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University of California
Berkeley, California

DANIEL E. KOSHLAND, JR.
SCIENCE, ACADEMIC SERVICE, PHILANTHROPY

Supplementary interview with Robert Tjian

Interviews conducted by
Sally Smith Hughes
in 1998 and 1999

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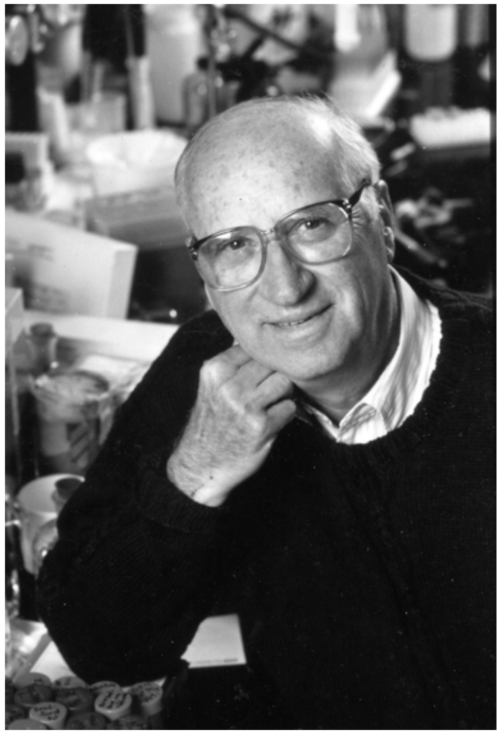

Daniel E. Koshland, Jr.

The Regional Oral History Office

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this oral history with Daniel E. Koshland, Jr.

Class of 1931 Endowment

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INTERVIEW HISTORY

Daniel E. Koshland, Jr., 1920-2007, was a man of many callings—scientist, journal editor, philanthropist, loyal alum, family man, and irrepressible spirit and raconteur. These thirty-or-so hours of interviews capture some of these callings and provide evidence of his two primary loves: his family and his science. As the only son of a prominent San Francisco family—Daniel E. Koshland, Sr. was chairman of Levi Strauss & Co., blue jean maker for the world—the initial assumption was that he would follow his father into the business world. But science drew him, biochemistry in specific, and particularly the field of enzyme mechanism. It was science in its many aspects that occupied most of Dan's working moments, in the form of laboratory research; the reorganization of biology at his beloved University of California, Berkeley; as editor-in-chief of the *Proceedings of the National Academy of Sciences* and then *Science* magazine; and through financial support of scientific institutions in the United States and abroad, including the Marian Koshland Museum of Science in Washington, D.C., a memorial to his first wife.

Dan died suddenly in August 2007, his plan to live to 100 thwarted. Aside from his passing leaving family, friends, and colleagues bereft, his review of these interviews was left incomplete. Yvonne Koshland, his second wife, kindly reviewed some of the interviews, adding proper names and making a few corrections. I am very grateful to her. Douglas Koshland, Dan's younger son, read some of the interviews on science, but as a newly appointed professor (2009) in Berkeley's biochemistry department—his father's former department—he did not have time to review them fully. It was left to me to review the interviews that Dan did not completely edit. My clarifications of what I believe Dan intended are in square brackets. For those wanting to know the science in full, Dan's formal publications are the best source.

A bibliography and a short interview with Robert Tjian, one of Dan's undergraduate students and an eventual department colleague, are appended to the oral history. Tjian—like his mentor a power in bioscience— provides a picture of the Koshland laboratory and a synopsis of Dan's science. Related information may be found in several other Bancroft Library oral histories, including Marian E. Koshland, *Retrospectives on a Life in Academic Science, Family, and Community Activities*, Dan's chapter in *The Reorganization of Biology at the University of California, Berkeley*, and Daniel E. Koshland, Sr., *The Principle of Sharing*. An extensive collection of Dan's correspondence and other documents is archived at the Bancroft Library. An oral history retrospective on the final years of Dan's life—the last interview in the present series occurred in 1999—is scheduled to begin in the summer of 2011.

The fifteen interviews compiled herein were recorded in Dan's unpretentious office adjoining his laboratory in Stanley Hall. On one wall, overseeing our discussions, was a Periodic Table of Desserts. (Dan was wont to escape for lunch at Alice Water's "Chez Panisse," on a few occasions with the lucky interviewer.) Telephone calls frequently interrupted the interviews. Not asked to cover my ears, I heard Dan's end of the conversations. The range of subject matter, from science to science politics to science publishing and beyond, testified to Dan's prominence in contemporary biology.

Some say that an interviewer should strive for distance and objectivity. I did try to ask hard questions—see, for example, the chapter on Dan's role in the reorganization of biology at Berkeley which turned molecular biology into a king-pin department, evoking lasting ire from his colleagues in organismal biology. But in the end I was swayed, like so many others, by the man's sheer joie de vivre, sense of humor, and full engagement in the world around him.

My hope is that this oral history suggests Dan's many contributions and conveys his love of life, science, and family.

Sally Smith Hughes, PhD

Historian of Science

August 1, 2011

Interview 1: December 14, 1998[1]

[Begin Tape 1, Side A]

Family Background and Education

Hughes: Please start with your upbringing and family background.

Koshland: I really had an absolutely idyllic youth. I lived in a family which was comfortably off in the Depression, so we didn't have financial worries. I had two wonderful parents, both of whom were exceptional in their own ways.

My father [Daniel E. Koshland] was particularly active in community affairs—both my parents really were—and felt very strongly that their children should be the same way. They meant active not just in giving money but in spending time and effort. For example, my father also worked hard and stuck his neck out for minorities. In the middle of the war [World War II] a lot of blacks moved to San Francisco, and he launched a program among businessmen to help minorities. A lot of the problems of modern cities were avoided in San Francisco because my father formed the Council of Civic Unity. The council was to help welcome the blacks to the City of San Francisco and develop programs, not only in his own business but others. He developed programs at Levi Strauss & Company for giving minorities jobs, long before federal action. As a result, Roosevelt asked San Francisco and the group my father headed to pass a ballot setting up an FEPC. He got the first FEPC law passed, the Federal Employment Practices Commission, that mandated no discrimination. Roosevelt had pushed for this, but he wanted it to be approved by voters to persuade reluctant or scared politicians.

My mother [Eleanor Haas Koshland] was stricken by multiple sclerosis at the age of forty, when I was ten years old. She was just wonderful. She remained a cheerful, active-as-possible person. Never complained. Just kept doing what she was doing. One of my family friends told me her effect in San Francisco was unbelievable. It was hard for her to walk; she eventually had to have a wheelchair. But she would appear at all the board meetings of organizations on whose boards she served. Attendance there was excellent because everybody said, "If Eleanor Koshland can get there, I certainly can get there." So she was a great example to everyone, but mostly to her children.

It was a great life. On the other hand, my parents expected that I do well. Nobody ever said anything, but it just was in the atmosphere that you were not supposed to be selfish; you were supposed to contribute. My sisters, Sissy [Frances] and Phyllis, and I all had to learn to be especially helpful because of my mother.

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[1] Dr. Koshland edited interview 1.

Early Interest in Science

I remember my father once said, "Where would you like to go to college?" Caltech and Berkeley were two places I was considering. I had considered Harvard but my mother's illness made that undesirable. I did a lot of reading in the humanities, and I decided Caltech was just a little too narrow, so I came to Berkeley, which I came to love, as an undergraduate [1937-1941].

Hughes: You were at that point headed towards science?

Koshland: In high school I really decided to be a scientist. I read *Arrowsmith* and *Microbe Hunters*—I remember them—when I was in grammar school, and then decided I wanted to be a scientist. I really thought at first I wanted to be a physicist, even though those books I mentioned were biology books, but then gradually really got more and more interested in biology.

Hughes: Was there anybody in your family interested in science?

Koshland: Nobody. Everyone thought I would go into my father's business [Levi Strauss & Co.]. But I decided to be a scientist, and my mother and father encouraged me, and that was it. I majored in chemistry when I came to Berkeley, and then went all the way through in chemistry. At the end of my years as an undergraduate, World War II broke out.

Hughes: You spoke of your first interest being physics. Why the switch to chemistry?

Koshland: Well, the books got me very interested in biology. You get physics first in high school. I liked that, so that's what I first decided to be. I took physics and chemistry, but I didn't take any biology in high school. By the time I went to Cal , I really decided I wanted to go into biology. Everybody told me, "Don't major in biochemistry; major in chemistry," because biochemistry was in a much earlier stage of its development. Everybody was telling me I would get better training in chemistry, which I did. I've never regretted that.

Chemist, Shell Chemical Company, 1941-1942

I was an undergraduate major in chemistry at Berkeley. At the end of my senior year, however, I was really sort of bored with chemistry. I remember I didn't know what I wanted to do. I didn't want to go to graduate school. One of the friends of the family, Felix Bloch, a professor at Stanford, told me, "Well, Dan, go out into industry. You'll either like it or you'll hate it, and you'll know what to do then." So I took a year off. In those days, a year off meant working all the time. I got hired by the Shell Chemical Company. I really hated the repetitious work, although the people were very nice. So I decided to go back into academic life.

Then World War II broke out. I tried to enlist in the navy, but my eyesight was terrible, so they rejected me. They told me if they should let me in, I immediately could sue for a lifetime pension because I was so far beyond the limit of acceptability that I could qualify as legally blind. I was very depressed by that because that war was a different kind of war from the Viet Nam War that my students know about. World War II was a war that everybody wanted to be in the army or navy and do their bit.

The Manhattan Project, 1942-1946

University of Chicago

I was working at Shell Chemical, and I got a phone call from Wendell Latimer, who said, "Dan, I want you to come in and see me." He was the chairman of the chemistry department at Berkeley. And so I came in, and he told me Glenn Seaborg had a job in Chicago, that he needed some people, and I thought you'd be a good person to go. I was working on aviation fuels at the time. I said, "I'm in a classified position, and I don't think I can change my job."

Hughes: That was considered a war-related position?

Koshland: Yes. It was also a classified job; in a classified job, you couldn't change jobs. If you were in a key industry, you couldn't just get a better job with more money. So I didn't think I could switch jobs. I remember Latimer just said to me, "This is the most important job in the world." That's all I knew about it. I said, "All right. If you say so, I'll quit my present job and go to Chicago."

I gave Shell Chemical two weeks notice, and I worked the two weeks, and I think I quit on a Friday and got on the train Sunday and went to Chicago. That was how quick it was. When I got there, Seaborg told me I was working on an atomic bomb. That was the first I knew it was an atomic bomb.

Hughes: Why did Latimer think of you?

Koshland: They were looking at recent graduates from the university.

I had a nice personal relationship with Latimer. I think I wrote it up in one of the books [*Annual Review of Biochemistry*,1996]. He gave an advanced course in inorganic chemistry, and I took it. I was one of two students. We were both pretty good students. I got A’s in all the midterms, and I did the three-hour final, and as I was walking out, Latimer picked up my final and said, "Would an A be good enough for you?" I said, "Yes, of course. [chuckling] How can anyone complain about an A?" He looked as though he were going to tear it up without even the need to read it. I said, "I just spent three hours writing that out. You're going to correct that final!" [laughter] At which point, I think Latimer must have thought I was out of my mind. When I went back to the dorm and told people what had happened, they thought I was crazy.

Hughes: Yes, I can imagine!

Koshland: Anyway, the next year there was a fellowship given at the university called the James Monroe McDonald fellowship, which was given to the senior who was most likely to succeed. I didn't even know about this. You never applied for it; the faculty just gave it to somebody. And I got it. I was totally bowled over, but I'm sure it was that [laughing] incident with Latimer, something obnoxious in my personality. But I learned one thing: being obnoxious wasn't all bad. That probably was very useful to me in my career.

Two other students—a guy named Bill Knox, who is now a professor of physics at University of California at Davis, and Ralph James, who actually has died recently—were also called up by Latimer. So he must have been calling a bunch of recent graduates who had just started in various jobs.

Hughes: They were particularly good students as well?

Koshland: They were all good students. So Latimer was picking out good people to help Seaborg. Remember, this was all top secret. So they could only have advertised it as a routine kind of Defense Department job, but none of us would have taken it then. Why move to Chicago when I was living out here? But I was told that it was very important. The others were told the same thing. So we all arrived there and became friends. I had a bachelor's degree. I hadn't gone to graduate school. So that was my first initiation into research—on the bomb project [1942-1946].

Hughes: I noticed that you were a group leader.

Koshland: That's correct. In fact, I had fourteen people in my group. It was a lot of people.

Hughes: How did that come about?

Koshland: Well, I guess I was the kind of person who organized things. As the people working with Seaborg grew, we had to work in groups, and Seaborg put me in charge of one group. The work I was doing went fairly well, and so he had more people doing it. I think half of them were Ph.D.s, and I didn't even have a Ph.D. But I was on the project first and probably knew a little more about plutonium. It's an element that had never been seen before. It was made by man. It was not even on the periodic table at that time. It required what was called solution chemistry. We figured out the chemistry by having the plutonium carried down by bigger elements. There wasn't enough in the world to see or weigh. We only had radioactivity by which to follow it. So we had to work out all the chemistry. That was our job to work out the chemistry of plutonium so bomb manufacturers could get it pure.

Hughes: Seaborg, as I remember, had isolated plutonium at the cyclotron here.

Koshland: He originally discovered it here by it's radioactive half-life, not by seeing it chemically. Then he was put in charge of the group in Chicago to purify plutonium. The Manhattan Project was divided up into parts. There was the physics part, to make the bomb. But the job that Seaborg was given was to purify plutonium so you could put it into a bomb. That meant getting it down to a pure element, and then it had to be reduced to a metal and then made into a bomb.

Hughes: You mentioned solution chemistry. Did you have any background in that?

Koshland: Yes, you have that as an undergraduate in chemistry.

Hughes: But you were doing a very different form of chemistry on the Manhattan Project.

Koshland: It was a totally different form. I had nothing to do with radioactivity when I was an undergraduate, so that was all new. It was new for everybody else. It wasn't just me. But we all learned it pretty quickly. We had to learn it.

There was nothing like informed consent that you have today. They told us at the beginning that this project was very dangerous. They calculated from the half-life of plutonium that it was something like a thousand times more dangerous than radium. There was a history of people who had died in the radium dial industry. Of course, those people didn't realize there was anything dangerous about radium. But we were told it was dangerous and we were to work in very elaborate hoods and wear gas masks and protective clothing.

Hughes: Oh, really?

Koshland: Yes, because it was dangerous to inhale or ingest even a little bit. All of us—this showed a different attitude because of the war—decided that our friends were out on battlefields, dying and getting shot. We said this was no time to be particularly careful, because it would slow you down if you had to have a gas mask on and things like that. So we all said that was nonsense, so we just went ahead without all the precautions.

Hughes: Was that across the board?

Koshland: That was across the board. We all decided that. That wasn't anything heroic I did. Then there were various things we had to do in emergencies. For example, at one point, I remember a big concrete production room in Oak Ridge was contaminated, and they asked for volunteers to go in with a fire hose to wash down the walls. We were only allowed fifteen minutes of radiation. We were all decked out with big coveralls and boots. So we went in the room and sprayed the fire hose around the room until they yanked on the cord that meant your fifteen minutes were up. There were all sorts of things like that happening.

Hughes: As I remember, there was really very little known quantitatively about the effects of radiation on the body.

Koshland: Yes. They knew it was dangerous, but nothing like the worry people have today. We had more radiation exposure. But basically, we used radioactivity all the time, and nobody spent a lot of time worrying about it. And it was right because the war was on, and it was really important to get the bomb quickly.

In the middle of the war, I remember, at Oak Ridge they got some captured German documents. Fission was discovered in Germany. There were some captured documents about scientists examining how to go into bomb-making. Now we know that Germany never did really go into it very much, but we didn't know then. And then Hitler came out saying he had a weapon that would win the war. Of course, he was referring to the V-2s. We thought maybe he was onto the bomb, too. In Oak Ridge we worked six days a week and frequently came in on the seventh day and did experiments. That was war, and that was the way things were going.

Hughes: How much did Seaborg supervise?

Koshland: Seaborg was my boss directly. The same thing happened to him. He was in a small group of seven or eight to start out with. When I arrived there, it may have been eight or ten. And then the group got much bigger, and I was put in charge of a sub-group. I may have done fairly well supervising them, so I got more people to supervise, and pretty soon it was a big group.

Oak Ridge

Later when the group became very big, Iz [Isadore] Perlman, who was working under Seaborg and later became a professor here, was put in charge of a number of groups like mine that went down to Oak Ridge. And other groups stayed in Chicago with Seaborg and some went to Los Alamos. I was one of the people that went down with Perlman.

Hughes: Why were you chosen?

Koshland: I don't know. They just divided up the work with plutonium that I was doing. My job at Oak Ridge was to put on a pilot-plant scale what we had discovered in Chicago on the test-tube scale. When you have fission, it creates some plutonium and at the same time makes lots of fission products, which are very radioactive. And you had to get rid of those radioactive elements because they would really ruin any making of a bomb. So the purpose of the laboratory at Clinton, Tennessee was to scale up from the test tube to pilot plant size.. And then the real plant to produce plutonium was going to be in Hanford, Washington, although we didn't know that at the time. So we were doing the pilot plant, but we also had to continue working out the chemistry of plutonium and fission products while we were scaling up.

So I think the division was that people who were the experts in plutonium solution chemistry went to Oak Ridge. The people who stayed behind were to convert pure plutonium to a metal. That I wasn't involved in. They were to measure the properties of the pure material. So the group was divided on some chemical basis, I think.

Hughes: Where do these organizational abilities of yours come from?

Koshland: God knows.

Hughes: That was the first test?

Koshland: Yes, I just did it. Some people just naturally do it.

Hughes: You hadn't had any high school or college experience in leading an organization?

Koshland: No, and I think most of the other people didn't either. I wasn't unique in that. But it was true that a number of the young people who probably had organizational ability were chosen to be heads of groups. And some Ph.D.s were chosen to be heads of groups. If you have advanced training, that doesn't mean you lack organization, but it doesn't mean you are automatically good at it.

Hughes: Did the war period point you in certain directions?

Koshland: Yes. That was pretty clear.

Marian Elliot Koshland[2]

By the end of the war I had gotten married [1945]. I met my future wife in Chicago.

Hughes: Say something about that.

Koshland: I made the best decision of my life. I saw a very attractive blond girl with green slacks on, and [chuckling] I said to myself, I've got to make a date with that person. And then the next day I saw her in a bookstore. I went up to her and started talking, and then we met at a dinner party, and then we started dating. As a result, we got married. On my fiftieth wedding anniversary, I mentioned the story, and she said, "I never owned a pair of green slacks." And so I said to her, "Well, you know, I must have married the wrong woman." [laughter] I was going out with a couple of other girls when I met her, but almost instantly we each recognized we were meant for each other. So from our second date on we just went out with each other. She was highly intelligent, had a great sense of humor, was just a wonderful person. At the end of fifty-two years of marriage, I loved her more than even the beginning of the infatuation. I was extraordinarily lucky, and as the years passed, I realized more and more how lucky I was.

Hughes: She was a student?

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[2] For more on Professor Marian Koshland, see the oral history retrospective: *Marian E. Koshland (1921-1997): Retrospective on a Life in Academic Science, Family and Community Activities*. http://bancroft.berkeley.edu/ROHO/projects/biosci/.

Koshland: She was a student at the University of Chicago. She had come there to go to medical school. She was very poor. As a result, she had to take a job. So she took a job in an immunology project trying to get a vaccine for cholera, in which she succeeded. She really was very good at research. One of her professors said, "You're never going to go back to medical school. You just love research." She made him a bet. She was determined at the time to finish up what she had originally intended. But she never ended up going back to medical school, partly because the war intervened, partly because she was very good at research, and partly because she planned to have children, and she would never be able to have children and practice as an M.D. It just was going to be too complicated, whereas in research she could manage both children and a career.

Hughes: Was it the cholera project which pointed her towards immunology?

Koshland: Well, I think that helped. She was a bacteriology major as an undergraduate. I think that was her first real brush with immunology and probably did point her towards it. But the doing of research settled it.

We were already going around together in Chicago, and when I moved to Oak Ridge, we were corresponding, and then we got married, and then she moved to Oak Ridge. When she moved to Oak Ridge she got employed on the bomb project, too.

Hughes: What was she doing?

Koshland: She worked on the biochemistry of plutonium because she was a little bit of a biologist, and the project needed to know how it was used in the body, how much of it was secreted, and things like that. She studied how plutonium passed through the body. Scientists knew nothing about it, and those were the first elementary studies.

It was hard to get a job at Oak Ridge. Everybody who was related to someone wanted to get jobs there. Bunny determined that she didn't want to use any favoritism, so she signed up as Marian Elliot, which is her maiden name, without mentioning that she was married to me. She was interviewed and got the job and was assigned to D.E. Koshland's group [chuckling], which was pretty funny. At that point, she couldn't say that she didn't want to work for me because she might lose the job. So we had to manage.

Hughes: You were married already.

Koshland: We were married already. But it led to arguments. She was a much more careful worker than I was. We'd get one experiment that was a very good result, and I said, "Very exciting, and we must go on to the next thing." And she'd say to me, "No, we've got to duplicate our good result first." I said, "I don't want to duplicate it. We go to the next thing. If that turns out to be wrong, then we know we made a mistake. But most probably we were right the first time." So my style of research was much more rapid and dangerous than hers, so we had some big arguments.

Hughes: Did it continue to be a point of contention?

Koshland: Not serious, but good arguments on choices. She was a very good scientist on her own. When we went back to graduate school, I went back to the chemistry department, and she went to an immunology department. Then we talked about research at our dinner table, but we never bossed each other's experiments again.

Hughes: So that was the only time you worked together.

Koshland: That was the only time we worked together.

Hughes: Probably just as well. [laughing]

Koshland: It was just as well, correct!

The Koshlands' Scientific Interaction

Hughes: Should we say something more about your wife and immunology? My scant knowledge of immunology in the mid-1940s is that it was a very young and ill-defined field.

Koshland: That's exactly right. It was. On the other hand, Bunny was a great help to me because I was pretty much on the chemical side of biochemistry and knew very little about the biology part. Something would come up and I wouldn't understand it, and she'd give me the biology background that I needed. And then every once in a while I'd give her a chemistry background. For example, she hadn't taken much math as an undergraduate. I said, "You've really got to take a course in calculus." Not elementary calculus—she already had that—but differential equations. I just felt it was good training. So that was something that she wouldn't normally have taken. When she got her Ph.D., she took a course in differential equations, which most immunologists didn't.

Hughes: When were you talking about science? All the time?

Koshland: Yes, sure, every day. We both were good talkers. We'd come home from work, and she'd tell me what she did, and I'd tell her what I did. When you're taking your Ph.D., you are also taking some courses. She took what was called Theoretical Biology, from a guy named [Nicholas] Rashevsky, a very out-of-this-world person. A lot of theoretical stuff and very complicated equations, so she was partly using what I suggested she take, differential equations. She was a young and very attractive blond girl. She was in this graduate course, and Rashevsky called her Miss Koshland, even though she was married. It didn't matter. But she was pregnant. The course started in September, and you couldn’t tell she was pregnant. But the child was delivered on January 1. [chuckling] The students had been asked for times to give speeches. Bunny didn't care that much, so she got December 17th, which I think was the last date of the semester. By then she was pretty big. [chuckling] Rashevsky called her up and said, "Now, will Miss Koshland give her talk." And she came forward in a very pregnant state. We got a big kick out of that.

Hughes: [laughing] This conversation that began in graduate school, and perhaps even before, went on throughout your life?

Koshland: Oh, sure.

Hughes: Eventually you had five children. Were they part of all this?

Koshland: We wouldn't have a long scientific discussion in front of the children. Bunny might mention something that happened in the office, and I'd say what happened in my office, and the kids would say what happened at school. But if we really wanted to discuss science in detail, we'd wait till dinner was over. But the kids all knew a little bit about what we were doing during our day. Of course, the kids weren't grown up when we were in graduate school. That wasn't until later on.

Graduate Students, University of Chicago, 1946-1949

Koshland: After the war I then went back to get a Ph.D., and so did she. We both went to the University of Chicago and got Ph.D.s at the same time [1949]. That was four years later, and some of my friends had started graduate school before they got drafted or went into the army, so they were getting their Ph.D.s at the end of the war. People allowed them to get a credit for their wartime work. But I didn't. You see, I went straight from a B.S. into the war effort. I thought I was extremely old after the war to be going back for a Ph.D., with very little chance of getting a job. But I decided to go back and get a Ph.D. and wanted to get it as quickly as possible—both of us, Bunny and me. And so we both got our degrees in three years, which is pretty fast for a Ph.D., even then.

Hughes: Did your war experience help in any way?

Koshland: Of course. I didn't use any of my actual research chemistry, but the experience of doing research certainly helped. I was just more efficient at doing everything.

So we both went to the University of Chicago, and the immunology building was across the street from the chemistry building. We graduated together, at the same commencement. I remember I had to walk ahead of her in the line, which is very unchivalrous, because Daniel came alphabetically before Marian.

Hughes: So she was going by Koshland at that point.

Koshland: She was going by Koshland. She published one or two papers with her maiden name, and a lot of people said you don't want to give that up because then you don't get credit for the early papers. But there was a woman that we knew—the last name was Harrison; she was married, and her maiden name was Davies, and she used her name as Davies professionally. I remember once there was an incident where one of her children was ill, and somebody called the place for Mrs. Harrison, and nobody knew who it was, and they didn't get in touch, and the child—I don't know what happened exactly, but it was really bad. They had to delay for six or eight hours before they finally figured out who the mother was, before the child was allowed to have an operation. Bunny decided she was never going to have two separate names. She signed all her earlier papers Marian Elliot Koshland.

Hughes: Why did you choose the University of Chicago?

Koshland: Well, because we both liked it there. A lot of the people who were on the Manhattan Project were from the University of Chicago, and we had both done very well, so we got a lot of offers. From Berkeley in particular. Melvin Calvin was here. And Seaborg wanted me to come back with him to go to graduate school at Berkeley. Calvin, I guess, was sort of pushed by Seaborg, who said, "There's a good student." Professors always want good students, and so we had offers. But both of us liked Chicago.

Hughes: You mean the university?

Koshland: The University of Chicago, yes. The bomb project was done at the University of Chicago, so we were familiar with it and knew a lot of the people there. And I really didn't want to come back and do isotope chemistry. I liked Seaborg a lot, but I really just felt it was time to go into biology.

Hughes: That’s what would have happened if you had come back here?

Koshland: Yes. I would have worked with Seaborg and not gone into biology. Those were really the two alternatives we considered. I suppose we should have considered a lot of others, but it wasn't all organized like today. The war was ending, people were going back to school, and there were a whole flood of events crowded in together.

[End Tape 1, Side A. Begin Tape 1, Side B]

Hughes: Did you take advantage of the G.I. Bill?

Koshland: I was employed by the Manhattan District; I was exempt from the draft so the bill didn’t apply to me. We had exemptions signed by Franklin D. Roosevelt, President of the United States, because we were not allowed to reveal what we were doing.

Roosevelt was a controversial president. I remember a northern Michigan congressional district, which hated Roosevelt, tried to draft Elton Turk, and they got a letter from the President of the U. S saying Elton Turk should not be drafted because he was on an important war project. He was drafted anyway. They said they weren't going to listen to Roosevelt. So he was drafted, went into the army, and the army just assigned him back to the Manhattan Project. So he kept on doing exactly what he was doing before, only for a corporal's pay. We weren't getting very much money, but he was getting less. But then it turned out to be a big bonanza because he had the G.I. Bill of Rights when he went back, so that paid for his schooling, so he didn't end up being too far behind. That happened to several others after that.

Frank Westheimer and the Application of Chemistry to Biology

So then I went to the chemistry department at Chicago.

Hughes: What did you do?

Koshland: I was looking for people who were doing something that I was interested in: applying chemistry to biology. Most of the professors there were doing interesting things with chemistry but largely applying it to chemical subjects or polymers. There was a young assistant professor named Frank Westheimer who wanted to apply chemistry to biology, so I became his first student to do that. I had to learn a lot, so I worked with him, although I had recently decided to go to Chicago as compared to Berkeley, based on some very famous people, like Harold Urey, who was a Nobel laureate. But when I got there, I found Westheimer to be doing much more interesting work, as far as I was concerned.

Hughes: What was he doing?

Koshland: He was working on enzyme mechanisms, which is what I really started out in. So that's what I worked on for my graduate degree and continued to work on as a postdoc.

Hughes: Had that interest come before you met Westheimer?

Koshland: No. I was interested in applying chemistry to biology, and he had a problem involving enzyme mechanisms, and so I essentially learned from him.

Hughes: Enzyme mechanism/enzyme action—

Koshland: The same thing.

Hughes: --was not the traditional way of doing biochemistry or enzymology, was it?

