that my copy of the *Times* was being delivered incomplete because the chemistry page was always missing from the science section. He laughed nicely, but in fact there is no chemistry in the thing still. So, for some reason, we just can't get that in, and we've got to figure out how to do it. I think most chemists feel that we don't want to devote our lives to something that the public pays no attention to and thinks we're just polluting the world. They have no idea the contributions. They have no idea that chemists invent drugs. I mean, they don't know any of this stuff. So that's in there, of course. Where the medicines come from and how the medicinal chemists find compounds.

GORTLER: Right. I think at one point, DuPont had this wonderful phrase—what was it?

BRESLOW: I think it was, "Better Living Through Chemistry."

GORTLER: People believed that for a long time.

BRESLOW: They dropped "Through Chemistry." I worked hard on them to try to get them to put that back in, and they won't do it, and they say they won't do it because they do things besides chemistry. Fine. We all do things besides chemistry. I drive a car, but so what? But the real thing is that they're, in fact, ashamed of their birth, and that's a crime. They're like immigrants who won't admit that their parents can't speak English very well. They just don't want to admit—

GORTLER: They certainly want to hide, for example, black powder, and things of that sort.

BRESLOW: Yes. They should be proud of who they are and what their strength is instead of pretending they're something else, pretending they're a life science company. Who are they kidding? Come on!

[END OF TAPE, SIDE 3]

GORTLER: You've been a consultant in industry since at least 1958.

BRESLOW: Yes. Way back.

GORTLER: Who have you consulted for and how do you think consulting fits into this whole picture?

BRESLOW: Well, I think it's a very good thing for both parties, honestly. I started off consulting with DuPont, probably 1958, maybe even earlier. I don't remember when I started. But I started consulting with DuPont very early. DuPont, at that point, had a program of signing up relatively young people who looked interesting. You know, they tended to do that. They picked up a lot of young people over the years. I found that a very interesting thing. I obviously didn't know much about industry, so I learned a fair amount about industry as a result of that. I also, of course, developed a lot of contacts there. I got to know Howard [E.] Simmons

quite well, for instance. A brilliant physical organic chemist who happened to be also in Central Research when he started, and eventually the head of Central Research. So I got to meet a lot of people, got exposed to a lot of different things and it made me think about things I don't always think about, and that never is a bad thing.

But I think what it does for them is it gives them a chance to expose stuff that otherwise is confidential. When we give a lecture, the question period is one of the important things for us. When somebody says, "Have you tried so-and-so?" We say, "Oh, my God, we never tried that. That's a great idea." They can't do that. They can't go out and give talks on stuff until it's so old and uninteresting that the company is willing to let them make it public, and in the middle of their research they really need somebody who'll hear their story and say, "Why don't you try so-and-so?" Or, "I really don't think that proves what you think it does." They don't have anybody who can do that. Within the company, people tend not to do that. The politics are such that you don't want to tell your supervisor you don't know quite what's going on, and you don't want to let a subordinate tell you something and make you look bad. So I mean, the whole thing is ridiculous. The political structure in all these companies is perfectly sensible, but it does make it hard for them to do the stuff internally.

So I find that it's very helpful for them. There are even crazy things that I find in some of the consulting where one outfit will tell me something that is really great, and then another outfit I'll talk to, in the same company, will have some problem they can't solve, and I'll say, "But you know, so-and-so has done this already." They'll say, "Oh, my God, I didn't know that." So you even are just helping to get communication back and forth, and also suggesting ideas, and also, frankly, what they get out of it is they get good contacts. I think all the companies where I have consulted, certainly DuPont, certainly Schering-Plough [Corporation] where I consult now—let's see, I'll tell you the places before we get too far off into other stuff. I started with DuPont, and then I went to Sterling Winthrop in Rensselaer, and that was because we were doing synthesis, but we also were doing some biochemical things related to thiamine, so somebody up there picked that up. It might have been Syd [Sydney] Archer. I'm not sure who picked that up. But they decided to get me as a consultant there. That was very good. So that was my first consulting in medicinal chemistry. I consulted with them for a long time. But then, Schering-Plough wanted me to consult in the steroid area because by then we were doing a lot of steroid functionalizations and there was stuff we knew about. So they first asked me to consult in the steroid area, and then they asked me to consult generally. Schering-Plough was twenty minutes from my house. I mean, I could go down there in the morning and do it all day and come back to the lab, and get things straightened out, which is what I still do. So that was very appealing. At that point, if I was going to be generally consulting with them, I couldn't also do another big drug company. So I quit going with Sterling and went with Schering.

Then at some point, fairly early in the game, I was involved with an operation which started off as a company called Synvar. It was a combination company of Syntex and Varian. This is in Palo Alto. Carl Djerassi called me up. He was, by then I think, organizing the thing or whatever. He asked me to be a consultant for it because essentially there was the organic part of it, which I did, but by then we were doing some computer calculations and I was a physical organic chemist, so he decided that combination might be a good thing for them. He asked me

to help find a president for the company, a director of research. And I did. I found one of my former lab partners, Ted Ullman, who was at that point at American Cyanamid [Company]. Ted was great. He was the director of research of that place up until a year or so ago, and Ted was terrific. So I then became a consultant with that operation and was with them for a very long time. Right from the founding. Essentially before the founding of the company, really, because I was helping to get it staffed. Then right up through a year or so ago. At a certain point, Ted left. The company was bought by somebody else. They began to change who they were. I decided I didn't need all that. Then there have been a few small operations that I've been involved in, in one way or another.

GORTLER: What did they finally end up producing?