Koshland: No, it was not. It was sort of an offshoot. A lot of enzyme pathways were being worked out at that time. But I was interested in how does an enzyme become a great catalyst? How is it so efficient? We were working on a very rudimentary level because very little was known about enzymes. It was difficult to purify one and so forth. So we were working at that level. We were among the first people working on it.

Hughes: And that was acceptable?

Koshland: Oh, yes. And I was acceptable even in the chemistry department, which was even more difficult. Westheimer was a very good chemist, and he was publishing in the chemical literature, too. So I guess they decided, well, okay, this is acceptable chemistry.

And secondly, my Ph.D. thesis got published in a chemical journal, the *Journal of the American Chemical Society*. If it had not been acceptable for publication, the department might have said this is really too new for us to be sponsoring. But it was good enough chemistry that they accepted it in regular chemical journals.

Hughes: Were there other centers where there were chemists whose interests were turning towards biology? I'm trying to get a feel of how unusual your area was.

Koshland: It was rare but not totally unusual. Somebody whom I met at Berkeley when I came back here was a guy named Esmond Snell. He was looking at chemistry in relation to biology—not mechanisms the way we were, but cofactors, vitamins, and things like that. So there were some people working on chemistry in relation to biology who were not doing enzyme mechanisms, which was what we were doing. People were realizing the body was doing a lot of chemistry, and you had to work out the chemistry to understand the body.

Hughes: And working with larger molecules than chemists were used to working with, is that not true?

Koshland: Well, proteins and nucleic acids are much bigger than the ordinary molecules of a classical chemistry department. They had one course called the Chemistry of Natural Products. To my utter astonishment, they didn't have anything about proteins or enzymes or carbohydrates or lipids in that course. It was all about terpenes and alkaloids, because they were small chemical molecules you could get the structure of. So the big molecules I was interested in were not really part of a classical chemistry curriculum.

Hughes: There wasn't a pecking order in connection with that?

Koshland: I think at the beginning, certainly—well, even for many years, a lot of the chemists looked down on the biochemists. They thought they were much better. Then the Nobel Prize started getting distributed more and more to biochemists and less and less to chemists, so then they started to change their minds, but it took them awhile.

Hughes: Westheimer today would have been in a biochemistry department, would he not?

Koshland: Well, he could have been in a chemistry department, too. Even *our* chemistry department at Berkeley, which is one of the most reactionary, now has biochemists in it. But yes, for a long time, there were a lot of members of the chemistry department who said they wouldn't take him in because, "We don't want his kind of work."

Hughes: How has your background in chemistry shaped your subsequent research?

Koshland: I would say the chemistry training was really good for me. A lot of people who went straight into biochemistry learned how to isolate compounds but didn't really know how to manipulate chemicals the way I did. And that basic training was very good. Number two is the fact that life is really chemistry. Physicists think physics is important, and basic laws of physics are of course important. But even the brain, which has electricity in it, is mainly chemical. Steroids and hormones and neurotransmitters and everything going around in your body and brain are largely chemical. So much of life is just chemistry that that basic understanding of chemistry was really very useful in all of my subsequent work. Now, you might say, had I been trained in genetics, that would have helped, too. It probably would have. But certainly, I've always been on the chemical side of biology. I got my Ph.D. in chemistry, not in biology, from a straight chemistry department.

Hughes: Somebody in the know could look at your body of research and say, "That scientist probably had a chemistry background," rather than biochemistry?

Koshland: From my work now, people would say, "Okay, he's a biochemist." But if they looked in more detail at my papers, they probably would say, "Yes, he was a chemist."

Early Research on Enzymes

Hughes: What was the topic of your thesis project?

Koshland: My thesis was on fermentation of glucose-1-C_{14}.

Hughes: Why that topic?

Koshland: It was a very nice experiment, which actually Westheimer devised. There was a way glucose was broken down in metabolism in the yeast cell which was considered to be essentially identical to the process in man. That was a postulate at the time. But even then, you couldn't give radioactivity to humans. Nobody knew very much about it. The known pathway predicted that the carbon would end up in one particular atom of a fairly complex molecule. So that happening by pure chance would be practically zero. Therefore, if you fed to the yeast radioactive glucose which was labeled in one position, you'd predict it would end up in one position in this final molecule, not spread all over. It would be interesting to test that. So that's what I did. I made this molecule, put it in the yeast, and then I isolated the final compound. Sure enough, that was exactly where it was. So that was a very important experiment.

Hughes: What about availability of radioisotopes right after the war?

Koshland: They were not very easily available. The only radioactive carbon compound was barium carbonate at that time. Now there are thousands of radioactive carbon compounds on the shelves.

Hughes: And you could buy barium carbonate?

Koshland: You could buy it from Oak Ridge, and it was very cheap but not the molecule I wanted. Barium carbonate was just the beginning of the phase. I needed hydrocyanic acid for my thesis which was the way I was going to make glucose-1-C_{14}. So I had to put barium carbonate, molten potassium, and liquid ammonia all in the same tube. There was a big explosion, and out of the scrapings at the bottom of the tube I got some KCN, and then I could convert that to hydrocyanic acid and use my synthesis. So that's the way I made HCN. Now you just buy it.

Hughes: Since you were in at the beginning of research on enzyme mechanisms, what were some of the technological limitations?

Koshland: At the very beginning, it was very hard to get a pure enzyme.

Hughes: Why?

Koshland: Because there are lots of enzymes in your body. Each little cell is maybe one millionth the size of a drop of water. Each cell has five or six thousand enzymes, and then different cells in your body have different enzymes. So if you take a little section of your body and grind it up, there will be thousands of protein molecules, and they're all very similar. So trying to separate one from the other was very difficult.

Hughes: Do you mean similar in weight?

Koshland: Yes, pretty much similar in weight and in properties. Gradually, we learned how to separate them, so now we can separate them pretty quickly and fairly easily. But in those days it was very difficult.

Hughes: When you learned how to separate them, was that a test-tube sort of thing?

Koshland: Yes.

Hughes: Or did techniques like electrophoresis come along?

Koshland: That was later. But I remember that coming along. [Arne] Tiselius got a Nobel Prize for that. Methods of protein purification were coming along. Before that you developed sort of hit and miss methods to purify proteins. And then Tiselius came along with electrophoresis, and that made it much better. Then chromatography was developed, and that also made it much better. So now the modern student doesn't know why anybody got a Nobel Prize for electrophoresis; it seems so obvious. But it wasn't so obvious at the time.

Hughes: Were difficulties in purification one of the reasons that people stayed away from enzyme mechanisms?

Koshland: No. Most of my early papers were really bringing concepts of organic chemistry into enzyme mechanisms. Some people hadn't really been trained in any of the theory of organic chemistry, and those people [who had] were in the avant-garde of organic chemists, so they were getting lots of jobs as chemists. So there weren't that many people who were interested in applying it to enzymes. We were a small group that was going ahead. But it gradually grew. Everybody recognized it was an important field. The field required a combination of chemistry and chemists who were interested in enzyme mechanism. I think the methodological difficulties were probably less important than the theoretical difficulties.

Postdoctoral Fellow, Harvard University, 1949-1951

Koshland: Then I had a postdoc at Harvard. I worked for a guy named Paul Bartlett, who was a very, very distinguished organic chemist, very uninterested in enzymes. He was a very nice person and very nice to me but very uninterested in what I was doing.

Hughes: Why did you go to him?

Koshland: Because I wanted to go to a very distinguished organic chemist. I didn't know whether anybody else would take me because I had come back and gotten my Ph.D. quickly, and I wasn't really trained to go into a biochemistry lab, so I didn't really think of very many other people. Harvard was also attractive as a good place to go.

Hughes: Bartlett wasn't worried about your dissertation field?

Koshland: Well, he was a little worried. I got an Atomic Energy Commission fellowship, which is a very special fellowship given to people doing something with radioactivity or things like that. Working for the bomb project, we had been deprived of the G. I. Bill of Rights. So we got a few of these fellowships. Physicists, chemists, anybody got them. If you got one—it was hard to get one—then you could choose anybody you wanted to work for.

I was to come to Bartlett's lab, and he wouldn't have to pay a penny for me. I had my own salary, but he would have to give me space in his lab, and everybody had limited space. He heard I wanted to work on my own project but not on something *he* wanted to do. I overhead one conversation. He called up Westheimer and said he was thinking about it, and Westheimer said, "Oh, no, this kid deserves it." So Bartlett said, "Okay, as a friend to you, I'll take him." So it was sort of being nice to Frank Westheimer that Paul Bartlett took me in.

I did a project totally different from what I was doing with Westheimer. I had a project of my own and published on it.

Hughes: What was it?

Koshland: It was on acetyl phosphate and acetyl phosphate mechanisms.

Hughes: Why?

Koshland: They were very, very important compounds. They had been discovered in this pathway that I was studying with Westheimer, but it was just one step.

Hughes: Within the yeast?

Koshland: It was one of the steps that was unimportant in my case. I wasn't studying it. I was studying the top step and the bottom step. But in the middle of the pathway were these acetyl phosphates, and people were discovering that they were very important in biochemistry. So I decided to study the mechanism of their action. That was something Westheimer wasn't studying at all at the time. I really wanted to do something different from Westheimer. I didn't want to do his problems. And so I thought this was a good problem to work on. Bartlett thought it was interesting, so that was it.

Family Time

At the end of my postdoc, which was two years, I had two children. I had one that was born when we first got to Chicago, and then a second was born while I was still a graduate student. I wanted to work. The job market was terrible, and it was very hard to get a job. So I came back from the first days at the lab at Harvard, and I told Bunny there were guys who had been around the department twelve years and hadn't gotten a job. I said, "Bunny, this is make or break. You're never going to see me in the next couple of years. I'm going to work night and day." [chuckling] Bunny replied, "You are not! You have two children, and you're going to be home every night for dinner and take care of the children." So that's what I did. I'd go to work early in the morning, and I'd come home for dinner. From about six to nine, we read the children stories and did whatever we needed to do with the children, put them to bed at nine o'clock. Then I'd go back to work.

Then I discovered it was a waste of time to go to work twice, so I'd just bring my notebooks home. You have to write your notebooks up. I'd find I could bring them home. Every once in a while I'd make a mistake and have to go back to work, and I discovered that the people were working ten hours a day. But they weren't working very efficiently because they would meet somebody and talk in the hall and do things like that, and I, under this limited time schedule, had to work very hard because I had to get home in time for dinner. So I discovered an important thing: if you think you have more time, you waste it. [chuckling] That was a practice we went on with the rest of our lives.

Bunny did the same thing. We'd both bring home our notebooks. From five-thirty to about nine P.M. was devoted to the children, and then they all went down, and then both of us would go to work and worked to about midnight.

Hughes: That's a long day.

Koshland: That's a long day, yes. She was a good role model for lots of other women. I was warned that you've got to have very good stamina to live that kind of schedule.

Marian Koshland, Assistant Professor, Immunology, Harvard

Hughes: Were you living in Cambridge or Boston?

Koshland: At Harvard, I was on a fellowship. Bunny got an assistant professorship in the department of immunology at Harvard Medical School. She worked for Howard Muller. Very famous name. Head of the department of immunology at Harvard. Very nice person. He liked Bunny, which was very nice, and so he made her an assistant professor.

She didn't have any money for her research. She didn't have a fellowship. There were very few of them at that time. He asked her what she needed, and she needed something like ten or twelve animal cages, which cost several hundred dollars apiece. He said, "Okay, I'll arrange it." That's all she heard. About three or four weeks later, she had a whole bunch of cages, all ready for her experiments. And then somebody in the department mentioned to her, "Do you know he made those all himself?" That was just typical of him, a very nice person. His wife was also a scientist. So he understood what women went through. She liked him very much, and he liked her, so it was really a very nice arrangement. She was doing that during the same period I was doing my fellowship.

Hughes: She worked full time?

Koshland: She did it half time. Then, when we came down to Brookhaven, we essentially continued that schedule.

Anti-Semitism

Koshland: I was at Harvard, and I was looking for jobs. I got a fair amount accomplished and got a couple of papers published. I remember the first year when I was looking for a job, a guy named Max Dunn—we might as well put his name in—was the biochemist in the chemistry department at UCLA, which absolutely would have been a perfect job for me because I was a chemist and he a biochemist. We got along very well. The interview was going wonderfully, and Dunn said, "We'll really want to have you out here" and so forth and so on, and then he said, "By the way, Koshland. What kind of a name is that?" I said, "German." Then I waited a minute, and then said, "And Jewish." He said, "Some of my best friends are Jews" and went on and on, but I never heard another word from him. I didn't want to complain. It's so easy to complain about something like that. But anyway, I never said anything.

The following year, Max Dunn came around again. Bartlett was chairman of the department. He had a big group. I think we had fifteen or twenty people in this group. Bartlett said to me, "Dan, Max Dunn is going to be at the medical school. He's going to be interviewing people. You ought to go over and look." And so I said to him, "Dr. Bartlett, I think it's no use sending me. I know Ralph Weston" (who was in the Bartlett group) would be a very good candidate. Why don't you send him instead of me?" I then told Bartlett about the incident the year before.

[End Tape 1, Side B. Begin Tape 2, Side A.]

Koshland: Bartlett was a very reserved New England type. I didn't even know how he stood on being anti-Semitic. He just exploded. He was just furious. I was sitting in the room. I didn't want to make a fuss. He picked up the phone, and he phoned the chairman of the department, William Young, at UCLA, whom he knew. He said, "Koshland has told me this story. I know Koshland. He wouldn't tell me anything that wasn't true. I think it's just a disgrace." He just laced into Professor Dunn. I was sort of embarrassed because I didn't want to make a fuss over it. The next thing I knew, I got an offer from UCLA to go out there. But it was a one-year appointment, and Max Dunn was still a big professor there and was the only biochemist, so I decided that was just silly to do.

Anyway, the story got back and Max then was removed from the recruitment effort. There were just lots of Jewish kids who were very interested in biochemistry. The chairman of the department, whom I later got to know, told me that Dunn would go east, and he'd come back and he'd say, "There are no people that are any good." Then the chairman found out a very large number of them were Jewish. That was really the reason. So once they figured this out, they got Dunn out of recruitment. Anyway, that was an amusing episode in some ways.

Senior Biochemist, Brookhaven National Laboratory, 1951-1965

The only job offer I had was from Brookhaven National Lab, so I went there. I really wanted to go into academia, but this was stopgap. I'd be there for a year or two and then go back to a university. Fourteen years later, we left. We really had a great time. I'm not sure that I wouldn't still be there if it weren't for the University of California, which is very special to me.

Hughes: Why was Brookhaven a good experience?

Koshland: A couple of things. For me as a chemist, it allowed me time to get my feet on the ground in biochemistry. Also, at that time, it was very hard for women to get jobs in science. There was a lot more discrimination. All these kids today think there's discrimination now. It's nothing compared to then. So we got down to Brookhaven. There was a medical department as well as a biology department.

We didn't want to work in the same department. We felt the two of us in the same department would be difficult for the chairman. Bunny applied to the medical department, and he didn't have any women in his department. He made the argument that it was very difficult to have husbands and wives, but he was really against women in the department.

So I said, "All right, Bunny. If worst comes to worst, I'll just find another job right away. We won't stay here very long." But then a job opened up. The head of my department, the biology department, was a guy named Howard Curtis, who was really a nice person and wasn't concerned about women versus men. The department had a symposium every year, the Brookhaven symposium, which became quite well known. They needed somebody to edit the volume. I said, "Bunny, do you want to do this? They really need somebody. You'd be very good at it. Why don't you say you'll do it if they give you a lab so you can work on the conference and at the same time have a lab?" So that's what she did, and Curtis said, "Fine." So she got a lab, and she was working.

I always compare it to Einstein. Einstein took a job in the patent office and could do it in a couple of hours, and then he did his research after that. Bunny had to spend a lot of time on the symposium the first year till she really knew what was going on, and then she got it very well. She kept doing it the whole time she was at Brookhaven, even though by then she had a pretty big lab. I mean, she did very well in the lab and so they liked her. So Bunny had a big lab; I had a lab; it was a rural town, and the kids could walk to school; it was really idyllic. And then I had a joint appointment at Rockefeller, which was a beautiful setup, so it was really pretty ideal.

Bunny's and my original plans were, when the kids finally grew up, we would then move into Rockefeller, spend our remaining years in the city, which was a little more fun for older people than the country. But we knew that city schools wouldn't work with the five children. And then the call came from the University of California, so that changed everything.[3]

Hughes: Children three, four and five were born in Brookhaven?

Koshland: No, three and four were born in Boston. They were twins. [chuckling] That was a big bunch.

Hughes: What were you doing at Brookhaven?

Koshland: At Brookhaven I was doing work on enzyme mechanisms. They were pretty good about it. I used radioactivity. It was all peaceful uses of atomic energy; that was the whole purpose of Brookhaven. They didn't make me work on a bomb project.

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[3] DEK stopped reviewing/editing at this point.

None of the work was classified. It was very nice. I got a pretty good reputation for myself. That was why I got an offer from Berkeley.

Hughes: I would gather that because you got an offer from Berkeley that there wasn't a great deal of stigma against working in a national lab. Was an appointment at Brookhaven parallel to having an academic position?

Koshland: It was similar. It was like having an institute position. Brookhaven National Lab was run by a consortium of universities. Harvard, Yale, Princeton, Columbia, Rockefeller University, and so forth were the ten institutions which ran it. Then they appointed a director, so it was sort of removed from direct management by the Atomic Energy Commission. But there was no stigma whatsoever, other than later on in the sixties. Kids here [at Berkeley] were against anybody who did [research using] radioactivity or was with government. But there was not a lot of prestige. Brookhaven was no worse than being, say, at the University of Oregon, compared to Harvard. It had no build-up of academic prestige. But it was a great place to work for the two of us. If you published good things, you got known. And so I got quite well-known. I was about forty-four, forty-five, that age. I was getting all sorts of offers. If you made an offer to anybody at Brookhaven, they'd leave in a minute and take a position someplace else. So I got an offer from Pennsylvania, and I remember Harvard, and a whole bunch of places. Bunny really liked Brookhaven, and I liked it, and so we weren't going to move.

And then I got an offer one day by phone from the University of California. I had been there as an undergraduate and really loved it. My family was out here. Bunny, who was an Easterner, said, "Well, you said no, didn't you?" I said, "Bunny, it's just rude to say no. If somebody offers you a job, you just don't say, 'No, I wouldn't consider it.' I told them I'd consider it. But I'll call them back tomorrow and tell them no." She said, "Fine." We went back to dinner, and then the next day she said, "What happened?" I said, "Well, you don't turn Berkeley down without visiting it." Bunny always said to me afterwards, she knew that first day we were going to move to Berkeley.

Bunny really preferred to stay in the East. I said, "You know, darling, if you really want to stay, I'll stay." She said, "Well, darling, you know, if you really want to go, I'll go." [chuckling] We went back and forth on this and discussed the pros and cons. Finally, one night, at two in the morning, she jabbed me in bed and said, "Wake up." I said, "What's going on?" She said, "I made the decision." I said, "What's the decision?" She said, "Well, either we stay in the East and I spend the rest of my life making it up to you, or we go to California and you spend the rest of your life making it up to me. We go." So that's what happened.

Hughes: [chuckling] It sounds as though Brookhaven functioned as an academic center. Were there any differences?

Koshland: There was no teaching, which was nice. That was particularly good for me because I was a chemist. So it was just as well I didn't teach at the same time because I didn't know much biology.

It turned out at Brookhaven I learned a lot because I was not only doing research in more biological subjects, using my chemistry, but then they asked me to be in a study section which was reviewing grants at the NIH. In a study section, you have to review all sorts of grants. I just learned an enormous amount from that. When I finally got a university appointment, it was really good for me that I had gone through all of that. And it was good for Bunny because she was bringing up these children, and she worked theoretically halftime. But Brookhaven really got its money's worth because she was working at least halftime. Then she'd come home, and we'd take care of the kids, and then they'd go to bed, and she'd work for another three hours.

It was early in the game for women to work. Some people implied to her that she was neglecting the children, and some people said wasn't I nice because I had to do all these extra chores because Bunny wasn't home doing everything for us. But it was great for me because I didn't have a wife who said to me, "Now, take me out to the theater. I've been working over a hot stove all day." But she always had the main responsibility for the children. I helped a certain amount. I took some to the dentist or something, but she was always the one who kept track of what was happening with the children.

Hughes: It's remarkable that you had a routine of at least three hours a night with them.

Koshland: We never accepted parties or anything during the middle of the week. It was well known the Koshlands did not go out Monday through Friday. We didn't go out a lot Saturday, either. Bunny was very insistent that everybody be together at the dinner table. Everybody got up in the morning at different hours because our kids were on double sessions. We were part of the baby boom generation, so a lot of schools were in double sessions. Some started at eight in the morning and some started at twelve noon. So some kids had to get up early, and some kids didn't. It was crazy. But everybody had to be home at the same time for dinner. That was a good system.

[End of Interview]

Interview 2: December 22, 1998

[Begin Tape 3, Side A]

Marian Koshland’s Career at Brookhaven National Laboratory

Hughes: Last time we discussed your career at Brookhaven, where you spent fourteen years?

Koshland: Correct.

Hughes: We went through why you ended up there and how your wife got an appointment as well. Please talk about her research in those years.

Koshland: I just got a sketch of her that has been written by a reporter at a Yale magazine who was writing up women in science and mentioned her. But her career was really interesting in the sense that she was one of the women pioneers who went into science at a time when it was really tough for women. It's tough now, in a way, but much less so.

When we moved to Brookhaven, she wanted to have a job, and I wanted her to have a job. I had a job in the biology department, and there was a medicine department. It really fitted her even better than the biology department, so she applied to work in that department. The guy who was the head of the medical department, whose name I have mercifully forgotten now, was really against women. There were no women in the department, and he made some argument, well, he couldn't hire her because I was already hired. He didn't believe in hiring the spouse of somebody who was already hired. It was a clearly trumped-up reason because there were a lot of wives and husbands hired --not [necessarily both] in science. But there was a woman who was assistant to the director of the lab, whose husband was a well-known scientist there. And there were other people. So it was not about Brookhaven National Laboratory policy.

Fortunately for us, the chairman of the biology department did not feel that way. I've forgotten how I found out about it, but we found out that there was a symposium that was run in which Brookhaven sponsored once a year a subject, say, in the fields of physics, chemistry, or biology, and published the proceedings. They needed an editor to run it. They had an editor in physics who ran it, but he didn't know any biology and had a hard time with it.

I found out about this and suggested that Bunny offer to do this. But I said, "You make a condition that you get a lab in exchange for that." So she did. The chairman of biology thought it was great idea because he was really very happy to have her, and so she got a job that way. She was very efficient and so she got the number of hours she had to do to run the symposium, which, of course, peaked when they had the symposium. A few weeks before and a few weeks after she was very busy, and the rest of the year was easier to do.

So she ended up running her lab. Long after she clearly established herself in her lab and didn't have to run the symposium anymore, she sort of liked it and continued it. They gave her an assistant. But I likened her to Albert Einstein, who took a job in the patent office and was able to do the work in the patent office in a couple of hours and had the rest of his time to do physics. We had other offers, and we weren't interested in moving because we really liked Brookhaven so much. In my opinion, it's conceivable that we never would have moved if it hadn't been for Berkeley.

Brookhaven as an Institution

Hughes: Was it an academic atmosphere?

Koshland: Yes, pretty much. It was run by a consortium of universities: Yale, Harvard, Princeton, Columbia, and so forth. They partly wanted to have the kind of facilities that were made available during World War II for atomic energy--namely, radioactivity, high-energy physics, various things of that sort. They realized that if they put up all these facilities at Yale and Harvard and Columbia and so forth, they would duplicate facilities, and it would be very expensive, so they decided to pool their resources and have one place doing this.

Brookhaven got going under that basis, and it really was very good. Brookhaven felt that it couldn't get good people by just being a service organization to the universities; they had to have good scientists who were working there all year 'round and were smart enough to handle these complex facilities. So Brookhaven ended up as an academic institute like the Rockefeller Institute or the Max Planck Institute. I was hired as a biologist. There were chemists and physicists, and we could do basic research. It was sponsored by the U.S. Government, which put the money in. Of course, as you know, now they're national labs: Argonne is outside Chicago; Lawrence Berkeley Lab is at Berkeley; Brookhaven is near Columbia, and so forth. At that time it was totally basic research. Now there's more directed research.

Hughes: From the start, did Brookhaven have a reputation that could attract top scientists?

Koshland: I would say yes and no. In the field of physics, it attracted some top people right off. In the field of biology, it certainly did not. I really took the job because I had no other offers. I wanted to go into academia. But the number of jobs for the number of people was rather small. Current students think it's the worst period of time in their lives, as though there were no other period like it. But remember, there were four years of war, where there were essentially no students at graduate schools, and then all of a sudden the flood gate opened up, not only because these kids came back--of which I was one--but also there was the G.I. Bill of Rights, so your education was paid for, which was a totally unique thing at that point in time. So the graduate schools were just flooded, and they turned out a lot of people.

There were a fair number of jobs because you had four years where these jobs had been depleted, but there were more people than there jobs, so it was hard to get a job. There was no academic job offered to me at the time. Brookhaven was the best job that was offered. I was very pleased to go there in one way because it was a job for me, and eventually Bunny got one. But I felt it was a let-down. At that time, I really thought it was not as good a job as I felt I was worthy of. But then, once I got there, it was really a very pleasant place. I could publish and--

Hughes: What about the caliber of your colleagues?

Koshland: A lot of them were very good, and then gradually it got better. It was sort of the showcase for peaceful uses of atomic energy. When Eisenhower built it up from that point of view, it got more and more prestige. I would say it never got to be, say, a Harvard.

Hughes: Were you obligated to work with some form of radioactivity?

Koshland: Not really. At the beginning, I think we all felt it would be fairer to the system if we did something like that, mainly because Brookhaven had to report to Congress what was done. But if we just did research, which the academic community thought was good research, that really helped Brookhaven a lot at that time. Radioactivity is so useful in every kind of research--chemistry, biology and so forth. Remember, this was the first time it was available. It was like a big new tool being available. So it was very easy to use radioactivity in your research.

Theories of Induced Fit and Cooperativity in Enzyme-Substrate Interaction

Hughes: You published your induced-fit theory while you were at Brookhaven.

Koshland: Oh, yes.

Hughes: That was 1958, I believe.[4]

Koshland: It was very controversial when it was proposed because it supplanted [Emil] Fischer's key-lock theory which was very widely known and very accepted. Part of the problem I had in getting my theory accepted was that Fischer’s was so widely known. I remember one of the reviews I got was that Fischer’s key-lock theory has been correct for a hundred years, and it's really presumptuous of some young embryonic--I'm pretty sure they used the word "embryonic"--chemist at Brookhaven National Laboratory (I'm sure they meant that Brookhaven didn't have very much prestige) to question the theory of the great Emil Fischer.

But I think the implications of what it meant were understood pretty quickly--at least that it was very important. I gave a talk at an American Chemical Society

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[4] For references to Professor Koshland’s publications, see his bibliography in the appendix.

meeting. The American Chemical Society picks up certain things to be in the *C&E [Chemical & Engineering] News*, which is their journal. I remember my speech was picked up for that journal. Shortly thereafter, Carl Cori, whom I didn't know at the time but later got to know, who was a very distinguished leader in biochemistry, invited me to give one of the major talks at the American Society of Biochemists on this theory, so I gave it, to a big audience. So people realized it was a very important paper.

Hughes: How was it received?

Koshland: I would say mixed. A number of people thought it was very interesting and really accepted it. It explained a lot of things that were anomalous. Other people said, "Well, I don't understand it all completely, but everybody thinks Emil Fischer is right. This young upstart [DEK]--somebody will discover something wrong with his theory, even though I can't figure out right now what's wrong with it." I had done a bunch of experiments, and we did some more, so I became more confident. The theory of Koshland, Nemethy, and Filmer was to explain a new phenomenon called cooperativity. Monod, Weinmann, and Chargeux published an alternate theory of how to explain cooperativity. Nobody had really explained the molecular basis of cooperativity before. Those two theories both explained it. It had been observed in a number of cases, but it was only phenomenology; nobody really had a theory about it.

Hughes: Well, since we're into it, why don't you give your definition of induced fit and cooperativity.

Koshland: Okay. Let's start with induced fit because that's easier to understand. Emil Fischer's key-lock theory was to explain how enzymes are so specific. "So specific" means that enzymes are frequently designed so they act in the most extreme cases on one compound and one compound only. To a non-chemist, that may not sound surprising. But in fact there are whole ranges of compounds which are called alcohols. That means, anything that has an -OH group. All these alcohols are very similar to other alcohols. In organic chemistry, you learn that if you do certain reactions with alcohols, they all react similarly, and if you do certain reactions with, say, carboxylic acids, they all react similarly.

What people found was an enzyme would react with *one* carboxylic acid and not with any of the others. An enzyme would react with *one* alcohol and not with any of the others. That was a distinguishing characteristic of enzymes as compared to man-made catalysts. It was extremely important. If you understood that, it would be very valuable to design man-made enzymes that had that characteristic. We found out fairly quickly that it was very important for biological systems. You really had to have that kind of specificity. So that was a very important theory in biology, and everybody knew it.

What Emil Fischer said was that the way [an enzyme] distinguished [a substrate] was that you had an -OH group sticking out at one end, let's say, and that was what reacted with the next chemical. But whether or not it ever got to the enzyme surface depended on the shape, and the shape was like a jigsaw puzzle or a key in a lock that has to fit in. It just simply won't fit in if it's the wrong shape. That was the theory of Emil Fischer. In fact, it explained almost everything.

Hughes: Was that theory based on solid evidence?

Koshland: Well, no.

Hughes: Fischer had no way of looking at molecular shape or structure, did he?

Koshland: No. But it's like a lot of theories. Up until very recently, we never saw an atom. In fact, you still can't see an atom; you see the results of an atom. So he had a lot of evidence in the sense that there were lots of experiments which fit in which his theory very well. But there was a certain amount that didn't fit well. Most people didn't notice that. It just happened that I was working away at Brookhaven, and it suddenly occurred to me there are some [reactions] that just don't fit the Emil Fischer theory.

For example, there are some molecules that are smaller than the natural substrate. You could argue, well, the reason they don't react is they're too small to be attracted to the enzyme surface; they can certainly fit because they're small. It's sort of like taking a key and cutting off one of the jagged edges, right? You would certainly be able to get it in, but it wouldn't work. But in the case of the enzyme, you see, there was no reason [for it not to react]. The reacting -OH group was there, and therefore if you got the smaller group, why didn't it react? Well, you say, it wasn't attracted. You took off a group that made it lose all its affinity for the active site. So we measured them, and in fact they hadn't lost their affinity. So now there was no way to explain it.

I got a couple of examples, but by far the most important example was water. Water is a universal solvent. It's around all the time, and it's a very small molecule. Water has an -OH group just like an alcohol, so it really made it very difficult to understand why water didn't act as a competitive substrate in almost every reaction. That was number one. I said to myself, there must be a certain minimum [molecular size] that you have to have, as well as a maximum. In other words, [the molecule] can't be too big because it won't fit into the jigsaw puzzle, but it also has to be big enough. And so I used the analogy of the hand in a glove. If you have too small a hand, you won't fill the glove up. And then you have some property which requires all five fingers to be filled or something [for the reaction to occur]. It's not a perfect analogy, but it was a good example.

If the glove is lying down on the table, it can be absolutely flat, just like the surface. So instead of having two rigid objects which fit like a key goes in a lock, I was saying it's like a hand in a glove. The glove, which was the protein, isn’t the negative protein for the positive substrate. It's rather like a negative glove, and then along comes the substrate and induces the change. That's where "induced fit" came in. The substrate causes a change, and as a result of causing the change, then [the protein] would react.

Hughes: Were proteins regarded as static molecules?

Koshland: They wiggled around a standard average. In other words, yes, they were [thought to be] much more rigid than what I postulated. In some of my early papers, I talked about a "flexible enzyme," and that phrase is still used. When they say "rigid," they didn't mean like concrete, but they meant it's like your fingers wiggling about but really never deviating very much. What I was saying was that it was wiggling like this [demonstrates greater motion]. I called that the flexible enzyme, that really changed [shape] in a major way.

I did all sorts of indirect experiments. This was before the era of crystallography. And then crystallography was discovered. The first crystallographic structures were done in England by David Phillips, on lysozyme, and by Fred Richards in the United States, on ribonuclease--both very distinguished chemists. I was just fascinated. What was going to happen? There were small changes, in fact, very small changes. But they said they were really not very important.

The big question of the induced-fit versus the Fischer theory is that when the substrate binds, it induces a change in the protein structure. That was the thing to look for, and I looked for it, and sure enough, there were changes, but they were small, an angstrom or something. An angstrom is very, very small. The two people who published this finding said, “Well, we can't really tell. This [change] is so small, it's not significant. Recently I have done some experiments that show they are significant. I had plenty of evidence for my theory already, but this would have been very, very powerful evidence.

Koshland: Yes.

Hughes: Did Phillips do the X-ray structure of the enzyme first in one position?

Koshland: He did the X-ray structure of the enzyme without the substrate and then with it. There were movements of, say, half an angstrom or one or two or three angstroms. That's very, very small. An angstrom is 10^{-8} centimeters. But the length of a carbon-carbon bond is only 1.5 angstroms; it's very small. I was a chemist. Most of them were biochemists. I was a chemist, so I said, "That's really pretty big on the scale we're talking about."

Hughes: It was enough.

Koshland: Yes, I said it was enough. But then, three or four years later, a man named [William S.] Lipscomb, who was a professor at Harvard, showed an enzyme changed ten or twelve angstroms when the substrate bonded to the enzyme. [Thomas A.] Steitz, who had worked with Lipscomb and is now professor at Yale, came out with another enzyme, called hexokinase. I wrote up a paper on why hexokinase was very important. I said it is an enzyme that works on sugar, which is an alcohol, which has an -OH group, and it doesn't work on water. So it was a perfect example of what I meant by induced fit. I said it happened to be an enzyme where water can't make the conformational change that I wanted, and glucose could. He did the X-ray structure and, sure enough, it was exactly right. It fit my theory absolutely perfectly.

[tape interruption]

Koshland: Most of the people who understood enzyme kinetics accepted my theory. But for people in other fields, it wasn't as acceptable. But then they gradually accepted it. The X-ray evidence was pretty incontrovertible.

Hughes: Was that process of non-acceptance the old "we have to be really convinced before we overthrow an old theory"?

Koshland: That's right. I didn't feel any hostility. It was sort of like the Bohr atom being replaced by the quantum mechanical atom. The Bohr atom, with the electrons around it, was a very successful explanation. But then there were examples of spectra that couldn't be calculated correctly from a Bohr atom, and gradually, therefore, the whole science of quantum mechanics arose.

There were other things that I haven't described to you that didn't fit in with the Fischer template. One was noncompetitive inhibition. Pretty rapidly, the induced-fit theory became quite accepted, and then it appeared in the textbooks and everybody accepted it.

Hughes: Before the crystallographic information became available, what were you doing to substantiate your theory? You spoke about indirect evidence.

Koshland: Yes, okay, I'll tell you.

[End Tape 2, Side A. Begin Tape 3, Side B.]

Koshland: [demonstrating] Let's say my left hand is open and my right fist comes in and fills up the palm of my hand. Then, if I have a chemical that will react with, say, the point of my little finger, it really isn't affected. It's going to react the same way with an outside group when the protein binds my fist or when the fist is gone. On the other hand, if this reactive group reacts with something in the middle of my palm, it will react very rapidly. But then I put my fist in there. The reagent can't in get there. That was called a protection experiment. That meant my fist basically protected the group that was blocked, so it couldn't react.

Hughes: I see.

Koshland: I said to myself, if I'm saying there's an induced conformational change, then the fist in my palm is going to protect groups that are blocked, but it also may cause a change which exposes some groups that were previously buried. Whereas the template hypothesis, the rigid molecule model, will never expose new groups; it may block some groups. I said, Well, I ought to be able to find an enzyme where binding the substrate induces the presence of new groups.

I looked for one. The enzyme that I chose was phosphoglucomutase. It turned out I was exactly right; it worked that way. That was an experiment that I think was pretty good evidence that the induced fit theory was correct. There was a sugar enzyme called beta amylase which also fit very well with the induced fit theory. I did a bunch of experiments like that, but they require sufficiently complicated [math]. X-ray crystallography was so visual and so easy, you didn't have to learn any complex mathematics to understand. A picture is worth a thousand words. My theory really became widely accepted then.

What I said was, the substrate must induce a conformation change sufficient to make it react. I didn't say it has to be one angstrom or two angstroms; I just said "sufficient." We didn't really know how big that number was. On the other hand, being a chemist and knowing that the carbon-oxygen bond was 1.5 angstroms, it did not surprise me that a movement of half an angstrom could turn something off. Whereas if you're a biochemist dealing with proteins in a very general way, it probably was surprising [that the conformation change was so small]. So your training had something to do with it. But It is correct for the scientific community to be resistant to [changing] a general rule which has been very useful for a long time, unless you can do an experiment that really nails [down the change]. Then you have to do a number of experiments, which is really just exactly what I did.

I wasn't saying that Fischer's idea was wrong. [I said, the substrate] was quite flexible, whereas before [with Fischer's theory], we were thinking more of a wooden jigsaw puzzle; the piece either fit or it didn't fit. I said, it's a hand in the glove type of fit, rather than a jigsaw puzzle type of fit.

Hughes: Well, when you first came up with the theory, were you appreciative of the fact that it might be very generally applicable?

Koshland: Oh, yes.

Hughes: You had only worked with one or two enzymes, right?

Koshland: I started to work with more and more. But the other thing was that I could read, and there were all sorts of phenomena which, it seemed to me, fit [my theory]. One was noncompetitive inhibition. Noncompetitive inhibition was mentioned widely in the texts, but there was no mechanism given to explain it. It was a little mysterious.

Hughes: With a noncompetitive inhibitor, you don't have the fist going into the palm.

Koshland: No. The noncompetitive inhibitor [theory] said something binds out here [demonstrating] and prevents it. I started thinking, How can something way out here [demonstrating] prevent it from going here [demonstrating]. One of the theories was there was electrostatic interaction. But electrostatics won't extend that far a distance.

Cooperativity

One of the things that the theory did explain was how molecules that weren't themselves part of the reaction could change the reaction. And so that led to the cooperativity. Now we're getting to the story.

Information developing at about the same time was that many enzymes are composed of a single protein, what's called subunit, one peptide chain. But a number of proteins are made up of multiple subunits. Hemoglobin, for example, is four largely identical subunits. There are other proteins that have four absolutely identical subunits. I asked myself, If the ligand induces a change in one of the subunits, how does that change the others?

Hughes: Now, please remember to describe, not demonstrate.

Koshland: Okay, my fingers are interdigitated. Then, if something binds to my left hand and my fingers spread apart, then inevitably it's going to force the fingers of my right hand to spread apart. So the two will be related. Starting out, the palm of my left hand and right hand are essentially identical, except they're in left and right asymmetry. But other than that, they're the same. If I have a ball, it would bind just as well with my left hand as with my right hand, assuming they're the same size and everything. On the other hand, if as a result of it binding the left hand, it causes a change in shape, then it's going to affect the way it binds to the right hand. That was what was observed in cooperativity. Things like hemoglobin--the first molecule of oxygen to bind made it easier for the next molecule to bind. That was what was called cooperativity.

Hughes: That concept pre-existed?

Koshland: The idea of cooperativity was known long before I did anything. It was one of the phenomena that had existed in the literature for a long time.

Hughes: Was the molecular mechanism known?

Koshland: No, the molecular mechanism was not known. Monod and I both proposed models for how this would work. Monod's model came out a little earlier than mine, partly because mine had big trouble getting published. My model came out in 1966, and Monod's came out in 1965. Mine was submitted in 1965, but I was not nearly as well-known as Monod was at the time. Monod's model and my model really explained most of the existing evidence at the time. There was no difficulty in explaining a lot of the cooperative enzymes.

Hughes: What was Monod’s model?

Koshland: His model was that the protein exists in two forms. He said, it's either in this form [demonstrating] or it's in this form.

[interruption]

Koshland: The protein was either in the closed state or wide open. I said it was in the closed state when the first one bound, which caused the second one to go partially open, and then when the second one bound, it pushed it all the way open.

My model was called a sequential model. That is, it went in stages, because that fit in with my idea of induced fit; namely, you induce a small change and then you induce the next change, and then you induce the next change. Monod's was called a concerted model, meaning that everything changed at once. That really meant you had to look at the individual molecules. There were two different phenomenological consequences of this. Monod's model always predicted positive cooperativity: the first [ligand] always made the next bind more readily because it opened all up to a model that was more attractive; otherwise, it wouldn't bind at all, and there would be no reason to bind.

Negative Cooperativity

The sequential model allowed not only positive cooperativity but also negative cooperativity; namely, when the first one bound, it could change the next subunit so it bound less well. My theory predicted that. There were no known examples of negative cooperativity at the time.

There were two [advantages] of Monod's model. One was it was simpler than mine, mathematically much simpler. And number two, the only known examples [at the time] were positive cooperativity, and his model only predicted positive cooperativity. In the beginning, everybody sort of thought Monod's model was the correct model.

But then, after I had come to Berkeley, a student of mine named Abby Conway, got the first example of negative cooperativity. And then the floodgates opened.

[End of Interview]

[Interview 3: January 6, 1999]

[Begin Tape 4, Side A]

More on Family Background

Hughes: We're going back to your family of origin.

Koshland: I am a perfect example of an unbelievably lucky child. I was born to two very unusual parents. My father was a Phi Beta Kappa at the University of California and later became president of Levi Strauss and was a successful businessman. Those were the outer characteristics, but inwardly, underneath, he was a very unusual person. He was a very charitable person, not only in the fact that he gave a lot of money to charity, but because he really was charitable towards everybody. I'm a little prejudiced, of course, because he was my father. But nevertheless he was a very unusual person in the sense that he really cared about what I think everybody would agree are the important things of life: being honest, being compassionate, being generous to other people, and working hard yourself. So I had a perfect role model.

The family was struck by tragedy in the sense that my mother, at the age of I guess thirty, had multiple sclerosis, which at that time was a very unknown disease. She was paralyzed and then sort of recovered, but, as is typical of that disease, didn't recover completely. She recovered enough so she limped a little, but she could still drive a car. Ten years later, she had another attack and that time she was a little worse off, and then finally she was bedridden. It was a very scary disease. I remember my father confided in me and told me what she had. He didn't want to tell even her what she had because there were reports in the newspapers which were very depressing. He didn't want her to know. But she was very smart and figured out she had a very serious illness.

Hughes: How did she explain it to herself?

Koshland: Well, we had a doctor who was a neurologist at UC [Medical Center, now UCSF] who diagnosed it. But other people didn't diagnose it right off. In fact, my aunts [Ruth Haas Lilienthal and Margaret Koshland Sloss] would belabor my father to get rid of this doctor because he pretended he hadn't diagnose it, but in fact he had. He predicted the course of the disease almost perfectly. He was a very distinguished neurologist.

We took my mother all the way to New York. Foster Kennedy--I still remember the name--was a very distinguished neurologist at Columbia University. He predicted she had an allergy or something, which the UC San Francisco doctor felt was almost malpractice. He was really furious about it. It was not that easy to diagnose. We were very lucky to have a real expert.

Hughes: Who was the UCSF doctor?

Koshland: A guy named Robert Wartenburg, very famous. Wrote textbooks and did all sorts of things. He was a German refugee. He had an adjunct appointment at UC. You remember, there were a lot of refugees, people who were in World War II. In some ways, he didn't have the status of somebody who was on the full faculty. Although, if you knew very much about research, he had been a very distinguished doctor in Germany and then had to flee. It wasn't as though he was really not as good. But my aunts didn't know any science; they thought he was incompetent. My father knew better, and I knew better, too. For the protection of my mother, Wartenburg didn't say what she had. My aunts deduced from that that he didn't know, which is not true.

My mother really needed to have help, and financially we were well enough off so we did have maids. On the other hand, it changed her life a lot because later on she couldn't drive a car, so one of us, my sisters and I, had to drive her up to the city [San Francisco]. To some extent, it was probably good for us. It put a degree of responsibility on all of us that we might not have had otherwise. My father was just wonderful with her. He was a good example of how to behave. Anyway, I grew up in a very unusual family.

Hughes: Did her illness mean that she couldn't be a mother?

Koshland: Oh, no. She intellectually was excellent, right up to the very end. After a while, she couldn't handle her spoon. Her spoon would just fall out of her hand, so she would have to be fed. It was really tragic. Then her eyes became blurry, so she couldn't read. It's a progressive disease, which is really terrible because it gradually deprives the person of their faculties and use of their limbs. In my mother's case, it lasted years. She died at the age of fifty-nine. She had many years of illness in between, and it progressively got worse.

Some people die very quickly because if it affects the heart muscle; you just die. Whereas it affected her limbs, so she lost the use of her arms and her legs, but not of vital organs. Anyway, it was something the family had to cope with. It's a way of saying that I grew up with a sufficient amount of responsibility but an enormous amount of love and devotion.

It was very important to my subsequent career because I really had so much security at home and so much caring for the approval of my parents that it really didn't matter that much to me how much the outside world approved of me. I was elected president of my high school class; I liked to be approved by my colleagues. But it was not that important that I felt I had to be popular on every issue, which is extremely important in my leadership later on at the university, where I had to do the reorganization of [UCB life sciences] or something which involved getting a lot of people mad at me some of the time. It didn't bother me that much because my father really made it clear to all of us--my mother, too--that if we went out in the world and we did the right thing and it was very unpopular, they didn't care. We were going to be a member of the family no matter what.

My father was a leader in civil liberties in the early days, long before the FEBC [Fair Employment Practices Commission] or any of the early things that [Franklin] Roosevelt did to try to help blacks get welcomed to San Francisco. That stance of his was very unpopular. It was very unusual for a businessman--not a labor leader--to take a lead in race relations. Levi Strauss and Company ended up hiring a lot of blacks and minorities and had a very good policy. He got a fair amount of criticism from other big employers. It didn't bother him very much. So I learned a lot [from him] for later use of my own.

Hughes: Was it his position at Levi Strauss that propelled him into the racial issue?

Koshland: I would say he was propelled into the issue and then used Levi Strauss as an example platform. It was a family business, which he and my uncle [Walter Haas, Sr.] ran. They were both very similar in political outlook. My father was, I would say, more liberal than my uncle, but it was only a shade of difference. My uncle was a very generous person also, so between the two of them, they had no problem. They really decided to help minorities. They also helped people who were parolees. There was a joke in the family: if you weren't a minority and had not committed some serious crime, you had no chance of getting hired at Levi Strauss and Company [chuckling], which is an exaggeration, but nevertheless has some basis in fact.

That was important because Levi Strauss and Company is involved in making jeans, which is a highly competitive business. It's not a business that's a monopoly in which you can do whatever you want. So they had to take account of labor strikes and things like that. If they thought it was the right thing to do, then they did it.

That kind of a background, you might say, had nothing to do with what I did later, because I went into science; I didn't go into the business. That was another thing: my father never pressured me to go into the business. Once, later in life, when I was about forty, I said to my father, "Were you disappointed I didn't go into the business?" He said, well, he would have liked it, but he wanted me to do whatever I wanted. That was the kind of background I grew up in. It probably had a big influence on my life.

My father had a really good sense of humor. He was a big kidder. He always said to us, if we wanted to know anything about sex, we could just ask him and my mother. We did. My younger sister [Phyllis later Friedman] in high school used to get some lurid stories from her contemporaries that she didn't understand. She would frequently bring them up at the dinner table. We were frequently allowed to have dinner with distinguished guests. (I remember one dinner with the president of the University of California and the president of Stanford.) Phyllis, at a lull in the conversation, said, "Dad, somebody told me this story," and she told a story that would make a longshoreman blush. [chuckling] My father said, "I'll explain it to you later." But that wasn't good enough for Phyllis. Of course, the guests got a big kick out of this and how my father was handling it.

A friend of our family, a gal named Agnes Brandenstein--I don't know whether she was a relative, but she was a nice lady who knew my mother and was very nice to my mother and came and visited her. Agnes liked to kid my father, and my father liked to kid her. It was discovered that Agnes was the source of some of these stories, that she frequently would come and during the cocktail period before dinner tell Phyllis a particularly bad story and tell her to ask my father what it meant. [chuckling]

My father found out about this, and he told my sister, who was then, I'd say, thirteen or something like that. He took her aside and he said, "Phyllis, I want to explain something about Agnes. Agnes is a very nice lady, and we like her very much." She ran a little gift shop in San Francisco, on Union Square. He said, "You know, that gift shop is just a front. Agnes is really a prostitute. She really gets her income from prostitution, and she pretends she has this store." He said, "There's nothing wrong. We still have her to the house, and we like her. But, on the other hand, she doesn't have the same sense of a dinner party that we have, so maybe you shouldn't repeat those stories. I'm glad if you tell them later, but perhaps you shouldn't bring them up at a dinner party."

Well, my sister was absolutely overwhelmed. She had a new view of Agnes. I remember the next party we had, Agnes came in, and my sister circled her the way dogs do when they sniff neighboring dogs. [laughter] She was meeting a genuine prostitute. Anyway, all of a sudden, Phyllis stopped telling these stories. When Agnes would tell her the story, Phyllis would always say, "Well, I'll talk to Daddy later." So it worked. Of course, it was a famous story in the family. My wife was always upset because she thought Agnes should be told, but Agnes went to her grave, never knowing this had been told about her. [chuckling]

I'll tell you one more story. The age when you could drive in California was sixteen, but a bunch of kids were getting licenses at fourteen. They were able to drive their parents' cars. I wanted to do this, and I told my father. Apparently, you could get the license at fourteen if your father would go in and say it was necessary for you to drive. In my case, I clearly didn't need to drive because we had a maid, but it would be convenient because driving my mother, who was crippled, was a big asset to the family.

So I asked my father and he said, "Sure, I’ll do it." He said it would be convenient, but he wasn't going to say we needed it. I was furious at him because I felt all the other boys' fathers did it, and it was the thing to do. My father said, "I'm sorry, I'm not going to lie." So we went down to the judge, I filled with pessimism. I knew I would never get it if my father wasn't even willing to tell a few lies.

So we walk into the judge's chambers, and the judge says, "Hello, Dan." "Hello, Joe," or whatever his name was. Clearly, he knew my father. My father said, "Well, my son would like a driver's license at fourteen." The judge said, "What is the justification?" My father said, "Well, you know, it would be really convenient. We have a maid, and we don't really need it, but occasionally it's good for Danny to run down to the store and get something. It would be convenient if he could drive." At that point, the judge said, "Sure." And I got the license and walked out of there. It was a good lesson. It told me my father was not going to lie, and it negated all these stories that you had to lie in order to get the license. So that was the kind of childhood I had.

Grammar School in Hillsborough, California

Hughes: Now that we're talking about the family, why don't you describe what a typical school day was like when you were in grammar school.

Koshland: We lived in Hillsborough, which was a residential suburb of the city of San Mateo, which is a bigger city. It was pretty rural. I used to ride a bicycle to school most of the time. I was, I would say, a couple of miles from school. I could walk, but it was slower, and I rode a bike a good fraction of the time. My mother or my father on rainy days would drive me.

It was really a very good elementary school [Hillsborough Elementary]. Practically every day I'd stay after school. We usually had a baseball game on the school grounds, and every once in a while, if there were too many kids, some of us would go over to some cornfield or nearby and play football or baseball. Football was usually the game you had to play if you went to a cornfield because the ground wasn't good for baseball. So you adapted to whatever had to happen.

Hughes: Was the game under school aegis?

Koshland: No. Usually, when school was over, you were allowed to use the school grounds. There were some tennis courts there, as I remember, and a basketball court, so kids would just hang around and play. If] there were too many kids playing basketball, then a couple of kids would play tennis. It was very easy-going in the sense that you just did whatever was available. The school took no responsibility. It was a different era--no people worrying about--

Hughes: Liability.

Koshland: Liability, yes. Now you'd probably have supervisors. We played basketball on an extension of the tennis courts. Somebody could have fallen down and hurt themselves, but as I remember, there was probably no supervision.

Hughes: Were you good at sports?

Koshland: I was medium good. I was pitcher on the grammar school team, and then I was second baseman on the high school team, and then, as we got to the upper levels of high school, my eyesight started to go bad, and I wasn't that good. But I was good enough to be a pitcher, and I was usually the quarterback when we played football. I was a pretty good football player, but I wasn't that big. I was nearsighted and also

I was pretty good at school. My interests then started going more and more toward science and college, so I didn't spend the time on sports.

Hughes: Was the grammar school a public school?

Koshland: Yes.

High School

I went to public grammar school, public high school. I should say I went two years to public high school [San Mateo High School], and then I went to Exeter, which was a private school, for two years, and then went on to college.

Hughes: Was it a philosophical stance of your parents, to send you to public school?

Koshland: Yes and no. I think that all of my kids and I are very pro-public school. We went to public school; they send all their kids to public school, and we're pretty much not for private schools. We felt that you want to mix with everybody in the sense that we didn't want privilege and in the sense that you just meet a very nice bunch of people; it didn't matter. So I don't think we thought it out that much, but we just sort of said public school is what we wanted.

My situation as a grammar school person was very similar to my children's. We were living in a place where there were excellent California public schools, and there was no real pressure to go to private school. But some of my friends at Berkeley send their kids to private school. My five kids all went to public schools, and they went to college at Harvard and various other places, so they've all had excellent training in public schools.

Hughes: You feel the same, that you had excellent training?

Koshland: I feel the same, yes. I had no problem.

I think most of the students who go to Exeter go on to Harvard. I could have gone on to Harvard, but I came back to California because my mother was so ill. By that time, the multiple sclerosis had gotten more advanced, so I wanted to be in a place where I could go home on weekends. But I think there was very little question I would have gotten into Harvard. Harvard wasn't as difficult to get into as it is now.

Hughes: Why were you sent to Exeter?

Koshland: I wasn't sent to Exeter. In fact, I think my mother really didn't want me to go. And I sort of didn't want to go. That's an amusing story. We had a cousin called Phil Lilienthal, who was eventually a professor at Johns Hopkins and an absolutely charming guy. I was about thirteen or fourteen, I remember. Phil Lilienthal would come out periodically, in summers, to visit his aunt [Ruth Haas Lilienthal], who was also my aunt. He was a cousin on the Lilienthal side, and she was an aunt on the Haas side.

Anyway, because he was six or seven years older than me, he was obviously looked up to as an interesting college kid. He used to tell really spellbinding stories about the times he fought with the Spanish pirates and things like that. It was totally baloney [chuckling], all made up, and we all sort of knew it was made up, but he was such a good storyteller, we loved him. Anyway, I thought he was just the greatest guy in the world.

At one point, he said to me, "Danny, you really ought to go to Exeter." Because he grew up a little bit in a tradition of private schools. I said, "I'm totally uninterested in going to Exeter." I was very happy at high school. As a result of that, I wrote to Exeter and said, "Okay, supposing I wanted to come, what would--" So they wrote back a very snotty letter, saying, "Since you come from the West, you'll have to go back a year." I was a sophomore. You knew they meant, education isn't nearly as good in the West as it is in East, where we really know what education is all about.

I was really angry. That just got me mad, so I wrote back and said, "What would it require for me not to go back a year?" They wrote back and said, "If you take the college boards and you pass those, you can come." Well, the college boards are given usually at the end of your senior year, so it was something for a sophomore to take college boards. But, on the other hand, they're given in subjects like Greek and Roman history and beginning and middle English and so forth.

I had to go down to Stanford and register and pay a little fee. So I said, "All right, I'll try it," with no intention of going. I went down, and I took the boards, and I passed! I get this notice that I passed all the college boards, and a day later my parents got a notice from Exeter saying I was admitted into my junior year. See, this was my sophomore year. [chuckling] So Exeter just assumed I was coming! And so I ended up going.

It probably was good for me because my mother had gotten worse. I thought I would finish high school, and I sort of had my eye on going to Harvard. I said, "Okay, I'll go east for a couple of years. It will give me a different environment. And then I'll come to the University of California for my college." And that's what happened. So it worked out very well.

Hughes: How did you, as a California boy, do in the eastern environment?

Koshland: It actually was very nice. It was not really difficult. It was different, I noticed. It's what I recommend to my students. A lot of them have come up through the California school system and go to Berkeley when they go to graduate school. I say, "It's good to go to some other part of the country, just because you learn about different ways of looking at things." And there *was* a different attitude. It was interesting and subtle. It was a good experience, going there. I'm glad I did because I think if I had just gone to high school here and gone to the University of

California and never gone East, it probably would have not been as good an experience, although I really enjoyed what I was doing here.

Hughes: Did you gain educationally in a way that you wouldn't if you had remained in California?

Koshland: Part of it was educational because the high school in California really didn't challenge me. It was really too easy for me. My mother was sort of angry that I didn't take five periods. I had four periods, and then we had this study period. We could take five subjects, but you didn't have to. So I took four because, as I told you, I took a bicycle or walked a fairly good distance. The challenge was that I did all my homework in one hour, in the study period, and then I didn't have to bring any books home. Books were a pain in the neck because they were added weight. So I set myself up little games like that. But it was clear I was not being challenged that much. What Phil Lilienthal did say was that Exeter was much, much harder. And it was. It really did make me work much harder. I did very well at Exeter but, on the other hand, I couldn't get all my homework done in one hour. So from that point it was good. Secondly, it was a different milieu.