BRESLOW: Well, he was going to do organic ferromagnets. The idea was you're going to take organic chemistry that Syntex knew, and the physics that the Varian people knew, and we were going to put that together in some way. The problem with it was it was all based on a theoretical model by a guy named Bill [William] Little, who was a physicist at Stanford. He said that there were certain structures that could be room temperature or even higher superconductors as a result of some sort of an interaction of dyes with a conducting site. What you need for a superconductor—you've got to get so-called "Cooper pairs." That is, when an electron passes by, it will repel other electrons, but in superconductors, another electron is attracted, and the reason it's attracted is when the first one passes, it causes some sort of a polarization in the system which then is attractive to the second electron so you get this pairing business, and that's what you need to make a superconductor. Little had this theory about how a polarizable organic dye would be able to do that, and so the company was founded for that, but of course, you can't found a company on an untested principle which half the physicists in the world were convinced wouldn't work.

Then Ted was looking around for where else could they go, and decided that the way to go was to take advantage of the ESR expertise of Varian with the organic expertise of making compounds that could be useful. So what they did is, they then went into the immunoassay business where they would take an antibody against morphine, and take a morphine molecule and hang a stable free radical on it, a spin label, and if that free radical was in solution, it tumbled rapidly and you got a relatively sharp signal. But if the morphine bound to the antibody, then the signal became very broad because the larger entity didn't tumble very fast and so then you got this big anisotropy. That was the idea, and then it turns out if there was morphine in the test sample, it would occupy the binding site and then the other stuff, the labeled morphine, would be freed and you'd get a sharp signal. So for a good period during the Vietnam War, there were soldiers out there running ESR machines on the urine of the soldiers to see if there was morphine in the urine, by putting this stuff in and seeing whether they got a peak in the ESR. If the peak went up, that meant the guy had morphine in his urine. That was where they started.

Then they went off that, and the idea was, "Well, ESR is all very amusing, but that's very complicated and people don't necessarily want to own an ESR machine just to analyze for things." So they went off into other areas and they eventually were in the immunoassay business and were very successful. They really founded a field of making antibodies that would bind something you wanted to test and then figuring out a way to get a signal out of that. That's what they did. That was fun for me. A lot of my people were there. A lot of my people went to DuPont. Physical organic chemists went to DuPont. A lot of my people went to Syntex, the Synvar partner. They eventually changed the name. They couldn't be Synvar anymore because somebody in Baltimore called Synthetic Varnish already had copyrighted Synvar. Then they became Syva—Syntex-Varian. That was what they were for quite a while. But now they've been absorbed by somebody else.

So let's see, then some small companies I've been involved with from time to time. One I'm still involved with now, is an interesting little outfit in Princeton that's doing things. Some of these are companies that were founded by former students of mine. There was one I was involved in in California for quite a while that was founded by a former post-doc of mine. There's one in Princeton that was founded by a kid I know who was a student here, just happened not to have been my student. So these little companies are sort of fun. For a while, E. J. Corey and I were involved in a company where we were being paid in stock, and so every year we had to pay the Internal Revenue Service [IRS] the value of the stock. Eventually, the stock dropped to zero [laughter], so the net result of our consulting was a significant loss of funds. [laughter]

GORTLER: You did mention in, I think, the Priestley address, that you consult for GM [General Motors]. How did that happen?

BRESLOW: Well, that was an interesting case. I was sitting here quietly doing whatever I was doing. I got a phone call from a guy named Robert [A.] Frosch, who was a physicist, who, I think, had taken his degree at Columbia. Anyhow, Bob Frosh called me up and said that there was a scientific advisory board at GM and they would like me to join it. My reaction was, "Well, I have plenty on my plate already and I can't see why I should be interested in this." So then he outlined what was involved in the thing, and first of all, they paid an awful lot of money, and secondly, you became part of the Product Evaluation Program, for which they gave you four cars a year to drive around at their expense. So I said, "Well, that sounds more interesting." So then I asked who else was on the committee, and it turns out there was—oh, God, there's a Nobel Prize-winning physicist and a lot of really interesting characters on this committee, so I thought, "Well, that's not so bad." So I talked to my wife about it, and her position is, "Look, General Motors is an important operation in this country. If anything you do out there can make the thing work better, then you should do it." So I did it. I did it for seven years. That's sort of the canonical time you can be on the committee. So I did it for seven years, and so I had twenty-eight or so cars during that period, which sounds like a great thing, and it's good except when you're parked in an airport and can't remember which car you have anymore because you

haven't had it long enough to know what it is. [laughter] So I did a certain amount of wandering around airports trying to figure out which car it could possibly be.

GORTLER: Okay. [laughter] You've been very active on a variety of editorial boards. Did you serve because it was sort of a duty to the chemical community? Was it valuable to your work?

BRESLOW: Yes. Oh, some of it is valuable. I don't think I've done all that much on editorial boards. You tend to be on huge numbers of editorial boards. The real reason we go on these boards, to tell the truth, is because you get the journal for nothing. I mean, I've got this giant pile of journals over there that come rolling in like water in a flood, and I essentially pay for almost none of them, really. So one of the reasons you do it is for that. But I would say that other than that—and occasionally one meets with these boards. Mostly these boards aren't even real. I mean, most of these boards don't even really meet. I've been on *Tetrahedron*'s board ever since I can remember and I don't think I've ever been to any meeting of a board there. You just get stuff. They send you stuff to referee if it's particularly a problem. Like if they're getting conflicting referee reports, "would you try to help sort out which one is right," and things of that sort. You do a certain amount of that. I mean, that's stuff I guess you all do because you have to do it.

GORTLER: So you don't have to do a lot more reviewing than you would otherwise?

BRESLOW: I don't think so. I certainly have been on boards of things where they've sent me something and I've said simply, "I don't have the time to do it." That doesn't represent a serious commitment of time. That represents a serious attempt to get free journals. [laughter] So it's not exactly the same.

GORTLER: For seventeen years, you served on the board of trustees of Rockefeller University.

BRESLOW: Yes. Now, that was a good thing. Yes, that was very interesting, and they're right down the street. I mean, it took twenty minutes to get from here to there. That was a very interesting thing. Partly I did that because Rockefeller, at one point, had a pretty good history of having strong chemistry, and then they sort of fell into the doldrums, and again, I think they didn't appreciate the extent to which they needed strong chemistry even to do their so-called "bio-medical mission," which is what they think they have. I got on that board in part—well, the first thing I did, more or less, was to help recruit Tom [Thomas] Kaiser into the place.

GORTLER: Yes. I was always surprised when he went there. He was a friend of mine from [University of] Chicago and Harvard.

BRESLOW: Yes, well, I worked on Tom hard, and he eventually thought it was a good thing that he had done it. He really started a great program there. He was very effective. His loss was a great loss. So that was partly it. Frankly, partly, it also was sort of fun. The board is an interesting board. You meet all kinds of people there you don't otherwise meet. I mean, I got reasonably friendly with David Rockefeller, so he invited me to things and stuff like that. So that's kind of fun. It's a different world that you live in there. It's a world in which, because I'm on that board, I keep every year, right before Christmas, getting fantastic catalogs from the major jewelers of New York about all these obviously hugely expensive jewels that they're sure I'm going to buy since who else would be on this board. [laughter] So it puts you in contact with a lot of people and some of them are actually kind of fun.

But that board is very different from most boards in one important respect. We have a scientific sub-board of people who are really good scientists. I mean, Joe [Joseph] Goldstein is on it, for instance. There are very good people on this sub-board. That board really does very serious second-guessing on all proposed appointments and promotions and sometimes says, "That's a lousy idea and you shouldn't do it." It also is very much concerned with how money should be spent in terms of new areas to invest in. Things of that kind. Things that most boards don't bother with. Also, we get to know the people. I mean, we actually spend a fair amount of time with the faculty themselves, giving them a way to vent whatever they're concerned about, and that most places don't do. That is great. I mean, we are scientists talking to other scientists, and they can complain about what they're complaining about, and if it sounds valid, the next thing you know, it'll be brought up at the board and something will happen. So that was very good. I thought we were making a big difference there, and besides, as I say, the fun of dealing with the people, you know, the people who are involved in that. The Rockefeller itself is, in biology, a superb place. So that was very good. I knew a lot of the people there. As I say, the members of the board themselves were sort of fun to deal with.

GORTLER: Have they replaced Tom Kaiser with somebody of similar distinction?

BRESLOW: Not really, but there is something cooking right now. I mean, I eventually reached the point at which I'd been on it for what, seventeen years, whatever it was. A long time. I figured that was really enough. But there is a candidate coming in right now who's actually very interesting and it's not definite yet, so I really can't say for sure, but I've got a call into the guy to find out what we can do to try and convince him to do it. I'm no longer a board member. I'm now a so-called "member emeritus" because at a certain point, you get off these things, but I don't know how much more active I'm going to be with it. I mean, I frankly think at a certain point, you should just let it go. But it is very easy for me to do things there, and so I'll still possibly play some role in it. That was a worthwhile thing, no question of it. You know, it didn't take a lot of time.

GORTLER: Your most recent big job outside of Columbia was being president of the ACS. What prompted you to take on that particular position?

BRESLOW: Well, there's a nominating committee. Once before, they'd asked me to run for it and I hadn't done it. I figured only two things could happen. One is that I could lose the election. That wouldn't be good. The other, I could win the election, and that might be even worse. That was my reaction. [laughter] So therefore, I decided it was a lose-lose situation there, so I simply said no. But this time I figured maybe it was my time to do it, especially because I thought this was a critical time in terms of dealing with the government and, frankly, also dealing with the public image of chemistry. Not to be in any way critical of it, I felt that it was important that one have a scientist that somebody at least had heard of. By then I had the National Medal of Science—I mean, I had some credibility in dealing with Congress. I felt it was probably important to do, and also dealing with the other scientific societies. I thought we had to do that. The American Physical Society doesn't do what we do. I mean, they go and they find the next Nobel Prize winner that they haven't asked yet and ask him to be president. A lot of the other societies have extremely well-known scientists. That's true in the rest of the world, as well. The Royal Society of Chemistry—you look at who those people are, they're never elected. Some committee goes up and says, "Your turn." We, of course, have this wonderful democracy. But the wonderful democracy doesn't always produce extremely strong people. Sometimes it does. I mean, Linus Pauling was a president. He was great. Ernest [L.] Eliel was the president. He was great. But it seemed to me that it was important that I wave around this National Medal of Science thing when I had to deal with things, and so I thought it was just my time to do it. It was a good thing to do, I think, frankly.

GORTLER: All right. During your year—or the period that you were president-elect and then president—did you feel that you managed to effect changes? Certainly this book is significant.

BRESLOW: Yes. Well, the book was a good thing. It was not the only thing. I did some things in *Chemical & Engineering News* that nobody had ever done before—really crazy. In principle, as the president, you're allowed to write as many as six so-called "Comments" in *C&E News*. Well, I did five (27). I didn't do the sixth one because I decided, like the Navahos, I want to leave one flaw in the blanket so a lot of people could shoot for the sixth. So I didn't do six. I could have because I had another thing that I did later. But I thought it was important that the president communicate with the members, and that's the way to do it. So I did a lot of that. A lot of the members appreciated it and said that they had not seen that much, and frankly, other guys haven't done that much, and I don't know why not. But really, the job of the president is not just to go around and give speeches in a few places. It was really an important job of communicating with the membership, and that's the way you have to do it. So I did that and I thought that was a good thing to do, and for most of the things I talked about with the members, I thought hit a chord. So I managed to do that.