I'll give you an example in which I think the West was better. One of the weekends after I had been there a little while and gotten to know a bunch of kids, a bunch of us went out and started playing baseball in an empty field. I think it was owned by the town, so whoever went there played and then, when they finished, somebody else could play. We had about eight or nine people, which was not enough for a good baseball game. There was a bunch of these kids waiting around. In my western tradition, which is much more open, I said, "Well, why don't we ask those kids to play?" They said, "Well, we don't even know them." I said, "What's the matter? We don't have to know them to play baseball with them." I was not that secure at that point--(I later on talked them into it)--so we didn't ask the kids. They were waiting around, and we were playing a game with inadequate numbers of people, and we could have added these people.

My son Jim is a good example. When he became a lawyer and moved out to San Francisco, he would play pickup games in Golden Gate Park where he met a bunch of other guys who played lacrosse. That's not a big game around here. But these were people who had gone to Eastern schools or had learned to play lacrosse somewhere or another. They'd meet at the corner of Golden Gate Park, at some field that was reserved for lacrosse players. I once asked him, "Jimmy, do you know those kids?" He said, "Yeah, Phil and Joe and--" And I said, "Do you know their last names?" He said, "No."

[End Tape 4, Side A. Begin Tape 4, Side B.]

Koshland: My feeling is regardless of whether it's a public college or a private college, you are making an inevitably class-line separation when you start going to college. I met a lot of rougher, tougher kids when I went to public high school than I've ever met at a university, East Coast or West Coast. I think that's a good thing in a democracy. I believe that for my children, so did my wife, and so all our kids went to public school.

Initial Interest in Science

Hughes: When did you become interested in science?

Koshland: I'm embarrassed to say it, because my story is so banal. I read a lot when I was in elementary school, partly because I was nearsighted, but I just liked to read. Among the books I read were *Microbe Hunters* and *Arrowsmith*. Remember, neither of my parents were scientists. Those are two great books. A lot of people have been influenced, as I was. So when I read them, I really wanted to be a scientist.

When I went to high school, I not only majored in college preparatory courses but also took chemistry, physics, mathematics--all the things you need to do to go into science. When I went to Berkeley as a freshman, I enrolled as a chemistry major. I was more interested in biological sciences, but everybody told me the way to do it was get good training in chemistry and physics first and then concentrate on biochemistry in graduate school.

Hughes: So you knew from the beginning of--

Koshland: High school that I really wanted to be a scientist. I never deviated. Except that in my senior year at Cal, I suddenly, for reasons that are not clear to me, decided I was bored with science, and I wanted to do something else. One of the good friends of our family said, "Well," he said, "the thing to do is go out in industry. You'll either like it or you'll hate it. A year is not that important at this point." I went into industry, and I hated it. I then went back into graduate work and got a Ph.D. and really loved it. I advise other people to do that. In other words, I probably would have gone on the rest of my life and said, "Well, I really am sort of bored with this. I'd better do that." Because you always get bored with anything you do. There's a lot of boring stuff in science.

I was offered a college presidency when I was at Brookhaven. At that stage, I didn't want to do anything else but science. So it solved a lot of my problems.

Sisters

Hughes: Let's talk more about family. You've mentioned your sister, Phyllis, but who else was there?

Koshland: I have two sisters, both of whom I'm very fond of. My older sister is Frances [Sissy] Geballe, who married my best friend in college, Theodore Geballe. He and I got to be friends in freshman chemistry and did a lot of homework together at times and really became very good friends. I lived in Bowles Hall, and he lived, I think, in Sheridan Hall, which was a co-op. So we never lived in the same dormitory, but we would meet after class and play games--touch football and things like that. We were really very good friends. Somewhere in the middle of the junior year, he took Sissy out on a date, and they became very close, and he eventually married her, very close to graduation. When we graduated [1941], World War II broke out, so we both went into the army. He went overseas, to Japan, to Guadalcanal. And I went to the East Coast.

My two sisters went to Berkeley. My sister, Sissy, who was about a year and a half behind me, was at Berkeley during the years I was here, and my sister, Phyllis, entered the year when I was a senior. The family was very large. Lots of first cousins and all living in this areas. Our grandmothers were the central source. We'd go to their houses and have parties, so I got to know my cousins pretty well. That was a big asset, which added to the feeling of belonging to a big family. And it was generally a very nice family, very few family arguments. I met people later in the war who had trouble meeting girls, but I met so many of my cousins that the whole business of girls and boys was just routine for us.

Grandparents

Hughes: Your grandparents were in San Francisco?

Koshland: Yes. My grandfather[Abraham Haas] on one side died before I was born, and Marcus Koshland on the other side died when I was two.

Hughes: So you don't remember them.

Koshland: There's a picture of me with my grandfather when I was two, but I don't remember. The grandmothers were there, and they were very important. A big factor in our lives.

Hughes: What were their personalities?

Koshland: Oh, they were very unusual people, both of them. My grandmother on my father's side [Corinne (Cory) Schweitzer Koshland] was a very active woman, very active in civic affairs, opera, Red Cross. She just did all sorts of things. She was a very interesting and very charming lady, but not very literary.

My other grandmother [Frances (Franny) Koshland Haas] was much more sedentary. She was at home. She was a big family person. She had a very quick wit and was very literary, but didn't do a lot of other things. I remember once my father said to her that we were having a dinner party, and she said, "Who are you having?" He mentioned that the president of Cal and the president of Stanford were coming down--it may have been the famous night my sister told the terrible story. Anyway, she said, "Why are you having *Dreck* like that? *Dreck* is a German word meaning junk. My father said, "What do you mean? He's the president of Stanford." "Well," she said, "you could have Uncle Phil [Lilienthal] and Uncle

Walter [Haas],"--the family. My grandmother's idea was if you had a family party that was the best. It was only because you couldn't have a family party that you had *Dreck* like the president of Stanford. We all kidded her about it.

Hughes: Did either of them take any particular interest in you?

Koshland: I would say yes and no. I was always very well treated, but I wouldn't say I was better treated than the others. I liked my grandmothers. My Grandmother Haas, very liberal, was lots of fun. And so was my other grandmother. They both had houses in San Francisco. If there was a prom in San Francisco, at the Mark Hopkins Hotel, it was convenient for us to change our clothes there. My date and I would do something in the afternoon, and we could go over and change at my grandmother's house. It was partly because I really thought my grandmothers were pretty charming women and helped me with my dates. [chuckling] Well, you don't want to bother with your family, but it was just the opposite with me. My grandmother would have drinks and hors d'oeuvres, and we'd talk for half or three quarters of an hour, and then we'd go to the prom.

Hughes: Were both grandmothers living in elegant houses?

Koshland: My Grandmother Koshland lived in an elegant house, and my Grandmother Haas did not. She could afford a more expensive house, but she just didn't like it.

Hughes: Was it ever a difficulty for you to come from a well-to-do family?

Koshland: Yes, it was very upsetting to me. I wanted to be just like everybody else. We usually had a Studebaker, which I thought was all right. Even so, it was a bigger one than a lot of my friends had, and I was sort of angry at my father for doing that. Then one year he got a Buick, and it was really embarrassing for me to be picked up in a Buick. So he never was allowed to park in front of the school. The parents were going to pick you up after school. They would frequently line up in front of the school. I used to stay after school and play baseball, and one of my parents would come pick me up about five-thirty. So my father would sometimes pick me up because he came back from San Francisco where he was working.

The Family Home in Hillsborough

Hughes: Was the Hillsborough house elegant?

Koshland: The Hillsborough house was a pretty big house, yes.

Hughes: How did they come to live there.

Koshland: They moved out from New York when I was about two years old, so I only know this by indirection. My father always liked the country. I don't know if it was free will, but my sisters and I all live in houses outside the city. One sister lives in Hillsborough; one sister lives in Woodside. My brother-in-law [Theodore Geballe] is a professor at Stanford, and I'm a professor at Berkeley, and I live in Lafayette. I don't think it's just an accident.

Anyway, my father moved out from New York, where he started his career, and joined Levi Strauss and Company, and then got a house on the peninsula. We rode horseback. He was a pretty good sportsman himself. He liked to play golf a lot.

Hughes: Had he been brought up in New York?

Koshland: He had grown up in San Francisco. He went to Lowell High School. He went to a public school also.

Hughes: Did he build the Hillsborough house?

Koshland: No, they bought the house from somebody else. He told me the incident. The lady who had it loved the house. She hated to sell it, but none of her children wanted it. The real estate agent told my father, "The woman really doesn't like the idea of selling the house, but we talked her into it. You're going to have one chance to see it; I'm sure she'll never let you back." They saw it, and they loved the house, and so they made a bid. She really didn't want to sell it, but finally she ended up selling it. And that was it. They never got to see it again before they bought it. It was in an isolated area.

Hughes: There was a lot of property?

Koshland: Yes. It's an enormous amount now, not so much then because there were a lot of big places. It was really out in the country. My father gave my sister and me each a pony. We would go out in the stables and just ride over the hills. Around San Mateo, there are small lots now and thousands of houses; you couldn't possibly do that anymore. But it was not unique at that point. It was about ten acres, so now that's a fair amount of land in California.

Hughes: Does the family still own it?

Koshland: My sister lives on about two and a half or three acres of the original property, and the rest of it has been sold.

[End of Interview]

Interview 4: January 15, 1999

[Begin Tape 5, Side A]

More on Induced Fit Theory

Hughes: I want to pick up on some things you said about induced fit in your article in *Protein Science*.[5] You started by saying that your initial interest in enzyme mechanism was influenced by classic papers by Hans Neurath and Robert Alberty. What was it that intrigued you about those papers?

Koshland: That's a good question. I'm going to have to think about it. I got interested in biology from the point of view of *Microbe Hunters* and *Arrowsmith*, basically solving medical problems. And then, because when I was an undergraduate biochemistry was very primitive, various people advised me to become a chemistry major because biochemistry courses weren't very good. They were very memory oriented and very old theory. So I majored in chemistry, intending to go into biochemistry when I went to graduate school.

But then the war broke out, and I ended up on the bomb project, doing inorganic chemistry, which had a lot of interesting implications for my career. After four years of war research, I considered going back to graduate school. I considered myself really old because I was twenty-six or something and my youth had been wasted, so I thought I'd better get through graduate school as quickly as possible. The quickest way to do it was to major in chemistry and then get associated with somebody in the chemistry department who was interested in biological problems.

If I took biochemistry--and biochemistry was very medically oriented--I would have had to take a lot of preparatory courses just to understand the basics. So I majored in chemistry, and fortunately for me, there was a young man named Frank Westheimer who was also interested in applying chemistry to biology. So I picked a problem, and that's what I did for my graduate work at the University of Chicago [1946-1949].

And then I went for a postdoc at Harvard [1949-1951]. I got one of these fellowships which allowed you to choose your own research problem, and so I started reading in what areas I'd like to go into and decided that enzyme kinetics was a particularly interesting problem. I hadn't done that as a graduate student.

Hughes: Why was it interesting?

Koshland: Understanding enzyme mechanism was really very important because it was quite clear that enzymes were *the* bedrock of all biology. Enzymes really run everything in your life: your nerves, your muscles, your thinking—-everything. So they were

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[5] Daniel E. Koshland, Jr., "The Joys and Vicissitudes of Protein Science," *Protein Science* (1993) 2, 1364-1368.

right at the core of things. People knew very little about how they worked except that they were magically powered. They did all these powerful things. So I thought it would be very interesting to look at them.

I read the papers of Neurath and other kinetic papers--Alberty and so forth--and got interested in that way. During my postdoctoral years, I worked on enzyme kinetics and purified enzymes, which was very much like the work of a chemist. That is, you could put into the test tube things you knew, whereas when you start studying a living organism, you're dealing with all sorts of unknowns.

Hughes: So enzymology was a more familiar ground for a chemist.

Koshland: It was more familiar for a chemist, and you felt you were in control of everything, and you could figure things out.

Then I finished my postdoc and got a job at Brookhaven [National Laboratory, 1951-1965]. I worked on applying enzyme mechanism to the problem of muscle and other things.

Questioning Emil Fischer's Key and Lock Theory

One feature of enzymes was explained by Emil Fischer's key-lock theory, template theory. It explained how enzymes could discriminate between very similar compounds in ways that ordinary chemical catalysts couldn't do: the substrate molecule could fit into the active site of the enzyme, sort of like a piece in a jigsaw puzzle. If the pieces fit, they go together; and if they don't fit, you can't put them together. So that was Fischer's theory.

I started to think about that, and I realized that I knew some examples that didn't fit that theory. They were examples that other people had mentioned but everybody just brushed to the side. "Well, you know, that doesn't quite agree, but what do we care? Ninety-nine percent of the stuff agrees." I decided that even though there were only a very small number of exceptions, they were very important.

I won't get too technical, but basically there was no way I could figure out how these exceptions worked. And then I thought of other things that also didn't fit. The more I thought about it, the more I said that this basic key-lock theory has to be changed.

Hughes: Were you the only person questioning Fischer's theory?

Koshland: Yes, absolutely. Everybody accepted it.

I had a heck of time getting it published because everybody knew the Fischer theory, everybody used it. I was a pretty young person, and I had published three or four papers. My reputation was pretty good, but certainly not enough to challenge the famous theory of Emil Fischer. One reviewer said, "The theory of Emil Fischer has been good enough for a hundred years, and it's certainly not going to be turned over by some little pipsqueak at Brookhaven National Laboratory." He implied that not only was I a pipsqueak but that Brookhaven wasn't that prestigious an institution.

Fortunately for me, at Brookhaven there was a very distinguished biochemist named Donald Van Slyke who had been at the Rockefeller Institute. He had decided to retire by coming to Brookhaven. They made him head of the medical division at Brookhaven to get him there. He was a member of the National Academy of Sciences, and he sponsored my paper for the National Academy. So I got it published [in the *Proceedings of the National Academy of Sciences*].

Hughes: Did he sponsor it because you were a colleague at the same institution or because he thought this was work that should be published?

Koshland: I will never know the exact answer, but probably a combination. He had talked to me a number of times, and we liked each other. He thought I was a young man that needed some help, and I think he thought what I proposed was plausible enough that he wasn't likely to end up looking stupid. But my work was not right in his area, so it was not really that he looked my theory over and said it was right.

I presented the theory at an American Chemical Society meeting. The importance of it was recognized by everybody right off. I remember there was a big write-up of it in the newspapers, the fact that somebody had challenged the Fischer theory. And it was plausible enough. It was good enough so people could look at it and say, "This makes sense."

The Hand-in-Glove Analogy of Enzyme-Substrate Interaction

My induced-fit model is more like a hand in the glove. To put the glove on, your hand has to fit. If your fingers are too big, you can't get the glove on. But the glove changes shape when you put your hand in it. That is an analogy that is easy to understand.

The induced-fit theory was very controversial. You had Fischer’s key-lock theory that everybody could understand and was taught in all the textbooks, and now you had somebody questioning it with sort of complicated experiments. I had done a number of experiments which I published in scientific journals. I was invited to give a lot of seminars. Gradually, the theory got accepted.

Hughes: One of the problems, if I remember correctly, was essentially technological, namely that you didn't have NMR [nuclear magnetic resonance] and crystallography to clinch this theory. So your experimental results were incremental.

Koshland: Yes and no. I think the answer is that I did some experiments which people who really understood enzyme mechanism would say, I'm pretty sure, were very convincing. You could explain them on the induced- fit theory and not on the old Fischer template.

Hughes: Was that that idea of active sites for enzyme attachment being either available or not available?

Koshland: Yes, that's partly true. They were complicated experiments. Crystallography did not exist when I was doing this, so I was doing enzyme mechanism, enzyme kinetics types of experiments. And then crystallography came in. Crystallography is like describing a boxing fight and having a moving picture of it. You can describe, "He hits me with his left hand, and I hit him with my right, and then he ducks and I miss." But you won't get quite the flavor of the boxing match unless you have a moving picture. Okay, that's basically what crystallography did.

Crystallography was a way of looking at the problem so that people who were not specialists in enzyme mechanism could understand. In the first couple of crystal structures, there were small changes [in the conformation of the enzyme]. Some scientists passed them off, saying those small changes don't mean very much. I felt the small changes proved my theory. I was a chemist and I knew the length of a carbon-carbon bond was 1.5 angstroms. So if you see movement of half an angstrom, that's a big deal. That's a third of the distance of a carbon-carbon bond. But if you're a biochemist and not very chemically trained, half an angstrom [conformation change] seems very small. An angstrom is 10^{-8} inches, a hundred millionth of an inch.

Hughes: Who was doing the crystallography that showed very minute changes?

Koshland: The first structures were done by [David] Phillips and [Frederick] Richards. They did the crystallography of lysozyme and ribonuclease. They showed there were actual [structural] changes, which now everybody accepts as being big enough to really make a difference. But at the time, some sort of pooh-poohed it. They didn't say anything negative; they didn't say anything positive. I wanted them to say, well, this proves the induced fit theory.

Hughes: What were the enzymologists saying?

Koshland: I've forgotten. I think the first structure was by [William N.] Lipscomb at Harvard. He did an X-ray structure in which one of the residues moved by twelve angstroms.

Hughes: That was convincing.

Koshland: That was plenty convincing.

We made a prediction that hexokinase was an enzyme that needed to have an induced fit because otherwise water would react a lot. The only way of keeping water out of active sites was induced fit. That was one of the first predictions of the induced fit theory. And Lipscomb showed absolutely unequivocally from X-ray structures that that theory was exactly what was predictive of hexokinase. And it turned out exactly right. So then everybody really accepted my theory.

Hughes: Wasn't Stites also involved with that work?

Koshland: Yes, Stites was involved both in the first work and the second. The first work was as a student with Lipscomb, and after it was his own lab.

Hughes: Were they inspired by your theory?

Koshland: I don't know what you mean by inspired. They were just studying enzymes for different reasons. Then they showed these big changes, and they said, "Oh, this really shows this induced-fit theory is right."

I was looking in all sorts of places to apply induced fit. Pretty obvious to me was that this idea of changing shape meant that you could bind a molecule not at the active site but somewhere outside the active site and cause a big conformation change which would turn on and turn off the protein.

Hughes: Why you did you think that?

Koshland: Well, because in something called noncompetitive inhibition, a molecule could bind to a protein and not affect the binding of the substrate at all but turn off the protein.

Hughes: How would that happen?

Koshland: There was really no good theory in organic chemistry that could explain anything like that. You could understand if some substrate bound to the surface, and you had a little molecule that prevented it binding correctly, then it wouldn't react. But this showed no evidence of the binding; it just stopped the reaction completely. Whereas induced fit offered a perfect explanation for that: when the substrate binds, it has to induce the proper alignment of catalytic groups. Catalytic groups may or may not be involved in binding. They're doing the catalysis. And so if you had a group that prevented the catalytic groups from lining up correctly, it could have no influence on the binding and still turn off the reaction.

Hughes: It seems to me that at this point you were moving closer to what the French group was doing. They were beginning to talk about two sites, one of them being the catalytic and one of them being--

Koshland: I produced a paper talking about the amino acid reactive site and other groups that I call the auxiliary amino acids, the ones that weren't in direct contact with the substrate. Monod and his group published a paper calling the auxiliary groups the allosteric site. That was really a much better name. That caught on. So we were really both thinking very similarly. He was in Paris, and I was in no contact with him. He referred to my paper on the induced fit when he talked about the allosteric site.

Then there was a separate property called cooperativity, which is known in hemoglobin, which is a very important protein because it's involved with our breathing and all the energy metabolism that we have in the body. It has what is known as a sigmoid curve [for substrate-enzyme interaction], sort of an S-shaped curve, which is a peculiar type, not the kind of thing that most enzymes have. Monod and I were both intrigued with that. We started working on a paper, and we submitted it in 1965. Apparently, he must have submitted his in 1965, too. But mine got rejected. It finally appeared in 1966. We were both trying to explain this sigmoid curve. You have to do some complex mathematics to do this. What Monod did was publish it with a theory which he called the--

Hughes: Concerted model.

Koshland: --concerted model. He also called it a symmetry model because he proposed that the subunits of a protein all preserve symmetry. You can change them, but they had to eventually preserve symmetry.

Hughes: Why?

Koshland: He just felt symmetry was a universal principle of nature. My theory did not say it preserves symmetry and was not concerted. It was sequential and non-symmetrical.

Hughes: Concerted meaning what?

Koshland: The idea behind both of our models was that hemoglobin and a lot of enzymes are composed of what started out to be identical subunits. Then as each substrate binds, it causes a change in the subunit. Let's say there are four subunits--four molecules of oxygen bound to four subunits. My theory was, as each one bound, it changed the individual subunit, and they fit into each other in a gradual pattern. Monod showed that you could also fit the sigmoid curve by [assuming] that the molecule changed suddenly, all four subunits changed symmetrically, so they all preserved symmetry to the final arrangement, and then gradually molecules bound to the changed hemoglobin protein. Both theories fit the sigmoid curve, but they predicted very different things for what happened in the middle. But there was no way of looking in the middle. They were only theoretical at the time.

Positive and Negative Cooperativity

I predicted that there would be some curves that would be much flatter and look very different, which I called the result of negative cooperativity. The positive cooperativity of hemoglobin was that the first molecule of oxygen that binds makes it easier for the next molecule to bind. I said in addition there could be negative cooperativity. At least for my theory, there was no reason why if you bind a molecule it shouldn't change the shape in such a way that the next molecule is harder to bind. That was called negative cooperativity.

Well, there was no example known in the literature of negative cooperativity. All the known examples, of which there weren't very many, were positive cooperativity, and Monod's model predicted only positive cooperativity.

The second thing about Monod's model was that it was much simpler than mine. It was easier mathematically. So people tended to associate with it. This is an interesting feature I've always felt was actually good for me, that everybody would start off their articles saying, "We tested the model of Koshland, Nemethy and Filmer, and the model of Monod, Wyman, and Changeaux, and sure enough, Monod, Wyman, Changeaux's fit the data better than Koshland, Nemethy, Filmer's." But they always mentioned mine because it was good to talk about a negative. There has been a tendency in science that if somebody has predicted something, a lot of people don't give that person credit because they'd like to think that they discovered it, whereas if the prediction's wrong, it's always nice to mention it.

Hughes: [laughing]

Koshland: I've told my students that it's good for them to be a little wrong. Anyway, for a long time Monod's model was seen to fit what was observed in nature, and Koshland just said the negative.

Hughes: Did you know examples?

Koshland: No, I didn't know any examples. So I kept my eye open. Then one of the students in my lab kept getting funny results. I saw in one instant that it was negative cooperativity. The girl's name was Abby Conway. You know, what Pasteur called chance favoring the prepared mind. My mind was prepared, and I knew immediately. I was very excited. We did some more experiments, and we proved it was correct. That was the first experimental example of negative cooperativity.

I remember giving a talk at the University of Wisconsin. The minute I finished my talk, a very famous professor there, Philip Cohen rushed up to me. He said, "Dan, Dan, you must come up to my office." I went to his lab, and he introduced me to one of the students. The student had gotten a curve which looked very much like the one my student had gotten that I was reporting on. It was such an unusual curve that he had not let her publish it. He felt there was something wrong with the data.

She was so excited when she heard the explanation. She knew she would get her work published and get her thesis out. He was a very nice person because he recognized right away that her stuff was really okay, and they should publish it. In fact, that [situation] had been repeated in a number of other universities. People had found negative cooperativity, and they just hadn't published the experiments because they hadn't believed them. They thought there must be something wrong. In fact, today there are more examples of negative cooperativity than positive.

Hughes: Your story reasserts the importance of an overriding theory. The tendency is to support it, even when there are discrepancies.

Koshland: I think that's very true of science. My experience is that theory and experiment are really like the classical game of leapfrog. You bend over and somebody leaps over you, and then they bend over and you leap over them.

[End Tape 5, Side A. Begin Tape 5, Side B.]

Koshland: In positive cooperativity, the first molecule of oxygen makes it easier for the next one to bind. What that means is that you either have a hemoglobin molecule which has no oxygen on it or four molecules of oxygen. It's very difficult to get intermediates. That is true in general.

Our lab has recently shown that the aspartate receptor has negative cooperativity. The first molecule makes it sufficiently difficult for the next to bind, so we can catch it at the intermediate phase and get the X-ray structure with one molecule bound, even though eventually two molecules finally bind. [As new technologies developed,] it is now clear that even those with positive cooperativity do have a sequential binding.

Induced Fit as the More General Model

Hughes: The Koshland-Nemethy-Filmer model is probably the more general model. But the Monod-Wyman-Changeux model works in some cases?

Koshland: Sometimes probably. Probably rarely. All enzymes probably have induced fit. I thought maybe there would be a class of enzymes that are induced fit and another class which are template, but--

Hughes: What about the class of enzymes that is not regulated, that functions at a steady rate.

Koshland: They have an induced fit. They just don't have a second site. They just don't have an allosteric site. The term allostery got very mixed up. Arthur Pardee, who was a professor at Harvard, did a lot of very good work. He called it a regulatory site, which was a good name. But it didn't cover all the [cases]. What happened in hemoglobin, there were four identical molecules, and binding of one molecule affected how the other ones bound, even though they were identical sites. A regulatory site is a better way of [describing] that when there's a different type of molecule. Allostery would cover both. It turns out nowadays you can define all of these things very precisely. During the period when the research was very exciting, the definition was not quite as clear, although I was sure I knew, and Monod was sure he knew.

Hughes: It sounds to me as though you started off with a problem in enzyme mechanism. But then, as you explored it further, you began to stray into enzyme regulation.

Koshland: Right. We were trying to explain enzyme mechanism. We came up with something that was very different than what anybody else explained. People understood that proteins seemed to change shape in the sense that if you heat milk, it precipitates out of the solution. That sort of thing. So that was never surprising. We were talking about a very precise and important change in the enzyme. But once we said this was true, you then thought of what the implications were. One of them was to explain this cooperativity, and the second was to explain the regulation. The regulation really fit in with the second phenomenon that Pardee and Umbarger had been interested in, which was called feedback. When you produce too much of a molecule, there's something in your biological system that tells you, "Stop making that; we've got too much." That's called feedback. We realized that the induced fit theory gave us a wonderful explanation for feedback. The allosteric sites, as Monod had called them, were really very good feedback sites or regulatory sites.

See, the negative cooperativity really was a big thing because that really did show that our model was correct. It didn't show it was correct in every case. It just showed there were a large number of enzymes that fit the Koshland-Nemethy-Filmer model and not the Monod-Wyman-Changeux. Then crystallography came along and did some precise measurements. So what you're saying is correct: most theories usually lead to new ideas that you hadn't thought of at the beginning.

Hughes: I presume that the French group, which was interested in enzyme regulation, came to the enzyme mechanism problem from the standpoint of regulation.

Koshland: No. The French group came in from genetics. Monod was a geneticist. He knew very little physical chemistry. I liked him a lot, he was a very interesting person. It was Wyman, a physical chemist from Harvard who was spending his sabbatical in Monod's lab, who explained the curve [in thermodynamic terms]. Monod wasn't trained in mathematics and wouldn't have known how to do the curves.

I heard Wyman talk many times. He was incapable of making things simple. He would explain in detail to you exactly how it worked, and he was right. He would discuss all the rate constants and things like that. Monod said, by doing this symmetry, we cut these extra terms down to a very few, and therefore the theory can fit it very nicely. It was a very important paper. They did really a great job.

Hughes: It sounds as though the people on the team complemented each other.

Koshland: They did. It was a little different on my team because Nemethy and Filmer were both a little younger than I was.

Hughes: What was their background?

Koshland: Filmer was a physical chemist, but he knew a lot about computers. He was really helpful to me because I knew the math and could derive mathematical equations but did not know how to use a computer. He put it on a computer, so we could plot out these curves very simply. Nemethy was a student of [Harold Sharagas?], who had done protein chemistry. He was also very helpful to me with the mathematics.

Both groups were interested in understanding cooperative proteins and get the mathematics of how the binding curve worked. I think it dawned on both of us about the same time that the feedback, the allosteric properties, the regulatory properties were one phenomenon. And the sigmoid curve, cooperativity, was another phenomenon. Although most regulatory proteins have that sigmoid curve, you were not necessarily thinking about [the two phenomena] totally separately, but you weren't necessarily using one to solve the other. The cooperative curve was an explanation of how the protein behaved, and that made it all the more plausible that some allosteric molecule would control the regulation.

Hughes: Dan, I realize that the data that each team worked with was somewhat different as well as the capabilities of the people involved, etc., but both teams were looking at the same molecule--hemoglobin--and were trying to solve the same problem more or less. How could the two teams come to different conclusions?