Then I did some other things that I thought were very, very useful. For one thing, for instance, it turned out, if you look at the prizes that we give in the American Chemical Society, we almost always give prizes to ourselves. The only one that was different is—there's a Science Writing Award that we give to somebody who isn't necessarily a scientist. That's all very amusing, but how come we're giving all these prizes to ourselves? Why are we not taking advantage of this prize business to do something with the friends of chemistry rather than with chemists necessarily? Friends of mine were involved in FASEB [Federation of American Societies for Experimental Biology]. I knew people in physics. I knew the people in mathematics, the guys who were head of the mathematics society. I knew these characters, and I had a feeling we were missing the ball because we were, again, so parochially concerned with ourselves. I got the ACS to start an award—I forget what we called this award—but fundamentally we give this to Congressmen. Public Service Award I think is what we call it. The first year, I said it has to be non-partisan, so we gave one to George [E.] Brown [Jr.] and one to George Porter—Porter, the Republican who'd been a great friend of NIH [National Institutes of Health], and George Brown, a Democrat, a great friend of science in general. Also a guy who's always telling us how we're screwing up by not making enough of a public fuss about things, not dealing enough with Congress. So we gave the first public service medal to them, and we've gone on to give it to other Congressmen and when we do this in Washington, we get significant press. We hold the thing in the Congressional offices. We get a lot of the people showing up. We have a lot of good will that has built up toward the American Chemical Society from the Congress because these guys come to these events where we give one of their fellows a medal. We try to continue it as a bipartisan thing so that the Democrats will make sure that they show up because they don't want to look bad in front of all the Republicans coming and none of them, you know. So that was a very good thing. We will continue that. That's a lasting legacy, which is a simple one, but gee, way overdue. As soon as I proposed it, people said, "What a great idea. Why didn't we ever do that?"

Then another thing which I had really worked on hard is the NIH itself, because NIH has a mandate to pursue health-related science, but they interpret that as the word "bio-medical." What they mean by that is they're going to do everything with cloning and biology, and it's shocking. I guess Bernadine Healey was the head of the NIH at one point, and they put out a plan for the future and I was, by then, dealing with all that. I think I was still president-elect at that point. But they had some sort of a future in which all the drugs were going to be made by, essentially, genetic engineering. You know, they had no idea where drugs come from. It's bizarre. So I raised hell about that, and they finally changed the book to put in a section that would call attention to that to some extent, but I continued to push that because the chemists on site at NIH had been really quite unhappy about the status of chemistry. They're considered to be sort of useful to have around, but surely they won't make any big contribution, you know? So I started to raise hell about that, and one of the things I did was to write things in the NIH news magazine that gets distributed within the site, about what a scandal this was and how important medicinal chemistry was and how ridiculous it was that they weren't doing it. You can't say, as an excuse, "Well, we're not doing it because the drug companies are doing it," because they think nothing of doing genetic engineering, although there's a whole

biotechnology outfit out there. They must understand the importance of medicinal chemistry. So I did that.

But then the other thing I did that really worked out is I agreed to fund, in part—and I think the ACS is still funding it in part; it's peanuts that we're involved in—a lecture series on site at NIH where we would bring in chemists who would give lectures that they couldn't miss. You know, Peter [B.] Dervan and people they just couldn't afford to miss. Peter Schultz, [Stuart L.] Schreiber, you know, people of this sort. Bring in those people in a lecture series that would be identifiably health-related chemistry. We've been doing that and we've gotten great backing. Harold [E.] Varmus—he's the head of NIH—was not a great enthusiast for chemistry. He's pretty much biological. But I think he has been very supportive of this series and has shown up at a lot of the lectures, has made some of the chemists directors. The seminars, and that sort of thing, which put the imprimatur on them, everybody should show up—that kind of stuff. That has been very helpful. I think it made a big difference, and the one piece of evidence I have that it makes some difference, whatever it's worth, is that in the president's budget, out of the administration, which must have come from Varmus at some point, the NIH part of it, they have a section about the NIH. In that section they say, "And it is important to take full cognizance of the major role that medicinal chemistry plays in the mission of the NIH." That was a good one. That was a real home run. Now, where it came from, God knows. We're all working on it. You can't say who did what. But that was a thing I really thought I had to work on and I think there's some evidence that it makes a difference, and it's important. If the guys on the site at NIH don't think chemistry's important, the next thing you know, it'll show up in the grants programs and then we'll all be dead.

Furthermore, right now, there are very few, if any, labs to which you would send somebody at NIH on site for a post-doc, and the drug companies don't recruit down there because they say there's nobody there. But that's bizarre. There should be a serious medicinal chemistry operation going on there with good people that you would send somebody to, where the companies would go down there because they know there are all these great people that they can hire. I mean, it should be one of the stars of the place. Anyhow, so that was another thing. I mean, you just pick up these things and try to do what you can with them. I thought I got a lot done, actually. I felt good about it.

GORTLER: I just worry that sometimes people go into the presidency there sort of as caretakers.

BRESLOW: Well, that's right, and I think it's a big mistake to do that because we have real problems and we have to deal with them. Let me tell you one more thing, if I can. I thought it was crazy that we were lobbying Congress, physics was lobbying Congress, biology was lobbying Congress. But mostly what we were lobbying for was to get an increase in the science budget. We could fight with each other later. So I contacted the head of the American Physical Society and the head of FASEB, and said, "Look, let's the three of us get together. Let's get our societies to cooperate on a program to try to get the science budget up. Then we can all battle

later about who gets which share." We did that, and we brought the mathematicians in, as well, and we also brought in Neal [F.] Lane, who at that time was the head of NSF, to sit in with us, and we had a dinner meeting and agreed to do this. We started this, and we decided what we would push for was a 7 percent annual increase in the science budget. That would be enough to double it in ten years. That, we thought, was a credible number. We bounced it off our people who have good Congressional contacts, and they tested this out on their Congressmen who said, "Yes, 7 percent, doubling in ten years, that passes the laugh test." I mean, if you come in and say, "Let's double it in two years," the people just think it's a joke. They said, "That passes the laugh test. You could make a case for that one."

So we did that. We started the so-called "7 Percent Solution." Eventually, over one hundred and forty scientific societies signed on to this program and we produced a giant, giant lobbying operation of millions of people who all had signed on to this 7 Percent Solution, and we got two Congressmen to come out in favor of it. Phil Gramm and [Joseph] Lieberman. In fact, we gave them one of these awards that I talked about earlier. Now, whether we're going to get that is another matter because every year, these guys have short memories. We'll see. But for a while, it worked extremely well. For a while, the NIH budget shot up, the NSF budget shot up, and the people at NSF are convinced that what we did was heroic, because they got a big increase at a time when it wasn't clear that it would happen. So that's another thing, and I think that will last. I hope it will last. That is, I hope that these scientific societies will cooperate in the most important thing, which is to get the budget up, and then they can always fight later about, "How come you're putting so much into that physics project? What about my project over here?" That nonsense we can do later within the agencies. So I think that was an important thing to do, too, and that was another thing I did during my tenure.

GORTLER: I can't imagine your having time for anything else, but you do have outside interests and you have hobbies.

BRESLOW: Yes. Not much. I mean, time is a big problem, obviously. But, well, of course, I'm not heavily involved in the ACS anymore. I'm not heavily involved with Rockefeller. You know, various of these things disappear. I've gotten rid of some of the consulting. So I'm down to pretty much Schering-Plough, and then this small company. But yes, my outside interests are not very extensive. I would say I play golf maybe once a year to remember which end of the club to hold. I don't play tennis anymore, which is too bad. I enjoyed that, but I just haven't done it recently. I play the piano. That's my relaxation. I like to do it. I used to play fairly seriously, although in my opinion not all that wonderfully, but my music teacher thought I was good. But anyhow, I used to play serious stuff. You know, Schubert, things of that sort.

GORTLER: When did you start playing the piano?

BRESLOW: Oh, probably when I was six years old or something. Way back. So I used to do that. But I got increasingly interested in harmony, which has a wonderful intellectual structure, and improvisational jazz, which you can do if you understand the harmonies well enough to know what to do with it. So I do mostly that now. I'd say I play my own version of a lot of standard jazz classics. You know, I sort of know what the melody is but I invent what one does with it. That's fun. I enjoy that. I'm not bad at it, actually. I mean to the point where, you know, I can do this without being embarrassed, and so that's not so bad.

GORTLER: Do you play with other people?

BRESLOW: I tend not to. Once I was in Yugoslavia, believe it or not, at the fiftieth anniversary of the Serb Chemical Society, before they started doing nasty things in Kosovo, and there they had a very good woman singer and she didn't have an accompanist, so I accompanied her, and we performed together. That was sort of fun. [laughter]

[END OF TAPE, SIDE 4]

BRESLOW: Anyhow, I do this piano business a little bit, and occasionally I ski. Not very often. I hardly ever have skied for a whole week in a row, but last year I was able to squeak out a week and do that. I scuba dive. I've been certified for that for a long time. Some people, when I say I'm certified, they assume that means insane. [laughter] Certified to dive. But diving, that's a great world, and I've always snorkeled, and many years ago I got certified to dive. So I've done that. I've dived in most of the interesting places. I've dived at the Barrier Reef and all kinds of places around the world. But that stuff is fairly time-consuming and recently, time has been fairly tight. Usually my wife and I have tried to take some sort of a tropical vacation of some kind where I would, let's say, dive for a few days, and then most of the time she and I would snorkel together and things of that sort. So, I like that. I do that kind of stuff.

But I don't do a huge amount else. I do things around the house. Obviously, I garden, and I happen to be the cook in the family. I'm a very good fast order cook, and my wife is heavily busy, and she does other things. So we sort of divided the chores.

GORTLER: Organic chemists are probably pretty good at that.

BRESLOW: Yes. I like to cook. I enjoy it, and it has the great virtue that I can decide what we're going to eat, and as far as she's concerned, if I'm willing to make it, she's willing to eat it. So it all works out well. She has plenty of other things she handles in the place, so I think it's a pretty good division of labor. So cooking is sort of fun, and I do that pretty much every meal.

Some things around the house. But not a lot. I do some exercise just so I won't fall apart, obviously. But this is my hobby here.

GORTLER: Yes. You've been given a great many awards and honors, but what I really want to ask you is, what are your greatest rewards? That is, what's given you the most satisfaction?

BRESLOW: It's very hard to say. Well, one of the things that certainly gave me great satisfaction was the National Medal of Science because that's a really good thing. The nice thing about it is it happened when my father was still alive, and they called me up in the morning—in fact, about 6:30 in the morning—to tell me that I'd won the National Medal of Science, and then they said, "Well, you can bring three guests to the ceremony at the White House." So I said to them—I had had some time to think about this by then—"Well, that's fine, but it's a little bit of a problem, because obviously I'm going to bring my wife and two daughters to the ceremony, and it's too bad I can't bring my father, who's a wounded war veteran." They just laughed and they said, "Okay. You get four!" [laughter] So, they knew what I was doing, and of course that was exactly right. But anyhow, I brought him down there and so he was at the ceremony where [President George Herbert Walker] Bush gave me the medal and that was pretty nice. That was really nice, because it wasn't many years later that he died. I think that was pretty gratifying just for that sort of thing.

GORTLER: I'm not so concerned about the awards. I mean, what satisfies you about your work?

BRESLOW: Ah! Well, several things obviously. It's nice to see the extent to which we open up things that other people then develop. That part's good. I mean, I've done a certain amount of hit-and-run. We did a thing and then we don't follow it up, and then other people pick it up and run with it, and that's fine. I think it's terrific. I'm happy with that. I mean, we were doing a lot of organic electrochemistry at one point, which sort of opened up the connection between cations, radicals, and anions by doing an electro-chemical interconnection, and that has turned out to be a very good way to do things, and several other people have picked it up and done things with it. So that part is good. It's nice to see that stuff. A lot of, frankly, the cyclodextrin derivatives as enzymes—some of that has been picked up by a lot of people, too. So that part is nice.