Koshland: Monod said, I'm going to simplify it by assuming that I have four subunits here and they all change simultaneously. I simplified it in another way. I said, first bind one subunit, and that changes the structure slightly so that the next one binds more easily, and then that changes the structure a little further, and then the next one binds even more easily, and so forth. So each of us made a simplification, and we just chose different simplifications.

I got to know Monod. I met him at meetings. He would say to me, "Dan, symmetry is a fundamental aspect of nature. You know, your face is symmetrical. You cut it in half, and the two sides of your face are identical." I would say, "You know, Jacques, structure may be symmetrical, but if you modify things, it's not necessary symmetrical." Which is really a specious argument, because we were talking about details. But that was how much our instincts and our backgrounds influenced our choices.

Hughes: Well, getting back to induced fit. Can you put yourself back to the mid 1950s, when you were formulating your theory? Did you already recognize that it might have general implications? Or did you think that the theory applied to only a few enzymes?

Koshland: I felt my theory was important very close to the beginning. It was probably when I got into the cooperativity that I said to myself, yes, this is very important in regulation, too.

In fact, I'm pretty sure I published a paper about the regulation and the allosteric sites, the regulatory sites, which was before 1966, sometime in the 1958--I've forgotten the date. But certainly we realized that the change of shape would cause it to have regulatory phenomenon. We knew that a protein, like cement, isn't absolutely rigid but, on the other hand, its fluctuations are all wobbling around a central average. What we meant by induced fit is when the substrate really did change shape. That's what we meant by flexibility. So that's '59.

Hughes: Is that when you began to use the term "flexible enzyme"?

Koshland: Oh, yes. Right at the beginning. Fifty-eight was when we published the theory, and '59 was enzyme flexibility. You write up a paper about a year before it gets published. And then in '66 came the cooperativity.

What you were asking is, did I have the idea that the induced fit theory would become a big, exciting talking point and there would be Gordon conferences on it--I would say no. In some ways it helped me, having an alternative theory, Monod's theory. Monod was a very good speaker--we both were, I think, pretty good speakers, so people liked to have us at meetings. I think that added to the excitement.

Hughes: It lit a little fire. And you probably loved that.

Koshland: I loved it. I had a good time.

Hughes: There were some names here that you haven't mentioned. This was in regard to negative cooperativity. You worked with Alex Levitski and Cedric W. Long.

Koshland: Yes. They were very important, both of them. They came on later. Remember, the induced fit theory was published while I was still at Brookhaven.

[End Tape 5, Side B. Begin Tape 6, Side A.]

Koshland: Cooperativity theory was a paper with Nemethy and Filmer, both of whom were in my laboratory at Rockefeller University. It appeared in '66, but it really means it was written up in '65 and probably even '64.

Hughes: That was the one you had trouble publishing.

Koshland: That was the one we had trouble publishing.

Hughes: What was Levitski and Long’s contribution?

Koshland: Nemethy and Filmer--

Hughes: No, no, no, no. Levitski and what was the other name?

Koshland: Levitski and Long both were postdoctoral fellows at Brookhaven. They worked on an enzyme called CTP synthetase, which is an enzyme that synthesizes CTP [cytidine triphosphate], which is one of the crucial nucleotides in the genetic code. This enzyme is a very important. It illustrated negative cooperativity in a very dramatic way. Positive cooperativity would mean when the first molecule bound, it made it easier for the next molecule to bind. In this case, when the first molecule bound, it not only made it difficult, it made it impossible for the second molecule to bind. It changed the structure so much that the second molecule essentially didn't bind. We found you could force the second molecule in, but it would be very, very tough. In most molecules. But in some you just never got the second molecule in. They really found this property in this enzyme, CPT synthetase. And we worked out some of the mathematics and some of the chemistry of it. They both worked on that together.

Hughes: They were enzymologists?

Koshland: They were enzymologists.

Hughes: If you had had a crystallographer, that would have been dramatic.

Koshland: Yes, except that at those times, it was very hard to crystallize any protein, and I wasn't doing that much crystallography myself. This was a very difficult protein. I don't know whether it's even been crystallized today.

Hughes: You mentioned Arthur Pardee who had been at Berkeley a few years before you came. I believe he left in 1961, for Princeton. Did he leave a residue of interest here in enzyme structure that you picked up on?

Koshland: No. But I did know Pardee because I was on a [NIH] study section with him. There was nothing left behind at Berkeley, and I didn't really know him well at all. Now he's a good friend of mine. But I read his papers, which were very good and very important. He was in Monod's lab during the development of Monod's theory, so I'm sure he must have contributed a lot to it.

Hughes: Pardee had a graduate student or probably a postdoc here.

Koshland: John Gerhart?

Hughes: That's it.

Koshland: And Cedric Long came from Pardee's lab.

Koshland: Pardee and I were both interested in the whole regulation-allostery subject. Pardee kids me all the time. He doesn't like mathematics. He says, "The minute a problem gets mathematical, I lose interest, and you start interest." It is really true. I mean, I like theory, and he doesn't like it as much. But he likes speculating about things.

A graduate student works with you and then thinks, Where should I go for my postdoctoral experience? [His supervisor] thinks, Who are the people interested [in similar problems] that aren’t identical to mine? So Pardee said to Cedric Long, "I think it will be good to go to Koshland's lab. He's interested in these general problems, and he's got a different approach to mine." Levitski was totally different. He was an enzymologist and was not interested in these problems at all before he came to me.

At the time, allostery was a very exciting thing. The Koshland-Nemethy-Filmer paper was a citation classic. It was very, very widely quoted. The Monod-Wyman-Changeux paper was in the same category. It was a big, exciting thing, partly because you got the principals to fight with each other. It was like a good cock fight. It was lots of fun.

Hughes: Yes, it sounds that way.

[End of Interview]

Interview 5: January 21, 1999

[Begin Tape 7, Side A]

Allostery: Howard Schachman and John Gerhart

Hughes: We have talked about induced fit and allostery, but we haven't mentioned Howard Schachman here on the Berkeley campus. I understand that he had a role in the debate about whether the French model of allostery or yours was the more correct.

Koshland: I think he had quite a role, not an enormous role, but maybe bigger because he was here. It became a bit of a conflict between the two of us, which it still is a little.

Hughes: On the subject of allostery?

Koshland: Yes. What happened with Howard was, a student named John Gerhart, who was a student of Arthur Pardee's at Princeton, came to work with Howard. John Gerhart had done some very interesting work with Pardee. It required the next step, using an ultracentrifuge. That was one of the things that Howard Schachman was a big expert in. They did a very important experiment in allostery with the centrifuge, which I think made Howard very interested in it.

Then, later on, [Jean-Pierre] Changeux, of Monod-Wyman-Changeux, spent a sabbatical at the University of California in the lab of Howard Schachman. Schachman became devoted to the Monod-Wyman-Changeux model at a time my model was being proposed and was the big competitor model. So Howard would go to various places and argue for the Monod-Wyman-Changeux model and say his data fit it. There were various faculty members who would get annoyed, as though he was obligated to support my model out of loyalty to Berkeley. But to be very fair, I think he didn't need to. I never felt that. I think he was wrong, and I think he turned out to be wrong. The particular enzyme he picked to fit the Monod-Wyman-Changeux model now quite clearly does not fit that model. I think he was incorrect, and I think he did overlook some really serious data.

When the two models were originally proposed, as is probably true of theories in general, they went beyond the experimental tools available at the time. Usually a new theory leads to the desire to have new experimental tools, and then the experimental tools come along, and they find things about the theory, and then you develop new theories again, and then you go back and forth constantly.

More on Positive and Negative Cooperativity

At the beginning of research on allostery, physical tools, like X-ray crystallography, hadn't been developed that much. One of the predictions that could be discovered in the Monod-Wyman-Changeux model and the Koshland-Nemethy-Filmer model was the question of positive cooperativity. Positive cooperativity, as I explained last time, was that if one molecule binds to a big multi-subunit enzyme, then it makes it easier for the next molecule to bind, and so forth. It's like a zipper that's stuck at the beginning and then, all of a sudden, zoom, it releases.

It turned out both models predicted positive cooperativity. But the Koshland-Nemethy-Filmer model predicted that there would also be negative cooperativity, that once you started [binding molecules to the enzyme], it became more and more difficult to put molecules on. The Monod model predicted clearly that that would not occur. When both theories [were first proposed], there was no known example of negative cooperativity. So in many ways that argued for the Monod model, which also had an appeal because it was simpler mathematically.

I was interested to get an example of negative cooperativity. I remember distinctly that one of my students, Abby Conway, came across an example which just fit perfectly. It was just exactly what I wanted. She didn't recognize it at the time. She was a very good student and very nice, but it was just one of those things that I had the theory in my head, and she was working on some binding properties. I immediately saw it, and we published the paper.[6] So that was the first example of negative cooperativity. Once that was in, all sorts of people discovered it. It was one of those things where probably lots of people had observed what turned out to be negative cooperativity, but they didn't publish it because it was so different from the normal curve [and they suspected the data was wrong].

I published a diagnostic test so it would be easy for people to discover it. As of today, there are probably more examples in the literature of negative cooperativity than positive cooperativity.

Hughes: What is the test?

Koshland: There are several ways you can do it, but probably the two simplest ways are, there's something called a double reciprocal plot, which is very famous in enzyme kinetics. It's concave downwards with positive cooperativity and concave upwards with negative cooperativity. I mean, it's that simple. And there's something called the Hill coefficient. The Hill coefficient, which is a method of plotting data, is 1.0 if it's conventional. It's greater than one if it's positive cooperativity, and less than one if it's negative cooperativity. So those are fairly easy kinetics tests you can do. That's why it's so easy to show [negative cooperativity] for a large number of enzymes. But it takes a while to figure that out.

There was a possibility that my theory was wrong, or that the theory was right but there was something in nature that selected against negative cooperativity, and so there were no known examples. Then, once we found one example, as I said, then all sorts of people found examples of negative cooperativity. People get

[6] Koshland bibliography #90.

intimidated. They get a result, and it doesn't look like anything anybody else has published. You say to yourself, "There's something wrong with it, and I don't quite understand what's going on." That's probably more true in biology than, say, chemistry or physics, simply because there's so much unknown. Your body has so many molecules in it, so many enzymes, hormones--so complex--that it isn't like a pure chemical system, where you know what all [the components] are. So people say, Well, it's something I don't understand, and I just better not publish it.

Hughes: What difference, if any, did it make that you approached the question through enzyme kinetics, and Howard Schachman used the ultracentrifuge?

Koshland: Howard was sophisticated. He understood kinetics, although it may have been that he was more related to his ultracentrifuge technique. It's possible. I did ultracentrifuge experiments. That wasn't my main interest. And he could do kinetics. It wasn't that either of us was totally committed [to one approach over another]. I think he just got involved in the Monod-Wyman-Changeux model.

Changeux, whom I met and I liked a lot, was much more focused. He was much more provincial. Monod and I had wonderful arguments. I really enjoyed talking to Monod. Changeux was much more the disciple who was less of a leader and worried about venturing out of the path that his leader [Monod] had led him on. I think that may have permeated Schachman's lab. They were both a little that way.

Allostery as a Major Research Focus in Biology

Hughes: I saw one wonderful reference of yours to "allosteria." There really was near hysteria for a while, wasn't there?

Koshland: Yes.

Hughes: Was it ever in your mind that the problem of allostery, which was focused on the protein aspect of the Central Dogma, took the limelight away from the focus on nucleic acids, the genetic code, and so on?

Koshland: The answer is I think nobody ever thought of it that way, partly because the field was so big. I'll give you a good example. Cold Spring Harbor each year picks a subject for a conference. One year they had a conference on allostery, and the next year they had a conference on the genetic code. I would say that those conferences were filled--lots of people--and not that much overlap, a little overlap, [in regard to attendees]. I was at Brookhaven Lab, and I think I was invited to be a speaker at the allostery one. I was also invited to attend the other one, and I didn't go because I was just so busy. I am sure the same thing happened to some people in the genetics area.

Hughes: There is some feeling, however, about how the history is told. Arthur Kornberg was quite pointed in his disagreement with [Horace F.] Judson's *Eighth Day of*

Creation[7], feeling that the biochemists' part of the revolution in biology had not been fully told.

Koshland: I think that's very true; I happen to agree with Arthur on that. Judson was heavily interested in the genetics part and clearly talked to a limited number of people, probably heavily oriented to [Francis] Crick, [Sidney] Brenner, [James] Watson—-

Hughes: [Gunther] Stent.

Koshland: Stent is a great historian, not a great researcher. He wrote a great book about it.[8] Judson's book was very narrow in the sense that it focused on a few individuals and gave their history. Crick is very bright, but he was very focused [on genetics].

Marshall Nirenberg, who got the Nobel Prize, was a biochemist who was at the National Institutes of Health. He did a crucial experiment which made it possible to work out the genetic code. He used no genetics; it was just straight biochemistry. Judson doesn't write that up at all.[9] But that doesn't mean the field as a whole didn't [appreciate the contributions of biochemists]. Arthur Kornberg was a very prominent researcher, and anybody who was really sophisticated in the area knew to read his papers. That's true of the area I was in, too.

Hughes: Was there any conceptual barrier in biochemistry between the smaller molecules which biochemists had historically worked on and macromolecules such as the nucleic acids which became so important after the Watson-Crick structure of DNA?

Koshland: I think it was a historical development in the following sense. It wasn't that they were more interested, because those little molecules are still very important today. For a while, the hottest thing was working out the biochemical pathways and getting the enzymes that were involved in those. As that started to wane, then it was the pathway of DNA and the pathway of replication. That merged in the area of genetics, so that genetics became part of it, together with biochemistry.

What happened in my area, allostery, is you really had to know the pathways. We got all the pathways. The amount of gold to be developed, the amount of new pathways, started to disappear, so it became less and less of an important frontier. Now, a new area came up: How do you regulate the damn things? How do you turn them on? Why do you eat when you're hungry, and what it is that tells your

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[7] Horace Judson. *The Eighth Day of Creation*: *The Makers of the Revolution in Biology*. New York: Simon and Schuster,1979. The Kornberg oral history is online: http://bancroft.berkeley.edu/ROHO/projects/biosci/.

[8] Cairns, Stent, Watson. *Phage and the Origins of Molecular Biology*. Cold Spring Harbor Laboratory: Cold Spring Harbor, New York, 1966.

[9] Judson’s book does treat Nirenberg’s work.

body, "You've eaten enough, and stop eating."? That's the regulation of the pathways.

Chemotaxis

Hughes: I read the paper that you wrote in *Science* last year.[10] There's yet a third era according to Dan Koshland, namely--

Koshland: You do your homework, don't you?

Hughes: [chuckling] Well, I try to. --the era of quantification. If I understand correctly, a purpose of your work on chemotaxis was to quantify a reaction that had been studied for a long time but not in a quantitative way.

Koshland: No. The early work we did on chemotaxis was really just to understand it. That did involve quantification in a way, partly because I'm rather mathematical and theoretical. I like that kind of thing. We really had to understand first what were the reactions. I'll come to what the quantification was in a minute.

Now, the system we chose was a very, very simple one. A little bacterium is probably the simplest organism you can imagine. It was also available for quantification, probably easier than any other thing. So it's probably the best understood sensory system in a mathematic sense, and probably the best one understood in the pathways, too.

Hughes: Those were reasons you chose it, right?

Koshland: We weren't sure. We thought it would be one of the simplest, and it did turn out to be, but it turned out to be more complicated than I thought. [interruption]

Hughes: I'll ask you a basic question: Why did you decide to get into chemotaxis?

Koshland: That's very good! You ask good questions, madam.

Hughes: [chuckling]

Koshland: It's ironic how I got in the field, but it shows a little bit how scientists choose problems. Allostery, we'd done a lot. It was beginning to wind down. In other words, we were doing about all we could with [our] techniques. I decided there were really only two ways to go at that point. One would be to go to X-ray crystallography and go after the proteins in a much more precise way, which is one thing that was being done. And number two, to go to a system where allostery was

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[10] "The Era of Pathway Quantification," *Science* 1998, 280:852-53.

important and really start to understand feedback regulation in a system that I could manipulate.

I decided the more exciting of the two would be a complicated system, to see how allostery and all that work. So then I said, well, what kind of system do I want to look into? Remember, this was now quite a few years ago, late sixties to early seventies. I said to myself at that time, because there was already a little genetics being used to understand the system, that I would want to use something that had a genetic component in it because you could knock out genes and get mutants. See, a mutation is very important because it can tell you what is essential.

For example, you can have a mutation that changes your hair so you're an albino. That's a well-known mutation. But that doesn't kill you. And then there can be another mutation that affects heart muscle, and that kills you. So mutations are good in finding out how important something is in a system.

The second thing is, there are a number of mutations that just impair the system a little bit, make it change, and that's a very helpful kind of mutation to follow up and research. So I said, I really wanted to take a mutation that does things to impair the system but doesn't kill, something that isn't essential. On the other hand, I wanted to have a very important system which was selected over evolutionary time, because then you know it's at the peak of its performance. So I decided you have to have some sensory system. If you're blind, that is really not good overall for the organism. Blind people would not survive very well in caveman Africa where your life depends on seeing things. On the other hand, an individual can be blind in the modern world, and that's inconvenient for them, but it isn't inconvenient for the species. So I [decided] a sensory system would be good.

Julius Adler at the University of Wisconsin had been studying chemotaxis in the bacterium. That struck me as being ideal because we knew a lot about how to do genetics in bacteria. Chemotaxis is a sensing mechanism where bacteria swim towards good things for them, like oxygen and nutrients, and away from bad things, like acids or high temperature. The bacteria clearly had a sensing system. I thought, well, we could study that.

Most people would think a bacterium is too small to have any kind of a sensing system. But Adler had done some nice work, and he had been preceded in 1893 by the man who really discovered chemotaxis, [Wilhelm] Pfeffer in Germany. He had done old, classical botany and zoology. Adler had used more modern techniques and brought it up into the modern era. It was Adler's paper that came to my attention, and then I read the previous one [by Pfeffer].

Hughes: Now, Adler's work came to your attention when you were looking around for a sensory system?

Koshland: Right.

Hughes: You hadn't been following this work.

Koshland: No, not at all. I was just looking around for a sensory system. And there was a young postdoc in my lab named [F.W.] Dahlquist. He had come to me from [Raftery's?] lab at Caltech. He was looking for a new problem. He had worked on enzyme mechanisms, and that's why he came to me, to work on enzyme mechanisms, which we haven't come to yet in our discussions but is a major part of my laboratory. He liked the idea of research on chemotaxis. He wanted to get into something new, and that's what he did. So that's the way I got into chemotaxis.

Hughes: Was that the first time you had used a bacterial system?

Koshland: Well, I had used bacteria, but incidentally, just growing them. But as far as studying bacteria, certainly it was the first time. I knew nothing about bacteria. I had to learn everything

Hughes: How did you go about it?

Koshland: Fortunately, lots of people in the department of biochemistry worked with bacteria all the time. I walked one floor below and asked Bruce Ames, who was a very well-known bacterial geneticist, a little bit about how you select for mutants in bacteria. Then I asked Michael Chamberlin, who was upstairs, how you grow bacteria. So you just go around and ask people, and most of them are very helpful.

Hughes: I noticed that in the course of your scientific career, you've used quite a number of different biological systems.

Koshland: Right.

Hughes: I would think that to introduce a whole new system would take quite a reorientation of a laboratory.

Koshland: It is true. A lot of professors don't do that. A lot of people have commented that I'm more willing to do that than most people are. I think most good people are willing at least to change quite a bit, because the world goes fast, and sometimes the field you're in sort of dries up. Professors who stick with what they've done all their lives tend to do very mundane things over and over again. Secondly, I had a lab of about ten or twelve people, and I had a number of people who continued to work on allostery while I started to work on chemotaxis. So if I had really found chemotaxis too difficult, I wasn't totally out on a limb.

Hughes: So you were hedging your bet.

Koshland: I was hedging my bet a little. But it turned out, the chemotaxis went very well, and as a result, I did more and more research on the topic.

Hughes: One of the first stages in your research on chemotaxis involved isolating the receptors.

Koshland: That was a big step. Dahlquist did a lot. We did some very early work which showed a number of things about how chemotaxis worked.

[End Tape 5, Side A. Begin Tape 5, Side B.]

Koshland: [*E. coli* has a length of] one micrometer. That's 10^{-6} meters. That's one millionth of a meter. That's very small. As you know, you can't see one with the naked eye. You must look through a microscope, and a pretty good microscope, too, not just any old microscope.

Remember, I was trained as a physical chemist, and it occurred to me that these bacteria could swim up a gradient, and the gradient was not a very big gradient. It was a concentration of glucose that, say, six inches up the gradient was 20 percent or 10 percent higher than it was six inches down the gradient. If you calculate the difference in the number of molecules at the tail of the bacterium and the head of the bacterium, it's not very many. That means the bacterium has to detect a very small concentration [gradient].

Later on, when we did the experiment really well, when I knew what I was doing, we found that a bacterium can detect a gradient that differs by one part in 10^4 between its head and its tail. It can tell the difference between 10,000 and 9,999. That's pretty good. As a physical chemist, I said, Geez, how could it do this? I mean, it's almost stretching theoretical limits. I won't get too theoretical at the moment, but there are laws about probability and distributions where you could just say it must violate.

So we started to design how to do it. Basically, there are two methods of detecting gradients in human beings. [In research], you always use an analogy to what you know and understand. One is how your eyes do it. You have two eyes, and they converge in such a way that you get a three-dimensional perspective. So you can see that that building is much further away than this window, let's say. Another example. You can't tell whether a fragrance is coming from one side or the other by the difference in time it hits your left nostril and your right. But if you walk along a ways and sniff again, if there's a gradient, you can say, "Oh, that's coming from south instead of north," right?

Bob McNab was in my lab at the time. He and I set up various experiments to try to find out how the bacteria did it. In those experiments which McNab did, which were very clever, we found out that in fact the bacteria use the nose model. That is, they really sense over time, and they really have a memory. So it meant that the little bacterium really has a memory. You say, well, a metal has memory of fatigue, but then you're using memory in a slightly different way. We meant a biological memory. Remember, a bacterium is a single cell; it's not like your brain. But it was able to tell time. It was able to compare its past with its present. We did a very nice experiment which showed that and published it in the *PNAS*,[11] and it made a big, big splash, right at the beginning.

Hughes: Tell me about that work.

Koshland: All right. One idea that I had at the beginning turned out to be not right, but nevertheless we did it. One way to detect a gradient is, say a bacterium swims towards a concentration of glucose. (Glucose is something it eats and can use very readily.) So maybe what happens is at low concentrations it swims rapidly because it has to find more glucose, and then, as you get to higher and higher concentrations, it swims slower and slower till finally, when it gets to the optimal concentration, it stops. So with that kind of a mechanism, they would all stop at the high concentration. The bacteria would just accumulate where there was the highest glucose concentration.

To test that we just looked at bacteria in the microscope at various concentrations of glucose to see whether the absolute concentration affected the rate in which they swam. We found out it made no difference whatsoever, absolutely none. So that eliminated that possibility. It also gave us a fair amount of information. So then we did experiments which also didn't work. I thought maybe if you cut off their flagellae, which is like cutting off your legs, then they could walk less rapidly. It would take them longer to move up a gradient, and we should then see some change of behavior. Those experiments didn't work very well at all.

Then we thought of the following experiment: Suppose we put the bacteria in a concentration of glucose, let's say, and we suddenly dilute. So the bacteria go from a solution of glucose which is, say, one molar to a solution that's one tenth as high as that. If you do that rapidly, and then look at how the bacteria behave, all the bacteria know is that they've gone down a gradient. And you can do it vice versa. That is, you put them in very low concentration and increase it. When we did that, sure enough, they changed very differently. In both concentrations, the high and the low, there was no difference between the head and tail of the bacteria. The glucose concentration was the same, uniform, so it was clear the bacterium was not comparing its head and its tail. So we said if the behavior changes at all, then it must be comparing its past with its present.

Then we said, well, maybe it is just the shock of change. But it wasn't true. If it was the shock of change, then it would be the same, whether we put the bacterium downhill or uphill. If we turned it downhill in glucose, it tumbled head over heels all the time; and if we put it uphill, it just swam smoothly for hours. So clearly its behavior if you put it up a gradient was different than if you put it down a gradient. It was clear it was comparing over time, and it knew that it was going downhill or uphill. In other words, it had a memory of the previous event.

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[11] Koshland bibliography # 187.

That experiment with McNab showed that bacteria had a memory. McNab was a photographer, and so we took some pictures of bacteria. I was sort of impatient with him because once we got the result, I wanted to announce to the world. He insisted on getting good pictures, and he was absolutely right. It made a big, big impression because the pictures were so visual; they really made the point.

So anyway, that was the first and probably most important experiment we made in chemotaxis because that opened up all sorts of other things. It not only solved a very important intellectual point, but it provided a method for looking at all sorts of other things. We could take any chemical and find out whether it was an attractant or a repellant. And then, using that, we proceeded to make mutations and find out what genes and enzymes are involved.

I wasn't alone in that. Adler was already in the field. A man named [Melvin I.] Simon at Caltech was working in the field. And a lot of people in my lab then went out into other labs and worked. McNab went to Yale, where he got an assistant professorship and is now a full professor. Dahlquist went to Oregon, where he was assistant professor and is now a full professor. So they have labs of their own.

Because we have a simple system, and we have very good techniques for looking into it, chemotaxis is probably not only the best- understood sensory system but one of the best-understood biological systems, that is, not only we know the individual steps, but we can quantify. There are a lot of other pathways that are known, but not many with as much quantification.

Hughes: What was it exactly that was exciting people?

Koshland: Oh, the idea of looking at a sensory system was very exciting. There weren't that many that were known that well. It was recognized that we were on a frontier of sensory systems, and it was one of the systems that was going to be solved first. Chemotaxis didn't dominate the field nearly as much as allostery did in terms of the number of people being interested, but there were quite a few people who were very interested in chemotaxis. All of us—Adler and Dahlquist and me--were invited to give talks at meetings, like Gordon conferences and things like that.

Isolating and Purifying the Chemotaxis Receptor

Hughes: What about the receptor?

Koshland: Well, the receptor was a very important part of it. The receptor--for those who aren't scientists--is a molecule on the surface of your body or a cell that detects something in the environment. For example, your eyes are receptors. They are receptors for vision. You have receptors in your nose for odors, and in your mouth, for taste. And then every individual cell in your body has receptors, which use hormones, which come and tell the cell how to behave.

Then we got some indication of what some of these receptors were, and we purified them. A very important receptor was the TAR receptor. TAR was a gene which had been identified by Adler. We found the TAR receptor, and one of my students, Elizabeth Wang, was the first to purify it. It was the first receptor of that type that was purified. There were some simpler receptors that had been purified before, but they weren't really total receptors; they were molecules that helped-- I'm trying to think of an analogy. Oh, you might say they were molecules that were partial receptors, the way you say if you're trying to get in and out of the rain, you have an umbrella and an overcoat. You really stay dry by having an umbrella and an overcoat.

Hughes: You need both.

Koshland: You need both, yes. So these were partial receptors. But this TAR receptor was the first complete receptor, in the sense that it was a combined overcoat and umbrella.

Hughes: Why was it difficult to get the whole receptor?

Koshland: It was very difficult because receptors are on the surface of cells, and an oily membrane surrounds the cell, whereas the center of the cell is water and the outside of the cell is water. So the molecules that have to stick in this trans-membrane region are a combination of water and oil, so they're not completely soluble in water, and they're not completely soluble in oil. So they're very difficult to deal with. Everybody knew they were difficult to deal with.

Elizabeth purified it, and part of the reason she purified it and was so successful was recombinant DNA had come in then, and she could clone it, and she could make a lot more. Receptors were in notoriously small amount, and they were very hard to isolate. She identified it, and then she cloned it. Once she cloned it, we could make a lot of it and then purify it.

Hughes: Did she come to the lab knowing recombinant DNA technology?

Koshland: She had to learn it. She came as a postdoc. I've forgotten who she worked with before. Anyway, it was something she picked up.

Hughes: Did she pick up the technique here?

Koshland: She picked it up here. I think there were people in my lab who already knew it by that time. They had in turn been helped by other professors and students in the department. A big advantage of being at Berkeley is that there are so many people doing so many different things.

Hughes: That was one receptor. Even the bacterium is going to have a lot of receptors, isn't it?

Koshland: Many. Well, for chemotaxis alone, there are probably twenty receptors, and then you have all sorts of other phenomena that need different receptors.

Hughes: None had been worked on?

Koshland: I think the chemotaxis receptor-- I was going to say it was the first receptor [identified]. I don't think it was. There was something called rhodopsin, which was a very important light receptor, which was known in mammalian cells and had been purified. Now we know a lot about that light system. A lot of people work on that. It is a very important system. On the other hand, it's a good deal more complex, and it was not possible to get all the ingredients of the system, the way you were able to do with chemotaxis. It's very important in biology to get *a* simple system as a model, particularly when you're doing it for the first time.