I get a lot of satisfaction out of seeing what has happened with former students. I mean, it really is true that you tend to think of these people, to some extent, as your children. It's totally outrageous because they're obviously doing it on their own, but still it's very gratifying to see how well Larry Overman has turned out, for instance. I played a major role for Larry. Larry was a post-doc with me and he was all set to go into the pharmaceutical industry, and I thought this was a big mistake. I really urged him and got him eventually to go to Irvine, where he started, and he has now turned out to be one of the really great synthetic organic chemists in

the country. So he branched off. Part of what I like is to see the extent to which people come through my place—some of it's fun to see that they then carry on with what we do, but some of it's fun to see how they branch off into other areas. Bob Bergman was a post-doc of mine, and you wouldn't even notice that by looking at what Bob does now, but Bob came into my lab and did some very nice things. He always speaks well about how important his time here was. What he has done is just terrific. Bob [Robert H.] Grubbs was my graduate student. Bob Grubbs is really a great fellow and has done wonderful things, absolutely wonderful things. And [John T.] Groves at Princeton [University]. I mean, there are just piles of these people who have done well and I probably have missed some important ones that I just happen not to remember.

GORTLER: The nice thing is we can add them in later if you want to do that.

BRESLOW: Yes. I probably have missed some people. But it's really gratifying to see their success because I have a feeling that they may or may not have come out with the specific technology that they now use; probably not. I mean, many of them have gone into other fields. But I think some of what they do must have been influenced by the way we operate here. So that feels good. They claim that it's true. I think it is possible to get a fair amount of good research—you may not be able to get the best, but a fair amount of good research—without banging on people too hard. I don't think you have to do that. I tend not to do that, frankly.

GORTLER: How often do you see your students? Or how do you see them?

BRESLOW: Well, every week we have a research group seminar where one of the students talks about what he or she has done since the last time they presented, and then the second half of it is students talking about something from the literature they find interesting. That, you see, I think is an important part. In other words, I think it's important to give these characters an education or have them get an education. Not just do research. So we have a number of things that we do here that are related to that. They have to do research proposals, all kinds of things, you know, that help them think about the sort of things they would do. Oh, mentioning people—Alanna Schepartz, my student. The first woman in the faculty in the chemistry department at Yale, and she shot up to a full professor like zip, and is certainly one of the stars in that department now. So Alanna is an excellent example of somebody who's done extremely well. Jean [A.] Chmielewski, who's at Purdue [University], is really a superstar there and she was a graduate student with me. There's a whole pile of people in the Midwest. I mean, Sam [Samuel H.] Gellman, really great at Wisconsin. Steve [Steven C.] Zimmerman, really great at [University of] Illinois. In Canada, Jik Chin. Those other people were all graduate students or post-docs. A lot of very good post-docs in very good jobs, including in Germany. Now, the chief organic chemist at [University of] Cologne, the guy who's the head of the organic division is a guy who was a post-doc with me [Albrecht Berkessel]. Went back to Germany as a bio-

organic chemist, a field that almost didn't exist in Germany and therefore he got all kinds of awards and shot up to this spot. So you can see things like that, and it's very gratifying.

Obviously, you get gratification out of the research, too. I mean, it's sort of nice to see things that you've done that really have made an impact, that people care about, and certainly if this cancer thing works out, it's going to be hard not to be excited about that. But the business with the people is nice, too, frankly. I mean, the business of turning out students who've done so well. I've just mentioned the academic ones, but a lot of the industrial guys are doing extremely well. I've got guys very high in Merck [& Co.], for instance, and things of that sort. Really, it's gratifying to see it. Because fundamentally, I can see the way in which what went on here was helpful to them, and that's really—maybe we fool ourselves about this, so I say, we think of these as our scientific children. To some extent we're kidding ourselves. Obviously, they have many other influences.

GORTLER: I don't think that's true. I think some of them are. I think they really are.

BRESLOW: Yes, some of it makes a difference. So that part is very good, I think. I frankly also feel good about some other things which are more personal. I mean, my two daughters—this I think my wife and I can share credit for. My two daughters always considered that they had to have a serious career. They really saw this as a thing they really wanted to do. They both became attorneys. Actually, one of them started off thinking of going into science, but in fact eventually became an attorney. They both became attorneys, but they're extremely successful. I mean, these kids are still in their thirties, and one of them is a partner in one of the major New York law firms, and is a superstar there. I mean, she lectures before the [American] Bar Association, she writes chapters on things because she's become a specialist in an important area, and she's the head attorney on deals worth more than a billion dollars, and things of that sort. So she's done extremely well. Then my other daughter has gone out to Los Angeles. She's a litigator. She was originally in the entertainment litigation business and had clients like Clint Eastwood, you know, seriously good clients. But she decided she didn't want to do that kind of practice because you couldn't control your life. I mean, you could end up in Saskatoon for six months pursuing some trial or whatever. You had no idea what was going to happen. So she went so-called "in-house" with Sony Pictures, in the litigation department, and she's now vice president. I mean, the kid's thirty-six years old and she's the vice president of litigation there. I mean, the kids are really great. But it's sort of gratifying to see how well they have done and some of it obviously has to do with the idea that one does take one's career seriously and do something with it, you know? You don't just sort of float through. So that's pretty gratifying.

I feel good about my wife's career, frankly. I mean, some of what I have done is related to keeping her career going well. Some of the offers I've had from outside have been interesting, but I've turned them down in part because I didn't want to disrupt her career. Why should one do that? It wasn't that important to do it. So she's now a full professor of biochemistry at Cornell Medical College. She was at one point acting chairman of the

department. She's really a good scientist. So that's gratifying, to see that I was able to do whatever I did without having to make a human sacrifice of my wife. That's nice, too, frankly.