Comparing Adaption in Different Organisms

Hughes: So some of the excitement was that you had an experimental system that others could use for their own purposes?

Koshland: Yes. I remember I extrapolated. I tend to like to do that, to generalize about other systems. I was invited to some big meeting on vision, and I discovered a phenomenon called adaption in bacteria. We found out why; the protein was covalently modified. So I went to this meeting of the people dealing with vision and rhodopsin, and I said a lot of adaptation [to light] is probably the same thing that happens in bacteria.

I remember at the beginning they thought that was ridiculous. Who is this biochemist who's working on bacteria coming and telling us how the eye works? It's obviously got to [require] a big computer operation in the brain. You can read a book in pale moonlight as well as in fairly bright sunshine. That requires adaptation of something like ten orders of magnitude, 10^{10}. The pupil can contract by a factor of about one-quarter. That means sixteen. So you get a factor of sixteen [in cutting light?] out. So that's one order of magnitude. Ten orders--you can't explain it all by the pupil of your eye. So most people assumed that in bacteria what happened is there's a computer network that feeds back and so forth.

What we said, as a result of the bacterial experiments, was no, it's chemistry. And that really has turned out to be true. I got a nice letter from somebody who argued with me, and she wrote me the other day and wanted me to talk someplace and said, "I remember arguing with you. You turned out to be right in that case."

Hughes: This work also involved conformational changes, didn't it?

Koshland: Sure. Receptors--I assumed there were going to be conformational changes.

Hughes: Why?

Koshland: Because I knew the sensory system was things like light or taste, and a lot of molecules you taste are not metabolized--something can taste bad when it's on your tongue, whether or not you eat or digest it. We assumed there would be allosteric changes. So you're absolutely right; I assumed that a sensory system was very likely to be allosteric.

It has turned out, essentially every protein undergoes allosteric changes and conformational changes. So it was not surprising that if I stayed in that field, that I ran across that again and again. Instead of looking at the actual protein chemistry, I was looking at how the system interprets it. That was the way I decided to go into it. Then, once I got the receptor--we recently have done the X-ray structure of the receptor--then I went back to my original love of proteins. So now I'm doing protein chemistry again. I'm delighted with that, but that wasn't something I could have predicted.

Hughes: Could one say that's your first love?

Koshland: Yes, it might be, although enzyme mechanisms are close.

[End of Interview]

Interview 6: January 27, 1999
[Begin Tape 8, Side A]

Even More on Chemotaxis

Koshland: Chemotaxis we went into largely because it was a sensory system on a sufficiently small scale that one could possibly understand. We started this in the late sixties and early seventies, and the tools were not nearly those that are available today. But I started it largely because I thought [genetics was a tool you could use on chemotaxis]. Genetics was already being used with bacteria. I didn't realize that recombinant DNA was coming in. But of course it did come in, and that made an enormous difference because recombinant DNA was absolutely wonderful for bacteria.

When I say "we," I mean my laboratory and the students in it, and the laboratories of Adler and Simon, who were the main other people [in chemotaxis research]; and then [J. S.] Parkinson, who was a student of Adler's; and Dahlquist, who was a student of mine; and McNab, who was a student of mine, but then got jobs in other universities. All were really very productive people and worked very hard, so the net result is we really worked but almost all of the scheme of chemotaxis.

The discovery that McNab made with me, that famous paper on memory which became very prominent, was extremely important not only because it explained the theory of how a bacterium could detect a gradient, which was really a pretty sophisticated thing if you examine it from the outside--it's an incredibly clever analytical device--but also was very practical. It set up a way so we could screen compounds that would elicit chemotaxis very easily. The net result is the field moved very fast.

Today I'm still writing reviews that are being referred to by other people because now, as we're looking at the more complex systems in higher organisms--*Drosophila*, which is appreciably simpler than man but still much more complicated than a bacterium--the bacterial system is still the most thoroughly understood sensory system available, because it's very manipulable. That is, with recombinant DNA you can put the genes in a clone and increase their amount or decrease their amount. Then you can test the mathematical theory. As things become more quantitative, it becomes more and more of an exciting model to use. My work has actually gone on, and I'm now more interested in the biochemistry of individual components of the system, like receptors, which are very important in general. But the whole system has become quite an interesting one.

Hughes: Do you want to talk about isolation of the TAR receptor?

Koshland: Well, Elizabeth Wang['s purification for the first time of the TAR receptor] was a very exciting event when it occurred, because very few membrane proteins of that sort had been found, and particularly not found in systems where you could manipulate them and study them. See, some membrane receptors had been found, but they were molecules that were in large supply in certain systems in the mammal. Because there was frequently a large amount of [receptor protein], you could purify it, but you couldn't really change [the system]. Whereas in a bacterial system, we not only could purify it, but we could also manipulate the other parts or the system and find how important the receptor was.

Sensory Adaption

One of the first experiments we did after Elizabeth discovered the receptor was to show that it was methylated. We showed that the methylation, the covalent modification of the receptor, was correlated with the phenomenon of adaptation. To explain what adaptation means: when you walk into a darkened movie theater, it's very hard to see around you, and you stumble on the steps, and you find your way to the seat by stepping over people's toes. And then you get up, say, a couple of hours later to walk out, and you don't really have any of those troubles. It's easy to see your way out. You think, well, there must be better lighting. In fact, it isn't. Your eyes have just adapted to the darkness. Then when you walk out of a movie theater, the daylight is blinding. You think, my god, the sun has gotten much brighter. But what has happened is your eyes adapted to the dark.

It turns out that the phenomenon [of adaption] we discovered in the bacterial receptor was really a very general phenomenon. It had already been reported that rhodopsin, which is the main receptor in your eye, is phosphorylated. That's also a covalent modification. So, being a brash young man, I generalized from two examples, my own and this other. I said the phosphorylation of rhodopsin must be the thing that allows the adaptation of rhodopsin. That was disputed vehemently at one meeting. A young lady who later became a professor at Princeton told me years later, "Well, you turned out to be right, but I remember fighting you at that meeting." Which was very nice of her because I had forgotten completely the event.

But anyway, your eyes adapt over so many orders of magnitude that everybody thought adaption had to be [mediated by] electronic circuitry that goes into your brain, and it must be something akin to a computer. And so to suggest it was just chemicals, that you just had chemical modification, was really quite revolutionary. But it has now turned out that [chemistry] isn't everything; it's part of it. The brain adapts to light over a much bigger range than [does] the bacterium. But a lot of it is chemical.

Hughes: Could you outline how chemical adaption works?

Koshland: You really ought to read the papers, but light on your eyes, sugar on your tongue, or an odor in your nose are really basically the same phenomenon. The minute [the stimulus] lands on your nose or your tongue or your eye, it deforms the receptor, sort of the way you squeeze a rubber balloon. Your fingers push in, but it will also bulge out some other place.

The protein gets covalently modified--that means it gets modified by chemical reagents--to partly correct it. It never will correct it completely, but it partly corrects at least the signaling system back to what it was. That's what adaptation is. It is a very important phenomenon. You can walk into a smelly room, like an old gym or even a place a skunk has been, and after a while you think, "Oh, my gosh, the odor has gone away." It really hasn't. And so the next person comes in and says, "My, this gym smells awful." But the facts are, your nose has adapted, and the new person comes in and thinks it's just as terrible as when you came in.

Hughes: Why is adaption biologically rational?

Koshland: It's extremely important. What we found was that your sensory system is designed to amplify very small signals. In fact, you can detect a single photon landing on your eye. So in order to do that, you essentially take a very small signal and amplify it, make it much bigger. It's the way, a microphone amplifies the voice. You can do it many times over because once you've said something, electronically you just expand it.

But in order to do that in the body, it takes energy, just the way it does with the microphone. You have to provide electrical energy. In the body, you provide ATP [adenosine triphosphate] energy, which is burning up sugar molecules, okay? To do that, you use a lot of energy. If, for example, you walk into a room [with a] bad smell, what you're constantly doing is generating energy to amplify those signals. You can say, "Now, look, there's no use doing it anymore. I've gotten the signal. I got the message." So you adapt. Since almost every sensory system has this amplification in it, you can detect very small odors. Almost every sense has this adaptation.

Hughes: What about pain?

Koshland: Oh, pain is a big adaptation. There are people who end up playing the second half of a football game with a broken leg. The body immediately sends out chemicals which dampen the pain. That's really quite a danger. Nowadays, we artificially increase that [dampening] by sticking drugs in people.

Hughes: You also described a competition between receptors.

Koshland: Okay, that's a little different. You have receptors for a large number of things so you can make intelligent decisions about the environment. But you do not have receptors for everything in your body. For example, there are a lot of compounds which you just don't smell. There are family arguments I could probably resolve easily by explaining some things. Somebody will go out in the kitchen--let's assume the wife--and says, "Everything is going fine." The husband comes in and says, "Oh, this smells awful." And she says, "It does not." And he says, "It does, too." And they have a big fight. But it turns out certain chemicals have certain receptors, and the wife might not have one and the husband does, so the wife really just doesn't smell the bad odor.

There's a famous but not so attractive example of the well-known fact that when you eat asparagus your urine smells bad. Some people say, "Well, no, it doesn't smell that bad." The compounds that you metabolize when you eat asparagus are probably the same for everybody. What's different is not everybody has the receptor to smell them. It isn't that you metabolize them differently; it's that you don't smell them.

But anyway, adaption's very important in chemotaxis and important in you. A molecule that's very [important] for the metabolism of the bacterium has receptors that give a big, big signal--either there's [a lot] of them or the signal is enormously amplified; whereas the [molecules] that are less important have [fewer receptors].

A good example is, there's a very attractive signal for oxygen. Oxygen is very important for a bacterium. Its metabolism is much helped by oxygen. So the net result is the oxygen receptor has enormous amplification, and as a result, if the bacterium has some oxygen in one direction and Chanel No. 5 in another direction, it doesn't care very much about Chanel No. 5 and will swim towards oxygen. Serine is a very good metabolite and has a very good receptor, whereas something like galactose--a sugar which is useful and the bacterium eats it, but it doesn't have any nitrogen, and it's not nearly as good as serine for metabolism--it will be not nearly as attractive. So the bacterium will swim towards the molecules that are best for it.

It's true of us, too. Pheromones, a combination of receptors that make somebody look attractive, are combined with seeing and brain function, of course, but the net effect in the human is to decide certain things look attractive or smell attractive, and other things don't.

Hughes: Where does the concept of competition come in?

Koshland: Because on the surface of every cell there are a variety of receptors. If there are two molecules, they can either compete at the surface of the receptor, or the receptors may change in the sense that the signal they transmit when they are affected is bigger in one case than the other. It's like the signs on a house which say, "Doorbells for Relatives" and "Doorbells for Acquaintances." It looks like the same doorbell, but one gives a loud ring and the other gives a little faint jingle, and you don't answer it if you didn't feel like it. So the [receptor system] is set up to make the signals proportional to the importance of the molecule.

Hughes: I read that you found that most of the receptors that you isolated had a dual function.

Koshland: Yes. In the case of the aspartate receptor, it did two things: It signaled that aspartate was there and affected the way the bacterium swam. And number two, it signaled adaptation, so the bacterium started to adapt.

Hughes: Is that universal?

Koshland: That's pretty universal. Almost every receptor not only responds to the signal but also starts the adaptation process.

Hughes: Was that known when you began to work on chemotaxis?

Koshland: No. The aspartate receptor really started that, and now [adaption] has been found with almost everything.

Hughes: You chose to look at serine and aspartate because those were important receptors for *E. coli*?

Koshland: Yes. We knew the aspartate receptor was a very important receptor. It and the serine receptor, which is almost identical, are probably the two most important in the bacteria.

Hughes: Are they there in greater quantities?

Koshland: They are there in greater quantities. After we got that initial discovery and had isolated the receptors, then we found the adaptation property. We knew that ahead of time. We had a little bit of an adaptation [response], but we didn't really know how it worked. Once we saw that[?], we saw there was really a very good general model.

In subsequent years, a number of the mammalian receptors came along, one of which was the insulin receptor, which is very important in metabolism. It has many features which are very similar [to the aspartate receptor] and the rhodopsin receptor and a lot of others. The more those came out, the more it was clear that the analogy between our receptor and these other receptors was pretty great. [interruption]

The Bacterium as a Model Neuron

Hughes: In 1983 you published a paper entitled, "The Bacterium as a Model Neuron."[12] I speculate that the title might be a clue as to how you got from chemotaxis to mammalian systems.

Koshland: Well, that's true. What I wrote was that the bacterium, if you think it over, really had most of the properties of a much bigger system but not, of course, all of the sophisticated properties of a human being. I think I wrote it could discriminate between two molecules that were very similar, odors that were very similar. If you gave an attractant in one way and an attractant in another, it could weigh which was the more important attractant and swim in that direction. They could choose.

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[12] Koshland bibliography #274.

People would say, "Well, that was just a hard-wired system, and the bacteria really didn't choose. It was really all instinct." But we really don't know how much is instinct and how much is human [choice?]. [OMIT? My wife Bunny and I always said we wanted to have a lot of children, and we ended up having five children. We went to my wife's fiftieth college anniversary, and almost everybody had five children. Where she went was a rather liberal, feminist school which felt educated women had an obligation to have children and get out and work and do everything. The message had been sent to her and sent to a lot of her colleagues. Was that free will? One of the great instincts, of course, is sex. A beautiful gazelle or a beautiful peacock--who is to say they're not just as pretty as a human being? You don't fall in love with a gazelle. That's an economy of discrimination. You'd just waste a lot of time falling in love with a gazelle, right?

I had my students write what they thought were general expressions of higher mental function: choice, judgment, discrimination, and things like that. Every one of those, the bacteria have in a much simpler system. A bacterium's a single cell, whereas your brain has 10^{12} neurons. It's amazing what this little cell can do. So I wrote this somewhat facetious article and pointed out A) that not only was it able to do all those things, but B) its biochemistry was probably very similar, only on a simpler level, than much of the biochemistry of the brain. That was really the point of that paper.

Hughes: When you started with chemotaxis, which obviously had to be in a bacterial system, was it with the idea of testing out these ideas and then moving to the mammalian system?

Koshland: Yes and no. The idea was to use it as a model system for learning what we could about sensory systems. Remember, your body system isn't just a sensory system. Your brain has to do a lot of things which are not just responding to the environment. Sensory system means really you're taking information from the outside and converting it inside. So that refers not only to outside your body, like seeing light and sounds and smelling, but each cell in your body has receptors on its surface which interpret signals they get from outside the cell to the metabolism inside the cell.

One of the most important signals in your body are hormones, which have a big influence on how cells grow and which cells don't, and so forth. The idea of having a sensory system is not only to signal from the outside of the organism to the inside of the organism, which is very important, but also signaling within the organism. So the sensory systems are a big part of your life. On the other hand, they are not all of your system. You have metabolism and a lot of other things which are not sensory.

Because we found something I had not expected in the beginning--namely, that memory was involved in even a simple sensory system--I got intrigued with applying this model to memory in higher neural systems. We did some of that, too.

Research on Memory in Higher-Order Organisms

Koshland: I don't know how much to say because the system now becomes sufficiently more complex, if you start to read the papers. But I can say that what I wanted to do was to duplicate a little of my experience of using cell lines. At the time, almost everybody wanted to use a model system such as *Drosophila*, which is the fruit fly. The idea of the fruit fly was that here's a simple organism for research purposes. Flies can learn. You can put them on water. Let's say you color the water blue and put sugar in it and color some other water yellow and don't put any sugar in it. The flies learn that the blue water has some nutrient in it, and they'll fly towards the blue water, and you can do tests for that. Then you can put out blue water with no sugar in it, and they'll still fly to it. After a while, they get mad at you. But the point is you can train them to do things like that.

I've forgotten how many neurons there are in a fly, but something like 50,000. That's $5x10^4$, whereas your brain has something like 10^{12} neurons. 10^6 is a million, so you have a million times a million. That's an enormous number. So to try to figure out how the whole brain operates is really impossible to do just straight out. What you do is get down to simple systems. It is a lot easier to take a fly and try to figure out how the 50,000 neurons work as a stepping stone to get to the human brain, and that's what a lot of people are doing.

I thought I'd do it a different way. I would take human neurons or rat neurons, which are very similar, and grow them in tissue culture, which means you grow them in a milieu that's like the brain, but it isn't a living organism, and you study how the biochemistry works. That was pretty avant-garde when we started it. We weren't the only ones--there were other people doing it--but not very many people were studying memory in tissue culture. They all said it has to be hooked up to five or six neurons.

Hughes: Isn't it the idea that memory has to be a higher-order brain function rather than simply chemical signals?

Koshland: That's correct. Anyway, we found [neurons in tissue culture] did give memory and the experiments were very useful. And then more and more people started to use [tissue culture to study brain function]. I think we had a big influence on that, although I wouldn't want to say we were the only ones doing it by a long shot.

[End Tape 8, Side A. Begin Tape 8, Side B.]

Koshland: You can say that you have memory when you bend a metal again and again and again; it eventually loses some of its resilience. Some people say, well, it has a memory of old events. But <u>you</u> have the memory. The molecules of metal have been changed in a way that they aren't the same as they were before. Well, in a neuron, the molecules are also changed. But in the metal, the system wasn't devised to be bent that way, whereas the neural system was devised to have a memory for the bacteria.

The bacterium is just too small to be able to detect the difference between the concentration of something between its head and its tail. As I said, it works by sniffing and then walking a certain distance and then sniffing again. It has to have a memory that is able to compare the new sniff with the old sniff.

Hughes: Does that general system operate in the isolated neurons?

Koshland: It doesn't operate identically, but it operates very similarly. We showed that, and we showed that it has adaptation and a lot of the other properties. But the difference is, the bacterium is one little cell, and it must process any information that gets in. Whereas in the brain, you have a certain section, a bunch of cells, which is specialized to receive light, and another section which processes smell. In a multicellular organism, you can have individual cells which are specialized.

Commonalities and Reductionism in Biology

Hughes: My understanding is that molecular biologists up until the early seventies had pretty much shied away from studying complex organisms, because they were complex and the tools weren't there.

Koshland: Right.

Hughes: Then technologies like recombinant DNA came in and new instrumentation. Did it surprise you--did it surprise scientists in general--to find that the systems that they had studied for decades in bacteria, in *E. coli*, had strong parallels with what was going on in mammalian systems?

Koshland: I would say possibly no. I think it surprised many of the organismal people, many of the people who studied whole animals, because whole animals tended to be so different [from each other]; a snake is different from a mouse. But there was an evolution argument that one had progressed to another, so there had to be similarities. When you looked at organisms, all of them had some similar systems; that is, every one had to have some kind of flow of oxygen. If you were a very little organism, you didn't need lungs. Some insects depend on just the flow of air through their body. But once you get a little more complex, you have to have blood, and you have to carry oxygen around to the tissues and so forth.

Biochemistry showed that yeast glycolysis was the same as it was in humans. That is, the human system was worked out by using the yeast cell because it was so much easier to grow and chop up than rats, and rats were so much more complicated. Once they showed [similarities] in those two [types of organisms], I think biochemists generally felt that you could break down complex systems into smaller parts, and those smaller parts would be duplicated in lots of different organisms.

Hughes: So it was more a technological barrier than a conceptual barrier?

Koshland: Well, I think it was conceptual, but I think that biochemists felt that in almost every system, the basic biochemistry was similar. If there was something slightly different, usually that was a big signal to you that it was important.

For example, there are a lot of bacteria that grow in this world. Many of them are not green. What you decide is that the green ones probably have photosynthesis because they're like green plants which have photosynthesis, and indeed that turns out to be true. Then there are blue-green algae, and then the question is were they more like the photosynthesis bacteria or more like the blue-green algae?

Hughes: And if you ask the right questions, you can find the answer?

Koshland: Well, technologically it was going to be very difficult. People kept not believing how much you could break systems down, even though the yeast system had been broken down. We found we could get a pathway of carbohydrate metabolism in yeast, and it was the same as the pathway of carbohydrate metabolism in man.

I'll give you an example. When [Arthur] Kornberg and [Severo] Ochoa showed that the DNA hereditary apparatus was just a series of enzymes, that was probably the last straw. Most people would have said the genetic code was so complex--and DNA was a big molecule--that something more complicated, like a computer, had to be involved. When they showed that the genetic code was really a series of enzymes and a substrate that happened to be very big, then almost everybody said you can break up everything [into component parts]. Even then, though, the brain was an order of magnitude more complicated. But now it's pretty clear the brain is just the same thing; it's a mixture of enzymes and so forth.

Hughes: The systems in the cell have important interrelationships.

Koshland: Oh, yes.

Hughes: So how do you establish those relationships if you break things down?

Koshland: You have to develop a very complex methodology. But it helps a lot if you have a basic clue from a simpler organism. I'm going to use a very simple analogy. Suppose the body is a swimming pool, and there are all sorts of things going on. Now, if you cover the swimming pool, and you have sunlight coming in, then you feed a human being some glucose, and it gets enough energy to swim the pool. As it swims, it exhales CO_2 and inhales oxygen, so you can measure the oxygen that's used up and the CO_2 that's exhaled, and you get an idea of the metabolism, okay?

Sure, things in your body interact with each other. For example, if you do things that slow down metabolism, then as a result you're going to get colder. And if you get colder, then the metabolism slows down. So they are very important interactions. But after you understand the system, it's easier to rationalize it. So that's the reason you do experiments on simpler systems.

Hughes: I think of biochemists as mainly breaking things down, but is that a false generalization?

Koshland: Yes. Metabolism goes two ways. Metabolism means the synthesis of molecules as well as their degradation. You want to learn both of those [pathways]. With what is called reductionism in science, you make the complex world much simpler. You work it out for the simple system. Then you must do [research] in the complex system to show that it works the same way in the complex system.

Hughes: I wish to read from an abstract that you submitted in 1982 for a conference on the Chemical and Biological Basis for Individuality? It's called "Individuality in

Biochemistry and Behavior," and it's about chemotaxis.[13] [Reading] "It is concluded that it will be advantageous to the species if certain controls of behavior remain statistical in nature. The same may well be true of behavior in mammalian cells and more complex organisms." Now, that was a teaser, as far as I was concerned, which I think probably you intended it to be.

A Statistical Basis for Bacterial Variability

Koshland: I'm going to look for another paper. [long pause as Koshland scans his bibliography]. Oh, this is it: "Non-Genetic Individuality: Chance in the Single Cell."[14] Remember, there was a famous book published, *Sex and the Single Woman*?

Hughes: I knew the analogy right away.

Koshland: You see, everybody thought that every bacterium was exactly the same. That was the business of instincts versus free will. We studied a number of individual bacteria because we could now study their tumbling and swimming. [We showed that] each individual cell was a little different. I pointed out that in fact it is known from statistics that the deviation from any one property-- If something is a hundred, and you have a random number--the numbers count up to be a hundred--then the error bar is usually the square root of a hundred. In other words, if it's a hundred, the determination of height or something, then the error in height is the square root of a hundred, or 10 percent.

Hughes: And that holds true pretty regardless of the subject?

Koshland: No, that's overstated. See, if something is an error and you have a hundred molecules, the square root of a hundred is ten, so ten out of a hundred is 10 percent. If you have 10,000 molecules, which is 10^4, the square root of 10^4 is a hundred. That's 1 percent, see? So the larger the number of molecules, the smaller the amount of net deviation is going to be.

What we pointed out in this paper is that bacteria were genetically prescribed very, very tightly. But there were a limited number of molecules, and insofar as they affected the life of the bacterium, they would be subject to more variability than in a bigger organism that had large numbers of molecules. So then we did some tests which showed they were really quite variable. That was important in terms of extrapolating to behavior in humans. I remember I gave that paper in a few genetic

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[13] Daniel E. Koshland, Jr. correspondence, 84/33, carton 6, binder: 1981 chron file in 2 volumes, Bancroft Library University of California, Berkeley

14 Koshland bibliography #206.

conferences. Some of the people in psychology, who don't want to believe anything is inherited, liked it. And I kept pointing out to them they really didn't like it. It was saying genetics may control the big organism even more tightly, see? So that was why we said, "Chance in the Single Cell."

It turns out that a bacterium has on the order of ten flagella sticking out of it. Those are not placed on the surface of the bacterium in any kind of systematic way. They just grow up randomly. So when the bacterium splits in two--say it has ten flagella--each little bacterium will not necessarily have five flagella. There's sometimes eight and two, sometimes six and four, sometimes five and five. So things like that arose. We said when you get down to small numbers, the variability can be quite great.

Student Research Projects

Hughes: Were there problems in introducing the mammalian cell culture system into your laboratory?

Koshland: Yes, it was a very different methodology because you had to use tissue culture; you did it in an [incubator?]. It was much more expensive, by the way. You had to be much more careful because your budget blew up very rapidly if you weren't careful.

Hughes: Did you attract students who already knew the technology, or did you train them on the spot?

Koshland: You train them. The kids come, being interested in biochemistry, and then they self-select a little bit. What you do as a professor at a university like Berkeley is the students know in general what you're interested in. Then they come around and you give them a specific problem, and sometimes they're interested in it and say they'd like to work on it. Some of them say, "No, I want to work for Professor X." Or some people say, "No, I want to work for you, but I don't want to work on that problem." So you tailor your problem to what students want, and then you influence them a fair amount.

Hughes: If you were trying to introduce mammalian studies into a laboratory, you'd be pushing them at students who came along, would you not?

Koshland: Correct. I'm working on Alzheimer's now, and students come and they said they'd like to work on Alzheimer's. Sometimes I say to them, "You've got to do more enzyme chemistry before you really can do something as complex as that." They usually accept that. On the other hand, if I say to them, "Well, I've got a better project on enzyme mechanisms," they may say, "No, I really want to work on Alzheimer's. If you don't want me to work on Alzheimer's now, then I've got to work for somebody else."

Two Sabbaticals at Harvard

Hughes: I learned from reading your correspondence in the Bancroft Library that your 1979-1980 sabbatical leave was spent at Harvard, presumably because it was a center of neurobiology. True?

Koshland: I'm trying to remember. I was on sabbatical twice at Harvard. Yes, it is true: I did go to Harvard in neurobiology. I worked for John Dowling, who was a neurobiologist, and met a lot of people there. [The choice of Harvard] was dictated by two things. One is because Harvard did have very good neurobiology, and I was interested in that. It also had very good biochemistry, and I was still doing a lot of that. And it also was near MIT. Remember, I had to go to a place where my wife could go to somebody, too. It turned out that MIT had some very good immunology, and she was really interested in going there, so she could go to MIT while I went to Harvard.

Hughes: That makes it tricky. A lot of things must be tricky when both husband and wife--

Koshland: Are career people.

Hughes: You finished your book on chemotaxis while you were on sabbatical.[15]

Koshland: Yes, that's right. I set out to do that book that year.

Hughes: And you did it. Was this about the time that you were making the leap into mammalian cells?

Koshland: No, that was some years before. I decided I wanted to learn a little neurobiology and how you handle more complex systems. I thought I'd work in Dowling's lab and do some experiments in neurobiology. It happened that it was not quite as easy as that. That is, Dowling was away a good part of the year, and anyway, he was working largely on vision, which was a very interesting system because it was one of the best developed [experimental?] systems. George Wald, who was in the same department, was one of the great authorities on vision.

But [vision] was really quite different from memory, which is what I was mainly interested in. It tended to get a little specialized. I learned how a lot of systems were being studied, and that was very interesting, and it was very helpful to me, in a general way. But I found I learned as much by reading as watching the people, although I did see the way they ran experiments.

Hughes: That's one of the purposes of a sabbatical.

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[15] Koshland bibliography #250.

Koshland: Exactly. Oh, it served a wonderful purpose, and it allowed me to go and visit people. Dowling was very nice because he gave me a desk and an office. I really did him very little good.

Hughes: I don't know about that! But I noticed you also gave some talks.

Koshland: I gave some lectures later on. I was the Robert B. Woodward Professor [in Chemistry, 1986-87]. Woodward was a very famous professor at Harvard who got a Nobel Prize.

Hughes: A chemist.

Koshland: He was a chemist, right. But among the Nobel Prizes [winners] are some people who are very famous and some people you barely remember, at least the public doesn't. But Woodward was very famous, and he was a big leader. When he died, they had a chair in his honor, and they still do. Once a year they'd have somebody come to the department and give a series of lectures. It was very fancy. For example, they gave us a house and free rent for the year.

Hughes: My heavens.

Koshland: My salary was paid, and my transportation there was paid, and everything. It was very elegant. That was in the chemistry department, and I was supposed to give lectures. I didn't know how many lectures. So I asked them and they said, "Well, [Albert] Eschenmoser"--who was a quite famous chemist--"gave something like fifteen or twenty lectures, and we thought that was a little too many. And then [Aragoni?] came"--Aragoni was from Italy, and Eschenmoser was from Switzerland--"gave one lecture, and we thought that was too few." So I said, "Six." So they said, "Fine." And that's what I gave.