GORTLER: The future of organic chemistry. But before we do that, since we started with physical organic chemistry, I wanted to say: where is physical organic chemistry today?

BRESLOW: There are obviously two directions that it has to go, and I think both are important. One is to increasingly complex systems. There is obviously the whole physical organic chemistry of proteins, of nucleic acids, of aggregates of polymers. I mean, there's a whole area there of complexity. Chemistry in general has been a reductionist science, where we try to take complicated things and reduce them to something simple so we can study it. I think we now have to expand in the other direction and worry about interactions, weak interactions, and all this kind of stuff. So that's fairly obvious and I think people do that.

But I think people are underestimating what's still left to be done. The simplest example: we cannot make a believable movie showing hydroxide reacting with methyl chloride in which you actually show the various directions in which the hydroxide comes in; you show the speed at which the attack occurs; you show the energy at all points of the reaction and the geometry; you have a lot of different angles at which you can attack with different probabilities and all of that. That one is almost simple enough you can believe the calculations. But you can get much beyond that and the theory simply isn't good enough to believe it. I think there is a very important part of physical organic chemistry left to go, in which a big piece of it will be theoretical and a big piece of it will be making sure the theory is right, and that's the kind of thing that we've talked about earlier, what we're trying to do here. I think it's still important to get to the place where you can say not just, "Well, I know it attacks from the back but not from the front," but something more than that. That's not a description of a reaction. You can do this on a computer. You just have no reason to believe that it's correct. So I think there's going to be a cooperation between theoretical chemistry and experimental chemistry to produce sensible checks of the theory. That's, to some extent, what we've been doing with this hydrophobic business—to try to get a picture of what the transition state seems to look like as judged from this exposed surface research, and whether that can be consistent with the theoretical predictions. So I think that's an important section. Then there are probably other things, too, that I have missed. I mean, there certainly is a lot of physical chemistry of excited states that's still left to be done by physical organic chemists, and there's a lot of physical organic chemistry of unstable species. There's probably a lot of physical organic chemistry to be done at 4° Kelvin, which is very different from what we do at room temperature. There's a lot.

The problem with the future business is, you can't make it restrictive because there are people with good ideas that happen not to be my ideas, and so there's a lot of stuff that's going to go on that'll be, I think, quite interesting.

Physical organic chemistry, to the extent that we now start dealing with metals seriously, which is what Bob Bergman has been doing now for years—I mean, that's a place. We can't be

stuck with carbon. We've got to start understanding what happens if you're dealing with an iridium atom somewhere in there, and how does that change anything. That whole physical metallo-organic field—it's not entirely physical inorganic because it's often organo-metallic, but that whole area is very important and it has all kinds of rules of its own and there's still plenty of stuff to be done there. So I think it's a real growth area.

The problem with it is that there's not enough of a clientele for it. There's a big clientele for the bio stuff because of NIH. They're the guys with the money. People get somewhat discouraged. If they do other, more fundamental physical organic that has nothing to do with bio-anything, then sometimes they think it's hard to get money and then the students don't want to work in the field, because why work in a field where you won't get a job when you finish? You know, there's all that kind of stuff. Physical organic chemistry has a big thing to do with the environment, for instance. There are a lot of areas where we can make a contribution.

But anyway, it seems to me that there's still plenty to do in our core area, and then in addition to that, we of course have to outreach both into large molecules and also away from this preoccupation with carbon chemistry only.

GORTLER: All right. Organic chemistry in general—what I see is just huge numbers of synthetic organic chemists out there building bigger and bigger molecules.

BRESLOW: Yes, and some of it you have to wonder about. I would say, synthetic methodology still has a lot to go. There's one area of what we worry about that has to do with synthetic methodology. Mostly we don't. But the one that I'm concerned about is when you want to do a selective organic reaction, you send in a reagent that hits the most reactive part of the molecule, and if that's not what you want, you have to block that in some way or activate somewhere else, and nature doesn't do anything like that. I mean, all natural chemistry is done by binding a substrate and using the geometric control of the catalyst substrate complex in order to direct the chemistry. So you can chew off methyl groups and leave double bonds alone, oxidatively. I mean, all kinds of wild stuff that we don't know how to do. Yet you know it can be done, because nature is doing it. So we've been pushing that for a long time. That's our biggest area, which is really synthetic methodology. There, I've had people working with me, post-docs—Barry Snider, let's say, who's a well-known synthetic organic chemist who was a Corey graduate student and came and worked in that stuff—and we invented a synthesis of cortisone using this kind of geometric control to carry a functionalization of a ring that otherwise was dead. I'm really interested in that and we're still pushing that. I still have a couple of people working in that area here now, trying to develop catalysts that will do these selective things.

A lot of people are now doing things related to that. I mean, some of [Barry K.] Sharpless' epoxidations, some of [Eric N.] Jacobsen's stuff, some of Corey's stuff, have to do with catalysts that complex in some way with a substrate and direct chemistry as a result. Often, frankly, they're interested in stereochemistry, but regio-chemistry is the one we've been more

interested in because of this bizarre idea that nature can chew off a methyl group and leave a double bond alone. We have no clue how to do that. So that's the kind of thing we're interested in doing, and I think that's the place that organic chemistry will continue to develop—imposing catalytic geometric control on reactions.