Hughes: Well, you may not have had a named lecture in 1979 and '80, but you gave some talks, not necessarily all at Harvard.

Koshland: I gave individual seminars but not a series of lectures. And then they wanted me to give lectures to the students.

Hughes: I want to ask about the opiate receptor, but is that too much to cover today?

Koshland: Yes, I think so. And secondly, that's pretty boring. I did a little on the opium receptor, but then I decided it was too complex a field, and I shouldn't be in it.

[End of Interview]

[Interview 7: February 16, 1999]

[Begin Tape 9, Side A]

Research on the Mammalian Opiate and Aspartate Receptors

Hughes: You decided to make some summary remarks about your work on the opiate receptor.

Koshland: Well, two things happened. One is I got intrigued about doing something with a mammalian receptor because there was a lot of excitement about them. I felt the opiate receptor was a good one to study because it was very important in cocaine addiction and because it was probably a good example of a mammalian receptor with all of its complications. So I looked into it a little bit and did find out that it could be studied.

Mammalian receptors in general are present at very, very low concentrations, so it's a big job to get one out. You have to get out a little bit of one, and then you can clone it, and then you can get a lot of it, because you can make it in test tubes and study it further. To get the opiate receptor out originally meant doing sort of a cute experiment involving radioactivity of the kind that is really only available at Lawrence Berkeley Lab and a few of the big national labs. We wanted to incorporate pure tritium into the sample at a concentration [at which] we couldn't afford any dilution. It was just a technical problem. And so we managed to do that. Even then, the problem in getting it out was very, very difficult.

We did some experiments that were really quite useful, which we published, which dealt with new compounds which had the same effect as an opiate. It was an interesting study because I had to sign all sorts of forms from the State of California about handling opiates, and I had to keep track of every little tiny microgram of material that I had, and so forth and so on.

But I decided that the bacterial receptor, which I had sort of left, was probably a very good example of the kind of receptor that exists in all sorts of other tissues and that maybe it would really be smart to look at that more intensely. So I gave up the work on mammalian receptors and concentrated on the bacterial receptor, which was probably a smart idea because we were able to get the crystallography and a lot of things that we really just couldn't get with the more complex receptor. It looks to me like they have very much a similar pathway. We're still working on the bacterial receptor.

Hughes: As a model?

Koshland: As a model. It's interesting by itself as a bacterial receptor, but it also turns out to be a very good model for the others. So I've sort of lost interest in the mammalian receptors, although we read about them all the time, and we discuss them, and I go to meetings where people discuss mammalian receptors and bacterial receptors.

Hughes: I understand that you were using a different form of affinity labeling in regard to the opiate receptor.

Koshland: Yes. Well, it turns out that the opiate receptor binds its substrate so tightly that we really didn't need to use covalent affinity labeling. Affinity labeling is used in several different ways. The normal way is that you make a molecule that binds to the active site and then makes a covalent attachment, so it's really stuck there. That's a very useful technique. But it was really not necessary in the opiate receptor work; we could find out what it was without affinity labeling.

Hughes: I got this information from a letter in which you wrote about peptide analogs of the enkephalins.[16]

Koshland: Right. The enkephalins work through the opiate receptor. We thought we could make a peptide analog and use a covalent modification. That was one of the things we were going to do. But then I decided just to concentrate on the aspartate receptor because it had the same adaptation. See, adaptation is a phenomenon which is true of every single receptor. We discovered it first in the aspartate receptor, and then it turned out to be true all over. Adaptation comes out as the fact that you can't get off a drug because you have withdrawal symptoms. Your body adapts to the drug, and therefore your system is raised so that when you go off the drug, you feel terrible. That's a standard thing that's known. Since bacterial protein has those same properties, I decided we might as well do the bacterial protein because it was a lot easier to investigate.

Applicability of Bacterial Work to Human Addiction

Hughes: Is the bacterial route a general approach to studying addiction?

Koshland: No. There are a lot of people who will say the way to do it is to study the mammalian proteins directly. Periodically, in philosophical journals, there are arguments about reductionism and the scientists who oversimplify things. I think there are hilarious examples, where people have done it too much. But in modern science, particularly in biology, reductionism has been extremely successful. So history is really on your side to look at almost anything which is a good biological phenomenon that will turn out to be very general. So there was very little doubt that research on this receptor would be a good step. It wasn't very adventurous of me to do that.

Hughes: Are people who are interested in addiction willing to consider your work on the bacterial receptor?

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[16] Koshland to Gordon Dow, Research Advisory Panel, San Francisco, February 6, 1980. D.E. Koshland, Jr. papers, The Bancroft Library, 84/33, carton 6, folder:1-7/1/1980.

Koshland: Yes and no. The people who are really on the frontier, know you pick up any clue you can, and the bacterial systems are bound to be very similar [to the human]. When they worked out the genetic code, for example, people were looking at hemoglobin and lots of mammalian [systems] and also bacterial systems and even viruses, which are simpler than bacteria. There are some people who will always say, "Well, if you really understand the bacterial system, you've still got to investigate the whole thing over again in mammals." But it isn't true. You may have to do a little more investigating, but usually it's a small extra bit. You essentially strip it down to the essentials.

Signal Transduction Research

When I got the Lasker [Award for Achievement in Medical Science, 1998], I had to write an article about what I was doing recently, and I knew I got the Lasker for the induced fit theory. But the work we were doing really related to how big the conformational changes are in the receptor, to get the changes transmitted. The receptor binds across a membrane. You get the signal from outside the cell into the inside. It's a very important barrier; if everything could get into the cell, it would louse everything up. The cell has a very impenetrable barrier which is designed to let in only the things you want.

The aspartate receptor lets in information from about a hundred angstroms, which is a long distance for a protein--outside the barrier, through the barrier, to the inside. Everybody thought, well, there's got to be some kind of big exchange or some kind of big amplification device; you have a little signal outside that gives a big signal inside. What we found is that the change outside that was caused by the binding of the ligand--that means binding of a stimulus, like a bad odor--was actually a very small change. It was transmitted as a very small change to the inside, and then it was amplified there by an enormous, big amplification device, which I won't go through here now.

It turned out that this study confirmed what I had originally said about induced fit: that the conformation change--you could have really quite small changes, and they would be [amplified?] So it ended up that I got from induced fit to allostery to neurobiology, and then it came back again because the neurobiology was telling me interesting things about enzymes that I hadn't expected before.

There's a whole area called signal transduction, in which the aspartate receptor is absolutely typical, and that's why it is so similar to the mammalian receptors. Outside your body you get the stimuli that we identify with the environment: light, heat, sound, pain, a punch in the eye, something like that. To some extent, those things which you know are outside your body and come in are very similar to the things that happen in your body with the individual cells because you have hormones and blood supplies and everything coursing through your body. A cell must grab only a few of the signals and nutrients coming by it. But it's got to get those. The cells of your body see only certain things that come by in the blood stream, and not others. What they see is determined by their receptors. Basically, you're repeating at the cellular level what you have in the whole organism.

Hughes: I see.

Koshland: Signal transduction starts when the signal hits your eye, and then there is a whole series of events until it gets to your brain, and then the brain sends signals back out, to move your hand or something like that, as a result of the signal. That's exactly what happens in the cell.

In signal transduction with aspartate, the chemical binds the receptor. You get information which may go to the nucleus of the cell and create some change there, which goes back out. The first step is, the information you get from outside goes through the membrane to the inside. That's what the receptor does. And then there's a cascade of events called the phosphorylation cascade and all sorts of other things which follow up on that. So those are all part of signal transduction.

The bacterial system, which was worked out by me and by a bunch of other very good investigators--Julius Adler of Wisconsin and Mel Simon at Caltech--is probably the best understood signal transduction system in the world today. It's sort of a model. Partly because bacteria are simpler than other things, it has been thoroughly worked out, and lots of other people have tried to look out for similar kinds of transduction systems in other organisms and with other events.

Koshland's Piston Mechanism of Receptor Function

We've come out of the aspartate receptor work with a model which I call the piston mechanism, which we're now studying by all sorts of techniques. I believe it is a very good model for how lots of receptors work. We're just exploring how it works with the aspartate receptor. That means not only finding out what happens with the aspartate receptor but also developing the tools to look at it. Now, both the concept of a piston-type motion and the tools will be very useful for other people looking at these other receptors. Whether it turns out to be a very general mechanism, time will tell. So I can't say right now it works. But I think it's a very good mechanism, and some of the tools we've developed are good for other people to use with these more complex receptors, to see whether they work.

Tools for Receptor Studies

Hughes: Well, say a word about the tools that you're developing.

Koshland: We're doing a combination of three things. One is X-ray crystallography, which we didn't invent. Receptors are in membranes, and they're very hard to crystallize, so we use genetic engineering to cut them into pieces, both of which are soluble. So that's an important technique. Then we used disulfide cross-linking, which Joe Falke, who is a postdoc of mine, invented while he was in my laboratory, and we've used it and he's used it, and now a lot of other people are using it as a way which is easier than X-ray crystallography. It doesn't give you as much information, but we've learned a lot about the protein. So part of our current research is to find out how much we can learn from the disulfide [cross-linking method]. And then we have something called spin labels, which is a technique invented by Harden McConnell, which is very useful for proteins you can't crystallize. So we're using that technique with receptors and finding out how good it is. Harden McConnell was the one who originally [developed] the spin labels, but he was trying to use them for antibodies.

Possible Clinical Applications

Hughes: Is it true that only recently have you moved into areas that could have practical application?

Koshland: Yes. I made a hybrid receptor between the aspartate receptor and the insulin receptor which could be used for therapy. Recently, I've been emphasizing work on Alzheimer's disease. That is, looking at a molecule called the NMDA [N-methyl D-aspartate] receptor, which is a very important receptor in understanding learning and memory.

Hughes: Why have you become interested in recent years in potential clinical applications?

Koshland: I guess partly because all biologists are interested in application. Basically what you're working on is biological systems, so drugs and medicine are right there in the background, all the time. In the case of the enzyme work, I have a number of practical applications, some of which we're working on, like getting rid of chlorinated compounds in the background. Those are incremental approaches, where I'm pretty sure we're going to succeed in making a little bit of a step, and that will be useful, and other people will make further steps. So I'm sort of saying, well, my career is beginning to come to an end. Let's not wait for everybody else to do something. Let's do something where we solve the whole thing ourselves. So I figure Alzheimer's is as good a problem as any.

Hughes: [laughing] You're not easily intimidated, are you, Dan.

Koshland: No. [laughing] Anyway, I'm still doing the work on enzymes.

Hughes: Did funding sources have any molding effect on your interest in practical application?

Koshland: I think yes. I think the times have changed, so in order to get a grant, you need more practical applications to get it, although theoretically the agencies like the NIH and the NSF say you don't have to have them. I have grants from both organizations. They would say to me--and probably correctly--that since I have a long record and have published a lot of things, I probably have to place less emphasis on practical things than a young person starting out. So I have that advantage. There are not many advantages of old age, but that's one of them. I have the grants, and I don't think there is evidence that further grants will be forthcoming if I'm a little more practical--I don't know. On the other hand, we are writing our notebooks with a view to getting patents.

Commercialization in Academic Biology

Hughes: What do you think about patenting in biology?

Koshland: Oh, I think there's no problem. I'm not really in a position where I need to make money at this stage in my life. I'm very well off. On the other hand, a patent is like a publication. In my case, [any royalties] will certainly be shared between the university, which will get part of the patent; the NIH, which subsidized a lot of the research; and my co-workers, who really came up with a lot of the ideas. So I think a lot of people will benefit.

Hughes: Do you have an opinion about the trend in academic biology towards practical application, making it more difficult to do basic science?

Koshland: There was a lot of controversy for a while, which was sort of ironic because biologists were supposed to be impoverished people. Biologists in the area of recombinant DNA--many of whom you've recorded for oral histories—-suddenly [found related] ethical problems. At that time, I was editor of *Science*. I read some things, and I couldn't believe everybody was making a fuss. Chemists who were on the staff of universities consulted for chemical companies; lawyers flew to Washington and got big fees to consult the government; architects built buildings outside the university; physicists had defense contracts. So [outside ties] were true all around.

This was being done right and left by academics, and it was just understood that chemists could be wealthy; lawyers particularly could be wealthy. But biochemists were not supposed to be, I guess. But now we're over it. Now the biotech industry has turned out to be big industry. The techniques, in my opinion, have done very well. You couldn't give the [patent royalty] money just to the investigator when the university had provided him a place to work and an academic salary and everything. The university certainly deserved part. And then the university shouldn't take all the money because NIH had provided the money for the research. NIH hadn't provided the building but maybe most of the [research] money.

Patenting was devised as a way to make you divulge your secret [invention] to the public, so the public could then use it and improve on it. Whereas if you don't have patents, people just keep everything a secret.

The College of Natural Resources/Novartis Agreement

Hughes: But this trend toward commercialization in academia is more than just taking out patents. We had a recent fuss on campus when the College of Natural Resources signed an agreement with Novartis. What do you think about that response?

Koshland: My feeling is, that was nonsense. It's sort of the same kind of trouble that concerned the genetic code and DNA processing. Scientists are learning about the inheritance of diseases. The ethical problems involved there--which are serious; I'm not saying they're minor--are exactly the same as those involved in DNA. It's just DNA does more of it [has more of them?].

When you examine some of these problems, all of a sudden people have vague fears. Their slippery slope argument is the one that really drives me nuts. They all say, well, if you do that, it isn't bad by itself, but you're on a slippery slope and then you go worse and worse and worse till something ends in disaster. Well, the slippery slope argument could apply to any invention. I'm sure when Edison discovered the electric light bulb, somebody said, "Well, God knows, we can think of all sorts of things that'll happen. Maybe the paparazzi are going to abuse electric light bulbs."

[End Tape 9, Side A. Begin Tape 9, Side B.]

Koshland: The Novartis deal is really a way of subsidizing a lot of basic research at the University of California, in an area--and I'm not in it at all--which has very little support, namely, the plant industry. That's a big, important area. I think it's very good for the university, and I think the people who are handling it are very sophisticated. Novartis pays a certain amount, the NIH pays a certain amount, the university pays a certain amount, and all of them get a certain fraction, if something very practical results from the research.

Orbital Steering

A number of years ago, I proposed a theory of enzyme action called orbital steering, which caused a lot of excitement and arguments at the time. Some people said, well, it was theoretically wrong and not worth investigating, and the small changes [in molecular orientation] we were talking about couldn't be that important. I argued for a while, and then gave it up because the calculation I made was in statistical mechanics, which is something chemists use a lot, but biochemists apparently don't know very much about at all. At that time, if I talked to a biochemical audience and used statistical mechanics, they didn't know what I was talking about. On the other hand, the chemists were very interested in enzymes, so after a while I realized I was talking to a blank space. And so I said, no use arguing; I've just got to wait till I get some method of proving orbital steering. In fact, there was no method at the time.

With X-ray crystallography, the tools are available, and I suddenly realized I could really prove that point. And so we've done that, I think, with several experiments, one with an enzyme and the other with this receptor molecule. Orbital steering is really getting widely accepted. In fact, everybody who had written about orbital steering sort of thought it was right, and they would argue about little points. Ironically, now that we've got the experimental method, and we prove it, a lot of people say, "Oh, well, that's obvious." [Michael] Polanyi once said, "When you make a big discovery, there are usually three reactions. The first is that it's wrong. The second is that it's banal; everybody knows it. And the third is I thought of it myself." [laughter] All that has been true about orbital steering.

I just gave [a talk on orbital steering] at a meeting at the University of California, Irvine. I called a postdoc whose work I gave at this meeting, and I said, "I'm getting bored with it. Everybody said, 'Oh, orbital steering is correct. We all know it's orbital steering.'" And so I said [to the postdoc], "If it isn't a fight, I've sort of lost interest in it." [laughter]

Hughes: What do you mean by the term orbital steering?[17]

Koshland: What I said in the induced fit theory was that the substrate must induce a change in shape of the enzyme to bring the catalytic groups into alignment. I felt that the changes didn't have to be very large. I was an organic chemist, and I considered the changes inevitably were going to be small because the carbon-carbon bond is only one-and-a-half angstroms; the carbon-oxygen bond is about one-and-a-half angstroms. Oxygen[-oxygen] was a little bigger--two angstroms. Those are very small distances. If the catalytic groups are lined up around those groups, they don't have to move very far to make a big difference. This is oversimplifying because we could go on about why they have to be bigger [changes]. Anyway, when I would give talks on this topic, people would ask me, and I'd say, "Oh, [the change in molecular configuration] doesn't have to be very much."

Then the X-ray structures came out, and the first X-ray structures showed rather small [molecular] changes. [David C.] Phillips did lysozyme and [Frederick] Richards at Yale did ribonuclease. Instead of saying, "Koshland is right, and induced fit theory is right," they said those changes are so small that it's not that significant. Shortly thereafter, [William N.] Lipscomb and Steitz and others did experiments in which the conformation changes were quite big. So then there was no question; everybody said, well, okay, induced fit is correct. I had also done a number of experiments in between. Then they found a lot of big changes, and lots of people kept quoting the big changes. They just assumed big changes were induced fit and forgot about the small ones. My Lasker Award paper was "Conformational Changes: How Small Is Big Enough?", meaning how small a change is really a significant change?

Orbital steering came out of a paper that I wrote in 1968--I still remember it--where I tried to account for the enormous velocity of enzymes. We made a calculation that enzymes were 10^{17} to 10^{20} times more effective than an organic catalyst. That's a very big number. Ten to the eighteenth [10^{18}]is a million million million. If you think in dollars, you can see how big that number is. Anyway, basically

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[17] The following discussion of orbital steering was moved for better continuity from its original position near the end of the transcript.

nobody had really calculated how big an enzyme was in terms of amplification or acceleration. We calculated it out and said it was a very big number, and then we tried to break it up into the various parts of catalysis that were known. One was acid-base catalysis; another was what I call covalent catalysis; one was electrostatic effects. And when we went through all the known mechanisms that you could think of in organic chemistry, we were still a number of orders of magnitude too low for the catalytic power of enzymes with known factors.

And so I said one of the missing factors was orbital steering. That is, you didn't just have to bring the two substrates together; they had to be lined up very precisely. Let's say you put a key in a lock. It has to fit, so you push it in parallel to the grooves. If you try to put it in from an angle, it's just not going to work. Well, in orbital steering not only does the key have to fit the lock--I changed that to glove fits a hand--it has to do so with the electron orbitals lined up to optimize this reaction. I said that introduces another factor, a big number, 10^8, and that was the thing that became controversial. People said, well, it couldn't be that big a number. What I've shown recently is that it could be that big a number.

Hughes: This experiment was done on a theoretical level?

Koshland: No, this was a regular reaction.

Hughes: On what basis could you postulate alignment of orbitals?

Koshland: Because in any chemical reactions, orbitals really are involved. Orbitals are the way you express in quantum mechanics how the chemical bond works.

[End Tape 9, Side B. Begin Tape 10, Side A.]

Objections

Hughes: People objected to the magnitude, not the concept itself?

Koshland: Yes. The arguments of Bill Jencks, a very prominent chemist at Brandeis University, were a little bit like the one I told you before. He said, "The magnitude is wrong. And in addition, it's just an entropy effect. Everybody knows entropy is important. Therefore, the argument is banal." Those two arguments, I felt, were both stupid, if you want my honest opinion.

Hughes: [laughing] Did you tell him so?

Koshland: Yes, I said so. I was at various meetings. I didn't say it quite as bluntly as that. I said, the calculation was correct, which it was. I won't go through the calculation now, but I said entropy is a general property of matter. There is an entropic component to what I was saying, but entropy isn't a mechanism; it exists all over. It's like saying, "You need gas in the atmosphere in order to operate a human system." Well, everybody knows that. If you say this one death was caused by carbon monoxide poisoning, and somebody says, "Oh, everybody knows gases are important. Why are you emphasizing carbon monoxide?" You say, "That's not very helpful. We can look for a leaky stove if we know the death is due to carbon monoxide." I think Jencks was just a little bit put out that he hadn't thought of orbital steering himself, if you want my honest opinion--which I wouldn't publicly say. That will go into my recorded history.

Another person who objected was [Thomas C.] Bruice. He had a better argument. He said the number was too big because he assumed 10^8 had to be involved in one reaction. I showed in the Diels-Alder reaction of two cyclopentadenes that the number was very close to 10^8. But in a lot of other reactions it would be less than that. But if you took the total orbital steering factor, it had to be calculated based on two substrates reacting and then a couple of catalysts reacting on those substrates. And if you threw in all of that, it would come close to 10^8 in lots of reactions. Bruice was really fascinated with that one part and sort of exaggerated what I said.

Hughes: Did Bruice accept your argument when you explained it?

Koshland: Not then. I gave a talk at his institution. He's a professor at UC Santa Barbara. He essentially said at a big scientific meeting that I was probably right--sort of reluctantly, but it was fun.

Hughes: [chuckling] But you're more than "probably right" these days?

Koshland: I think so.

Hughes: Has orbital steering been incorporated into science?

Koshland: Induced fit is now accepted. I think orbital steering is getting there. It's not there yet, I'd say. But people start using it: they say, "Oh, that reaction goes fast because of orbital steering." I hear more and more of that at meetings. In a few years, they'll say, "Well, everybody knows that.

Single/Double Substrate Displacement Reactions

Hughes: I want to go way back--I think this was Brookhaven work--to single/double displacement reactions.

Koshland: Yes, that really goes back to my enzyme work. Now, when I'm so busy I can't account for the hours of the day (which is probably good for me at this point), I recall that some of my best discoveries were made at a time of more leisure, and maybe I should deliberately make an effort to have more leisure. I think everybody says that.

The single/double displacement problem is intriguing. I had moved to Brookhaven, and I didn't have anything in the lab. I had ordered some equipment to get going and do some research, and I really had time on my hands. Since I had been trained as an organic chemist, I said, “Well, why not apply some organic chemistry to enzymology and biology?” Displacement reactions were well known in organic chemistry. The question was, how could you apply them to enzymes?

I had thought of this idea: according to the Walden inversion, when there was a displacement reaction, there was an inversion of configuration. You could examine biological materials when there were inversions, even though you couldn't see the chemical reaction.

Hughes: Where was the inversion occurring?

Koshland: It's on the carbon atom. I think it's probably not necessary to go into detail. But anyway, what we could do was apply chemistry to biology and in that way really learn something very new about biology. I said, "Okay, I've found articles in the literature," and I didn't really do any work. I mean, I did a lot of mental work, but no physical work; I looked up these reactions.

It was sort of ironic because, when I got enough reactions to be pretty sure my theory was right, I got ready to write it up, and I was going to send it to the *Journal of the American Chemical Society*--because the American Chemical Society is what I knew; I was an organic chemist. They had invited theoretical articles, the kind that I thought I qualified for, so I sent it in. They sent it back to me, saying they didn't want it; the article was just theory. I said, well, you invited theoretical papers. They said, "Oh, we meant mathematical articles. We didn't mean chemical reasoning."

As a result, I sent it to *Biological Reviews*. This was really the first major publication I sent in after I moved to Brookhaven. See, I was a chemist and knew very little [about biology]. It turned out *Biological Reviews* was considered a very prestigious journal by biologists. It got published there, and it got a big splash, and lots of people paid attention, much better than if I had published it in the *JACS*. That paper really helped a lot in my career.

Hughes: Why were biologists so interested in it?

Koshland: Because *Biological Reviews* was a quite famous journal that published everything, all across the whole biological spectrum. My article was really very, very extreme in the sense that it was on the chemical end of biology. They had many more articles about how birds mate and all sorts of other things. Lots of biologists read it. Any well-run journal, people tend to read because the editor is condensing down a lot of literature that is not important, to just give you the gems that are important. *Biological Reviews* was recognized as one of these journals, and so people read this article by this peculiar young man who now had a job at Brookhaven, which was not a very famous place. But anyway, it got a big splash. And so I got a lot of attention as a very young assistant professor.

Hughes: But surely the attention the article attracted wasn't just because it was a bit unusual to have a chemically-oriented article. It must have been its content.

Koshland: Oh, it was a very good article.

Hughes: But what was there about it that got people thinking?

Koshland: It really cut across very different disciplinary lines. It was a different way of thinking about enzymes, and it condensed a lot of information that was in little pieces. Any good theory does something like that. It was a little different from my induced fit theory that came later. It was the kind of thing somebody says, "Eureka, of course, you've found it. It's just obvious it works." And nobody had thought of putting those things together before. And so it was very nice because instantly people thought it was important.

Induced fit, which followed, was I think a more general and a more important hypothesis. But, on the other hand, when you first looked at it, it [didn't seem] necessarily true, and so people argued about it and resisted it a little bit, and it took a number of years to actually prove that it was correct. Whereas the single and double displacement was a perfect one for me to start a career with because it instantly caught a lot of attention.

Hughes: What was it about?

Koshland: If a reaction occurs on an enzyme surface, there are two ways it can occur. One is when you have two substrates: substrate A interacts with substrate B directly, and the enzyme changes the atmosphere around it to facilitate the reaction. The enzyme is the catalyst. The second type of reaction is that the enzyme takes a more active role and forms a covalent intermediate with one of the substrates, which is then pushed off by the second substrate. That's the double displacement. The other is single displacement because there's one displacement of molecule A and a molecule B. Double displacement says A will react with the enzyme to form a covalent intermediate, and then that covalent intermediate reacts with B and then forms AB. It turned out that that generalization related to the stereochemistry, and it was true of all sorts of different enzymes: kinases, phosphatases, hydrolases, dehydrogenases. Anyway, it was the kind of thing where enzymes that were considered to be totally different and worked by different mechanisms were [found to be] all similar. And so it cut across fields and made you think differently about enzymes and also gave you some generalizing principles and some techniques for finding out whether you were right or not.

Fermat's Theorem is very famous in physics. I'm not a physicist, but it just struck me as intellectually exciting, and so I enjoyed reading about the solution of Fermat's Theorem, even though it didn't help me in my work. Well, single and double displacement, which was not nearly as big a deal as Fermat's Theorem, nevertheless was a unifying principle, and lots of people could use it. But lots of other people couldn't use it, but it was just intellectually interesting, and so they read about it and said, "Ah, isn't that nice? Even though I'm not going to use it myself, I'm glad that problem is solved."

Hughes: What were the tools that you came up with?

Koshland: The tool we came up with was stereochemistry. We found out there was an inversion of configuration, and one of the things with carbohydrates you could use an optical [rotation?]. In other cases, you used what's called exchange reactions. In other cases, you actually isolated and caught intermediates and showed that they were inverted in configuration. So there were a number of different tools to be used. It meant that even though I had described a number of reactions, lots of people could then say, "I'm studying these other reactions. Is there single or double displacement in them?"

Hughes: So the work was seminal on both a theoretical and a practical level.

Koshland: Right. I was invited as a rather young person to talk at the Faraday Society. I remember that was pretty interesting for me, too. I went over--

Hughes: To London?

Koshland: I think it was at Oxford. I've forgotten where the meeting was, but it was lots of fun. I'll tell you an amusing story about me. I had been to the American Chemical Society meetings and things like that, but this was a very hoity-toity, invited meeting. They had a banquet the night before the sessions open. A guy named--what's his name?--was chair of the meeting. He was chairman of the department of biochemistry at Oxford. Very suave and good speaker. He called on someone and said, "Now, my good friend, so-and-so, would you say a few words." These people got up, and I was impressed that they talked the way my English teacher in high school told me you were supposed to talk. You have a beginning, a middle, and an end. I'm going to do this, then you described it in some detail, then you say, "I've done that," and sit down. Wonderful.

I listened to them a while and was enjoying myself, and then I got terrified. I thought, well, Koshland--they've flown him a long way. Even though he's very young, somebody might ask him to say something. What would I say? I really didn't enjoy any of the rest of the program because I was preparing what I was going to say. I found out the next day--which I should have known--that all the people who were called on had been told the night before that they were going to be called on. That is, of course, always true. Every once in a while, you are called on spontaneously, but more and more at meetings people are asked, would they like to say a few words, and they know ahead of time.

Hughes: This work on displacement reactions would generally fit into the field of enzyme mechanisms?

Koshland: Yes, it was definitely enzyme mechanisms.

Enzymology Mid-20th Century

Hughes: I read something that gave me the idea that that field of enzymology was not particularly well developed. We're talking about the 1950s?

Koshland: Right.

Hughes: Well, is that true?

Koshland: That is true. I wasn't absolutely the only one. There was Esmond Snell in the department of biochemistry at Berkeley, that I joined later, who was one of the pioneers in applying chemistry to enzymes. A guy named Gerhart Braunitzer in Russia also did a fair amount, working on vitamins. A lot of chemists were working on identifying and purifying compounds, but as far as mechanisms, I was one of the early people. Frank Westheimer, whom I worked with at Chicago, was also one of the early people working on enzyme mechanisms. There were relatively few of us at the time.