Then there are big areas that organic chemists are finally doing. Right now, you can look around and see people are suddenly taking carbohydrate chemistry seriously. For a long time, it was considered a separate field, a division of carbohydrate chemistry, but not part of organic chemistry—bizarre. Some of the really brilliant advances in carbohydrate chemistry were even not widely known. I mean, Ray [Raymond U.] Lemieux started doing conformational analysis on carbohydrates long before organic chemists figured out what was going on there. They had, within their own community of carbohydrate chemists, stuff that organic chemists were not noticing for a while. But now it has changed and a lot of the synthetic people are doing carbohydrates increasingly. Obviously, Sam [Samuel] Danishefsky is doing carbohydrates; Dan [Daniel] Kahne is doing carbohydrates; Bill [William] Roush is doing carbohydrates. Then, of course, you've got other classes of molecules that people are now willing to do that they haven't done before. I mean, polymer chemistry is an area that I think is going to have to be increasingly not some separate field done only by polymer chemists, but a thing where people are really doing serious studies of detailed structure. Polymer chemistry, I think, is going to move back into the mainstream of chemistry, as carbohydrate chemistry has done, and people are going to do increasingly interesting things with polymers, with well-defined structures of polymers.

So I think there will always be, in chemistry, this need to make new molecules, new materials, because as I said before, we've just scratched the surface of the numbers of possible molecules. Medicinal chemistry is an increasingly sophisticated field. The people in the medicinal business are really learning an awful lot about drug interactions with macromolecules and receptors, and so I think that flavor is going to get into chemistry itself. You see something already which I think is in the right direction: the Committee on Professional Training has now finally indicated that biochemistry ought to be part of the undergraduate education of chemists. I think it's absolutely crazy not to. I mean, absolutely crazy for people not to know what DNA is, not to know any of the simple transformations. When they learn about the aldol condensation, not to know that there's an enzyme called "aldolase" that does things, and how it functions. Because if you know that stuff, you can invent new chemistry. So it's crazy for people not to know that. So that kind of thing is going to be needed.

But it's a big question you've asked. I don't know. I actually gave a lecture on this recently at the Council of Chemical Research on what the future is of all these fields, and I tried to talk about what the analytical chemists were trying to do and what the physical chemists are trying to do. I have some idea what it is. My way of doing this was very straightforward. I looked at the people who I thought were the most inventive and saw what they were trying to do, and that's at least the immediate future. But I think there's always going to be chemistry. Some people think not. I think they're absolutely wrong. There's always going to be chemistry because we are so special, because we create new things. There's almost no other science that creates anything. We create new things, and that creation involves an intellectual creativity in

realizing what to do, what to make, and why to make it, and what to do with it when you've got it, that is very special to our field. I can't believe it's going to disappear unless it turns out it disappears because our message is so poorly sent and received that nobody thinks we're doing anything.

GORTLER: Last question. Do you have any advice for aspiring young chemists or young people who are even considering the field?

BRESLOW: Sure. There are a number of things that I talked about in the Priestley address that are sort of interesting characterizations of the research process. I mean, one thing that they really have to understand from much of what we do in science, we ask leading questions, and you have to understand that that's what we do. You have to have an idea and then you have to ask nature, "Is this right?" It's not just conversation. So you really have to formulate questions in such a way that they can be answered like that. There's natural rhythm in all of research, in which you sort of start off with a great idea and you start off with something and then in the middle of the whole thing it just doesn't work as you planned, and I call that "Act 2" of the play, and you've got to hang with it, because in Act 3, with any luck, the thing is finally resolved and the protagonist emerges triumphant, and that's where the fun is. But Act 2 isn't bad, when you're wrestling with the problem and trying to solve it. So you should not assume that because things are going badly, they can't work out.

But the other piece of advice I gave, which I think is real, is that when you pick a research project, it has to be something where, if it's successful, you'll be proud to publish it. If it succeeds and you still have a feeling, "Gee, I don't know. Do I want to publish this?" then that's a big mistake. It's not a bad idea to pick some sort of a general, large goal, for instance, like our goal of making small molecules that will duplicate everything you can do with an enzyme. That's a big goal, and we're not going to succeed in doing that, obviously, but that goal in front of you, I think, gives you a stimulus, some sort of direction of where to go. I think it's a very helpful thing to have a big goal of some kind, and to aim for that big goal. The other thing, of course, is at the beginning, young chemists have got to establish that they know how to drive before they get in the race, and so you've got to get stuff done and published and all the rest. You've got to understand that this is more like a hockey game than like an ice-skating exhibition. You don't want to just skate up and down the ice gracefully. You've got to get the puck in the net. You've got to get the thing actually done. You can't get a block at the end, "Well, this is pretty interesting. Maybe if I do more, it'll be even better," and you keep putting it off, and putting it off, and don't get stuff done. The smart people of mine who have failed have failed because of that, because they never could bring themselves to get the thing done and push on. You've got to do that. You've got to do that stuff.

GORTLER: We've talked a lot about big science, and you do big science. Is there still a role for chemists in some small institution?

BRESLOW: Oh, yes. Sure.

GORTLER: For a couple of graduate students?

BRESLOW: Oh, sure. I think absolutely, or just doing it with good undergraduates, you know. A lot of small colleges, they do with good undergraduates working in the summer. No, there's a role for that, and I think it's perfectly fine. You've got to pick a goal that is not preposterous, but you could certainly pick a goal that would be perfectly reasonable. I mean, the people who have been working on microwave chemistry, for instance—putting things in microwave ovens to try to see what they can do—you can do that. That can be small stuff. Yet you can come up with good stuff, especially if you can get products out of the microwave you don't get other ways. Then you've got something very interesting. So there are things of this kind you can do.

A lot of people do chemistry focused on their local environment. Worrying about things in the agricultural area, worrying about what happens to some of the insecticides if you put them in dirt and things of that kind. These are important questions and you can actually make a local impact and do perfectly good stuff with that. So there's plenty of stuff that you can do, focused either on local things or focused on what particularly appeals to you, that you decide is not fashionable, maybe not heavily funded because it's not very biomedical, but still looks to you like an interesting question. There's plenty of stuff to be done.

GORTLER: Thank you very much.

BRESLOW: Okay. Thank you.

[END OF TAPE, SIDE 5]

[END OF INTERVIEW]

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