Hughes: Did your background in organic chemistry have a role?

Koshland: Oh, yes, my background in organic chemistry was very important because organic mechanisms were what I just assumed enzymes were working with because enzymes were carrying out very important organic reactions. Then later on we learned more about inorganic reactions. But we knew more about organic mechanisms. Single/double displacement was applying organic chemistry to enzymes.

Hughes: Does that explain why many biochemists, most of whom may not have an organic chemistry background, shy away from mechanism studies?

Koshland: Well, almost anybody who did biochemistry had to have organic chemistry first. They just didn't specialize in it very much. It was one of the prerequisites for biochemistry, along with physics and everything. They knew the language, but they just weren't that interested in mechanism. Early biochemistry, the time I was working in it, most of the people were interested in [metabolic] pathways. Pathways hadn't been worked out yet, so most of the people were doing things like that.

Hughes: Later structure studies become very prevalent, did they not?

Koshland: Correct.

Hughes: Working out the structure through crystallography.

Koshland: Well, enzyme mechanisms became more and more important, and there were more people doing enzyme mechanisms and statistics and kinetics of enzyme action.

And then crystallography burst on the scene, and then structure became very important.

Evolution of Enzyme Function and Biological Clocks

Hughes: I read several of your papers on the evolution of enzyme function[18]--which I found very interesting, by the way. You made the point that there was less emphasis on the functional aspects of enzymology, which you maintained had to be the driving force behind evolution.

Koshland: Yes.

Hughes: We've talked about why people avoided enzyme mechanism studies. Biochemists were oriented towards other problems.

Koshland: And also because enzyme mechanism was more difficult.

Crystallography arose, and the [amino acid] sequence of enzymes became easy to learn. People had automatic machines that did sequencing, so they could correlate a lot of data in evolution with the sequence of the amino acids. So that became a big field. They discovered that there were mutations in the sequence of amino acids as a result of evolution. There was, say, one amino acid change for every million years or something like that. It was sort of a clock. As a result, there was much more emphasis on the structure. As the amino acid change occurred every million years, you tried to correlate that and to relate whether the baboon came ahead of the chimpanzee [on the evolutionary scale] or something like that.

Function has got to be the way that you select for survival of the fittest. If you have an enzyme function that works better in the Ice Age, then those people who have that enzyme are going to survive. That's the theory. Allan Wilson, who was one of the professors here, became very prominent in that field, looking at the biological clocks and whether we were descended from the apes.

The paper you're talking about I wrote for a scientific meeting. I like to say something interesting and a little provocative, and so I pointed out that you could trace certain areas of evolution of function, which must have been a very important part in evolution in the selection of these things. And the mechanism by which they did it was having mutations which changed amino acids and changed the structure. Nevertheless, the real reason for selection was function.

Hughes: If we're talking about the same paper, which was in the *Federation Proceedings* in 1976, you postulated that there was a general drift in enzyme capabilities. In

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[18] See, for example: D.E. Koshland, Jr., "The Evolution of Function in Enzymes," *Federation Proceedings* 1976, 35, #10:2104-2111.

general, the progression was from catalysis, to specificity, to regulation, to cooperativity.

Koshland: Correct. And each of those were further refinements.

Hughes: How did people respond to that idea?

Koshland: In general, they liked it. A lot of people in evolution who were specialists in structure took not very much notice of it. On the other hand, a lot of other people were sort of intrigued by it. Today, I have more evidence because this idea that there are small changes [in the molecular configuration of enzymes] fits in with that [theory of evolution in enzyme function] very well. People are taking note, and I might even write another review, bringing [the theory] up to date, because I think the evidence for it is very much better now.

Hughes: Is the flexible enzyme at the core of this concept?

Koshland: Yes and no. The flexible enzyme helps a lot in evolution, if you think about it. It was almost essential for the regulation part. It isn't absolutely essential for the others. You could imagine evolution if you didn't have a flexible enzyme. You could have a whole bunch of different changes and still not have a flexible enzyme. But we now know more, and the flexible enzyme offers opportunities that we wouldn't have otherwise. And it's very difficult for me to imagine anything about regulation if you don't employ flexible enzymes.

Reporter Groups

Hughes: We haven't talked about reporter groups.

Koshland: I can tell you about that. I was at Rockefeller, and I was looking at conformation changes. That was in the early days of induced fit, before protein crystallography. I was thinking of things I could do to prove the induced fit theory. So I said [to myself], I have to have something near an active site that will tell me whether or not there's a conformation change. I recognized I couldn't put it right in the active site because the active site is such a small, sensitive area that by putting it right in there, it would probably perturb the whole reaction. So I said, I'll put it in another group--which I did--a chromophoric group which would change color if it was right near the active site and there was some perturbation that occurred at the active site.

I thought, what should I call this new phenomenon? The classic thing you do is to invent some Greek name, like allostery, that everybody will think is an exciting, new phenomenon. But I decided on "reporter group." The concept was intriguing because in the chemistry that I was talking about, there was really no way you could have a group that would respond to environment changes around it which wouldn't perturb the environment a little bit. There had to be some interaction of the chemicals. It was really like a reporter. If a reporter goes to a banquet and is reporting what the speaker says, it's inevitable if the reporter is there that the speaker knows that he better say it a little differently because it's going to appear in the press. So the reporter perturbs the event. So I thought "reporter group" was a good name for it because there was a reciprocal action. The reporter said what happened but, on the other hand, the existence of a reporter perturbed the event a little bit.

Hughes: A little, but not enough--

Koshland: To change it fundamentally.

I had this idea, and I gave it to a student, Meryl Burr, who is now a professor at the University of Washington. She told me that a distinguished professor at Rockefeller told her this was a very bad problem, and she shouldn't work on it because nothing would ever come of it. I was furious. I was just a young assistant professor. To tell a student they shouldn't work with me I thought was really not very nice. In retrospect now, I realize he may have meant it in a very nice way. This was a poor student who was being led astray with a terrible problem. But it turned out to be a very good problem. It got written up, and the term caught on, and it's now used extensively in the literature.

Hughes: For many reactions?

Koshland: Yes, many other reactions that I didn't do. They use the term "reporter" with very much the same idea. So that was an idea that caught on.

[End of Interview]

Interview 8: February 23, 1999

[Begin Tape 11, Side A]

Catalytic Power of Enzymes

Hughes: We've been discussing your science, and I think the category that has not been talked about sufficiently is the catalytic power of enzymes. Would you describe your work, please?

Koshland: Sure, I'd be delighted because it's one of my favorite subjects and one I've done a lot of work on over many years. I think my fascination with the catalytic power of enzymes really started in graduate school, where really for reasons of laziness I decided to get my Ph.D. in organic chemistry. I had decided to be a biochemist earlier in my career, in fact, when I was in high school. When I went to the University of California, I was told by everybody, "It's really smart to major in chemistry. It's a very solid, highly developed field, and biochemistry is just starting. And the professors in biochemistry at Berkeley are not that good." So, as I told you, I majored in chemistry as an undergraduate, with the idea that I was going to do graduate school work in biochemistry.

But then the war broke out, and I went straight from chemistry into work on plutonium. When the war ended and I went to graduate school, then I felt I was very old. I was twenty-six years old, which in my opinion then was ancient. Therefore I should get my degree as quickly as I could. If I majored in biochemistry, I was going to need a lot of biology courses as prerequisites, so I decided to get my Ph.D. in chemistry. I was already decided to work on the chemical side of biology, and then I found an inorganic professor named Frank Westheimer was also interested in biochemistry, so I asked if he would like to take me as a student. He said yes, and it worked out wonderfully. He was really interested in enzyme mechanisms, in a slightly different technical way than I was.

Once I finished my graduate work and postdoc, I came back to this problem that I was fundamentally interested in, the catalytic power of enzymes. In other words, why were enzymes such enormously good catalysts? When I say "enormously good," nobody had really calculated how good. I did some calculations. People thought maybe a thousand times better than known inorganic catalysts. My calculation came out with something like 10^{12} better. No one had systematically tried to calculate the numbers I did, and almost to my own astonishment, I came up with numbers of 10^{12}, 10^{15}. Ten to the twelfth is a million millions, which is considered a trillion in the current national budget discussions. That was an astonishingly large number. In order to get that number, I had to make a new theory, which we published in the *Journal of Theoretical Biology*,[19] and it made quite a splash.

Hughes: Can you outline what you said?

Koshland: The argument was, how could you compare an enzymatic reaction with a chemical reaction, which is very difficult to do, for the following reason. In chemistry in solution, if you have two molecules, A and B, coming together, you say something is proportional to the concentration of A and B. The standard practice is you give a rate constant which is based on one molar--that's A is one and B is one--and then a constant, which gives you that rate based on actual measurements at much lower concentration of A, the rate in [?].

What happens is that on an enzyme surface you hold A and B together in juxtaposition to each other and then observe a reaction. So now the question is, how do you relate those to the organic reaction where they collide randomly? What is the concentration of A and B relative to each other, as compared to the one molar state in solution? Nobody had solved that problem or even tried to think about it very much. I thought about it for a while and had a real difficulty in thinking how I could do it. I said, Okay, they're in solution in concentrations A and B. Maybe the way to do it is to consider solids. Suppose there were two solid molecules.

I decided, for complicated technical reasons, that that was not a good way. I finally decided, if you have water, and it's the only thing in solution, it's fifty-five molar when it's pure water. That's probably as close as you can get anything next to something else. If one of them was considered one molar, which is sort of a standard state, then you consider the other fifty-five molar when they're held right next to each other. That idea aroused some controversy afterwards, but nevertheless I really think everybody now thinks it's right. That idea made it possible to say what the non-enzymatic rate would be in respect to the enzymatic rate. That was really a big breakthrough.

I followed that up in later papers, really trying to calculate what were the regular organic factors that made that rate much bigger. That is a problem that I've been following up a good fraction of my life. In other words, it keeps coming back. I get off on chemotaxis and doing this and that, but I've always been fascinated by that problem. It's very important because if we could duplicate the power of enzymes, we could really do all sorts of things. For example, right now I'm working with an idea for helping the environment. If we could modify an enzyme so it could clean up oil spills, that would be very useful for the world. And that probably needs some real understanding of enzyme mechanism and why you have a such a good catalyst.

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[19] D. E. Koshland. “The Comparison of Non-enzymatic and Enzymatic Reaction Velocities.” *Journal of Theoretical Biology*, 1976, 2:75-86.

A lot of my research and many papers have been devoted to a least getting the pieces. What I've decided is basically there isn't one single blinding thing. Enzymes are not superconductors. Enzymes really are very smart organic chemists, if you want to say it that way. They've really been selected over evolutionary time to carry out the kind of processes that we are familiar with in organic chemistry. But by combining them in very clever ways, they get this enormous catalytic power. That's a good summary. I guess I published fifty or a hundred papers on the catalytic power of enzymes.

Hughes: So that was your first love, your abiding love.

Koshland: My abiding love. The induced fit was part of the puzzle but not all of it. It's the kind of problem we did enough, so a lot of students think it is solved. Therefore, they are less likely to work with a professor on enzyme mechanisms. That's sort of sad because it's harder to get people, but there are some people still very interested in it. And I'm still doing it.

Hughes: You attract students who want to work on enzyme mechanisms?

Koshland: Yes.

Koshland's Most Significant Research

Hughes: Dan, if you had to pick one piece of work that you are most proud of, what would it be?

Koshland: Oh, I don't think it would be possible to pick one. I think the theoretical understanding of enzyme mechanisms would be certainly one of my favorites because I know it really broke open a whole very important field. Induced fit was certainly another one. I had no idea how many things would be generated from it when I started it, but I knew it was very important. And the understanding of memory in bacteria. That certainly in many ways ranks high. I think it is probably less important than the other two, although it shook the biological community more. It got a lot of publicity and attention for the reason that one picture is worth a thousand words.

Another problem was half-of-the-sites reactivity, which is technically more narrow, but I really liked it. We had a very peculiar phenomenon; we couldn't understand it. We suddenly realized we were dealing with only half as much material as we normally would deal with. I could explain that as, you see somebody in a mirror, and somebody points out to you, there's really one person, and the other is a mirror [image]. That's not a bad analogy. In other words, a simple idea resolves all sorts of discrepancies. That's what happened in half-of-the-sites reactivity. I remember I presented the idea at a big meeting, and everybody else liked it, too. It probably wasn't nearly as important as the others, although it solved an important problem. But it was just sort of elegant. Every once in a while you do something that's elegant, and you like it.

Hughes: What work did that come out of?

Koshland: That came out of allostery. That's a really important concept in allostery.

The reporter group research was pretty interesting, too. I was pleased with that, partly because, as I told you, a Rockefeller professor told me it would never amount to anything and told my graduate student she shouldn't work with Koshland because he was putting her on bad problems. So when it turned out well, I was pleased.

A Chemist's Introduction to DNA

Hughes: What is your memory of the Watson-Crick announcement in 1953 of the structure of DNA? Was it of interest to an enzymologist?

Koshland: Yes, of course. Remember, I was just getting into biology. See, I was a chemist, and I got interested in enzyme mechanisms, which is a very chemical side of biology. That was exciting enough, but I didn't have to learn very much biology. I remember giving a speech in an ACS [American Chemical Society] meeting. Somebody asked me the question, "Where did you get your enzyme?"--meaning did I get it from a rat or a horse or a plant. I said, "I got it from Worthington Biochemical," which was a chemical company that sold enzymes. Everybody burst out laughing because it was quite clear it was a chemist talking, not a biologist.

On the other hand, there was another factor in those days. The literature was much smaller, and I remember having to read up a lot because when you went to a place, they would not only ask you general questions but also discuss, "Well, we read in the *JBC*"--that's the *Journal of Biological Chemistry*--"last week of so and so, and how do you think your new theory relates to that?" I found that you really had to have read the *JBC* because everybody thought you were sort of a dope if you just said, "Huh? I didn't read it." So the net result was when the literature was smaller, everybody was expected to be up on what everybody else was doing.

So my colleagues who were in DNA--and I wasn't doing very much in that--really thought working out DNA structure was a very important finding. I remember reading about it and thinking it was exciting. Of course, I couldn't foresee that it would lead to recombinant DNA and all that. But it led very soon to proof that the replication of DNA was explained by this structure of [James D.] Watson and [Francis] Crick. I knew that was very important because that was the mechanism for heredity. Lots of people very quickly recognized that it was really a big discovery. Crick was already pretty famous but had never done anything like that.

Crick was a physicist at the MRC [Medical Research Council], which is a very good research place, so he was well known for that but never had done anything that was particularly spectacular. And Watson was totally unknown. He was just a young postdoc who had left Caltech and was doing this work. So it was pretty astonishing. But it wasn't nearly as big at the time as looking back on it everybody [now] realizes it was.

Hughes: Did the discovery of the double helix draw your attention to large molecules?

Koshland: No. I was already dealing with large molecules. Proteins are big, big molecules. If anything, bigger than DNA.

Hughes: But DNA was a different kind of big molecule.

Koshland: Oh, yes. DNA is quite different from proteins.

Hughes: I'm meaning in the sense of carrying the code, carrying information.

Koshland: Well, an enzyme carries a lot of information--maybe more than DNA. DNA carries hereditary information. That's very, very important. It was not that it carried more information; it carried a different kind of information, and it did really set the stage for the genetic code.

Hughes: When you say an enzyme carries information, you mean in the sense of its conformation?

Koshland: Right. It's three-dimensional shape, you see, is designed to carry out catalysis, which our whole body depends on, so it really carries a lot of information. But you don't inherit the shape of one protein molecule or another. What you inherit is the DNA which tells you the sequence of amino acids in that protein.

Hughes: Yet people use the term "informational molecules," usually meaning the nucleic acids, right?

Koshland: That is wrong.

Hughes: Isn't that an enzymologist's viewpoint, when you talk about enzymes carrying information?

Koshland: I think you're right that some people use it to refer to nucleic acids, maybe reporters. But it is certainly a bad use of the term. For example, a hormone is an informational molecule. Let's say, you see a saber-toothed tiger running at you. The immediate thing that happens is all sorts of adrenalin rushes out of you, and it really tells you to get scared and to run like hell out of there. So you can't really say that adrenalin isn't an informational molecule.

DNA is the <u>hereditary</u> informational molecule, and that was a very important finding. In fact, DNA is like a linear string of beads, instead of a three-dimensional piece of clay. When it was first discovered by [Oswald] Avery and [Colin] McLeod and [Maclyn] McCarty that DNA was the carrier of hereditary information, a lot of people felt it was too simple a molecule to carry information.

It took a while for them to convince everybody. They did very elegant experiments to convince people.

Hughes: Did you have that bias toward proteins yourself?

Koshland: You're probably correct in saying that I didn't notice DNA as much. I was very much involved in protein chemistry. Nucleic acids were not nearly as big a field of interest. The number of people working in nucleic acids was much, much smaller than the number working in proteins. It reversed in subsequent years, and now it has gone back to probably the original proportion. But proteins were really very much the big thing. People knew they didn't know how proteins worked, and the proteins were very important in catalyzing all the dynamic parts functions of your body. Heredity was only one part of that. The protein chemists weren't that excited about nucleic acid chemistry. I would hear about it at meetings, partly for the reason that you had to read all the *JBC*. Looking back on it, you're a little ashamed. You should have been more excited, but you weren't.

Hughes: In a way, it's very understandable. You were a protein biochemist.

Koshland: Correct. The nucleic acid stuff was really a very difficult world. The techniques for handling it weren't as well known. A lot of messy stuff was done with it . People would occasionally talk about how they were very excited by this work of Avery and McLeod, and you'd listen to them. But they were also excited about finding one different kind of base in tRNA [transfer RNA], and that wasn't very interesting to a protein chemist, and you didn't know quite how all [the discoveries] fit together.

Arthur Kornberg[20]

Hughes: Arthur Kornberg came into your life--in the late fifties?

Koshland: Late fifties. There was an incident which I'm always sort of embarrassed by. The head of the department said to me, would I be willing to have Arthur Kornberg visit my laboratory [at Brookhaven] for the next summer?

Hughes: When he was still at Washington University, St. Louis?

Koshland: He was still at St. Louis. He was really not in my field at all--not doing anything that I was doing. But I had developed a technique, looking at O_{18} [an isotope of oxygen], that Arthur thought would be very useful and was sort of interested in the lab. I don't know whether I'm telling tales out of school, but I'm going to say it. It turned out the head of the department particularly wanted me to take Arthur into my lab. I was sort of annoyed because I was very busy, and I had been invited as a

[20]See the oral history with Arthur Kornberg at http://bancroft.berkeley.edu/ROHO/projects/biosci.

very young man to talk at the Faraday Society, which was a big honor, and I really wanted to go. My wife wanted to go to England, so it was going to be difficult if Arthur Kornberg came to my lab, to leave in the middle of the summer. The chairman of the department said I could go to the meeting, but he'd like me to have Arthur in my lab at least for some of the summer. I said, "Fine."

Well, it turned out Arthur was already a very prominent biochemist. He didn't have the Nobel Prize yet [1959], but everybody thought he was very good. He came to my lab. I was doing it sort of reluctantly because it came at a time when I really needed to concentrate on my own stuff, and I sort of felt he was being imposed on me.

I later found out that Arthur had been planning to come to work the previous year with a guy named Martin Gibbs, who was a carbohydrate chemist, and there was a problem with Kornberg's security [clearance]. It was the tail end of the McCarthy era. And so the plan was canceled at the last minute. Kornberg had done something liberal. There were some questions. Even though Brookhaven had no secret work, it was an Atomic Energy Commission institution, and they felt it would have bad publicity [if Kornberg came]. I don't know whether Kornberg or the lab held it up, but I would guess the lab. As a result, Kornberg didn't come that summer and was pretty annoyed--correctly, in my opinion. So it was very important that this incident be cleared from the record. It was important for Kornberg that he be able to come to Brookhaven, and something happened so Gibbs couldn't possibly take him the following year, so they asked me to do it.

Actually, Arthur came to my lab under less than optimal circumstances. But he was a very nice person, so I got to like him. I mean, there was no problem with that. It's just that we didn't do as good a job as I think we should have because I had to leave a month after he came, to go to England.

Later on he invited me to give a seminar at St. Louis. I was very mathematical, and he is not mathematical. I think we admired each other, but sort of from a distance. I knew he was doing very well, and I think he heard that I was doing very well, but he really didn't understand what I was doing, and I wasn't very interested in what he was doing [enzymatic replication of DNA]. I knew it was important work, but I wasn't reading a lot about it. We really became friends when he moved out to Stanford [1959], and I moved out to Berkeley [1965]. He has gotten very close to my brother-in-law, who is a professor at Stanford. So we got to be really good friends over the years.

Recombinant DNA

Hughes: Well, one of the events that unraveled from the Watson and Crick work several decades later was recombinant DNA.

Koshland: That's right.

Hughes: The first paper on the cloning technique was published in 1973 by Stanley Cohen and Herbert Boyer. Did that work make any impact on you when it came out?

Koshland: Absolutely, a big impact. I remember distinctly: Boyer gave a seminar in our department just in the beginning, mentioning his idea of the sticky ends [of the restriction enzyme to join DNA segments] that was a crucial part of the recombinant DNA procedure. You can take some DNA out of something and stitch it into the bacteria and then grow it, and the bacteria will function with the [foreign] gene there.

Boyer is a very low-key person. He just let this out in a very easy-going, laissez-faire type of manner. He presented the method clearly and said this is possibly new, but he didn't trumpet it, the way some people would: "Now I've done something great for the world." He presented it very low key. But I remember everybody standing around after and saying, "My God, that was a very interesting talk. The implications of this are really big." We were talking about how you could take genes from one organism and put them into a new one.

Hughes: You weren't talking about industrial application?

Koshland: We had no idea about industry. We just said research-wise it meant you could do all sorts of things. You could study genetics very differently, and you could move genes. I was still mainly a protein chemist, but I listened to my colleagues who knew a lot more about DNA, and they all said, yes, that's what the implications were.

I was working on chemotaxis at the time, using classical genetics. It occurred to me that we could use recombinant DNA to study this problem. And so I did it. It really helped my research a lot. In fact, I did it with the help of Tony DeFranco, who is now a professor at UCSF, at a time which was well ahead of people like Julius Adler, who were in the field of chemotaxis before me. Adler, in fact, was a postdoc with Arthur Kornberg. I was always surprised Adler was very slow at doing it. One person who did use recombinant DNA in chemotaxis after me was Mel Simon, who's very good. He is now at Caltech. At that time, he was at UC San Diego. He saw the advantage of recombinant DNA.

Hughes: Now, was this mainly for cloning the receptors?

Koshland: No, it was at that time just to understand some genetics of bacteria, to really understand the chemotaxis pathway.

Hughes: What aspects were you cloning?

Koshland: Well, for example, it was important when you got a mutation, you had to find out where the mutation was, what gene it was in. Recombinant DNA made it possible for us to find that out.

Hughes: Who was actually doing the recombinant work in your lab?

Koshland: Oh, several people were. Tony DeFranco was one, Jean Way another.

[End Tape 8, Side A. Begin Tape 8, Side B.]

Hughes: Did people come to your lab knowing recombinant DNA technology?

Koshland: No. Tony DeFranco and Mark Snyder were graduate students who had to learn it at Berkeley. Sharon Panasenko came to me from Stanford as a postdoc, and she did know something about it before my lab.

Hughes: Well, Stanford was a hotbed of recombinant DNA research.

Koshland: I don't think she knew recombinant DNA, but she knew nucleic acid chemistry.

Hughes: Do you remember which lab she came from?

Koshland: I think it was Bob Lehman's. Since I wasn't that much of an expert, they would get the problem from me, and then they'd go up and talk to Mike Chamberlin or somebody else in the department who was really a nucleic acid expert. And that helped them a lot. It's one of the great advantages of Berkeley. We have lots of people who are experts in various things that the lab director only knows peripherally.

Teaching Nucleic Acid Biochemistry

When I came here, the traditional approach of the biochemistry department was that the first year a new professor doesn't have any teaching. They told me in the middle of the summer that a professor in the department had been killed, and therefore they needed me to teach one of the elementary courses, a survey course in biochemistry. They were embarrassed, but they said they were short-handed. Could I do that? I said okay, and I started teaching the things that I knew very well, which were enzymology and proteins. But then as part of the course--it was a survey course which covered all of biochemistry--I had to teach nucleic acids. I was barely one step ahead of the students. I would read the textbook and go to the literature and read what I was going to give on Wednesday and then rush around when the Wednesday lecture was over to get enough information for Friday.

In the process I really learned a lot about nucleic acids. So when it came to my research, I wasn't nearly as afraid of this recombinant DNA. I used it as an example in many speeches, to say how important teaching was in my research and that a lot of professors who don't think they want to teach very much because they want to spend all their lives in research are really missing a bet, because I think your teaching does help your research a lot, and vice versa.

The Recombinant DNA Controversy and Biotechnology

Hughes: Did you take any active part in the recombinant DNA biohazard issue?

Koshland: I was interested in it but not directly involved. It was the kind of thing we discussed a lot.

Hughes: Your research involving recombinant DNA must have been subject to the recombinant DNA guidelines.

Koshland: Oh, yes.

Hughes: Talk about that.

Koshland: The first thing I remember is that Berg proposed a moratorium [on certain types of recombinant DNA research]. It didn't affect me very much at all. In fact, around the time I became chairman of the department [1973], there was what we called the P3 [physical containment level 3] facility, where we had to conform to certain guidelines. It was expensive from the point of view of the department, but we decided to put in a P3 facility. So we really felt the moderate approach of Berg [towards biohazards] was correct. There were people like Kornberg, who I think were basically correct but we thought were politically not correct because they said the biohazards issue was all nonsense made up by the public. I guess I thought it was sufficiently possible that recombinant DNA research might be dangerous. I felt it was unlikely it would be dangerous, but we ought to be careful. So we were careful.

When Berg proposed a moratorium, I wasn't doing any research at the time which would make me hold back because of the moratorium. I think in about the middle of it, I wanted to do some work with chemotaxis, using recombinant DNA, and I probably decided not to do it, just because I thought it was a good idea to conform with the moratorium. But it didn't affect my work very much.

Hughes: How did the guidelines affect others' research?

Koshland: It meant that some people in the forefront had to give up experiments. It meant that I had to do more cumbersome experiments. I felt the [NIH] biosafety guidelines were one of those things that it was a good idea to do, and I wasn't giving up too much to do them.

Hughes: Stanford and UCSF professors were among the first to go heavily into biotechnology. What are your opinions about why Berkeley wasn't represented in that first wave of entrepreneurs?

Koshland: Oh, I don't think there was anything very complicated. Recombinant DNA was a very interesting idea, and the people were Boyer at UCSF and Cohen at Stanford. It's inevitable when that happens, that the people who are your immediate colleagues learn of the technique fast. We thought it was an interesting technique but had no immediate use for it. But then, as I told you, I decided I wanted to use it with chemotaxis.

[Julius] Adler, who had been in Kornberg's lab, was professor at the University of Wisconsin. He was trained in a nucleic acid laboratory and was even slower than I was to use recombinant DNA. It may just be geographical spread. I think it was something as simple as that. Berkeley was just across the bay. Even though the biochemistry department had snapped up recombinant DNA, a lot of the other departments that could have really used it, weren't using it. That became a little bit of an impetus to have the big reorganization of Berkeley biosciences.[21]

Hughes: What about the ties that UCSF and Stanford faculty very quickly established with the biotechnology industry--becoming consultants to industry, forming their own companies?

Koshland: The big biotech revolution which occurred here in the San Francisco Bay Area was a result of a couple of things. First of all, the whole Silicon Valley relationship of new scientific ideas in computers became tied up with the venture capital community. It was really important that these venture capitalists, most of whom didn't understand the science but did sort of vaguely understand this was stuff of great practical importance, were willing to put their money in it. Then the ideas were really good, and they made money. And then it got around. Oil wells were not doing nearly as well, so the net result was that the electronic industry as an investment area really caught on.

And then people began to get bored at doing computer things, and at this miraculous moment, biotech appeared. Partly because it was very glamorous and new and was perceived to be a new industry, like computers, it was gone into. It turned out that the immediate uses of biotech were more complicated because you really had to have a drug if you were going to make an industry success. I think a lot of people didn't realize at the beginning that drugs were more complex than computers.

Then, from having a very exciting start, people would talk about Genentech having recombinant growth hormone. Well, it turned out that growth hormone didn't work that well and didn't do what people thought: making short people taller and so forth. Unlike computers, many of the little companies developing a drug had to sell out to Merck and corporations like that, which had the equipment to put a drug on the market. Then investors became disillusioned. There was a period where nobody was interested in investing in biotechnology, and it gradually got back up again.

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[21] Koshland discusses the reorganization of biology at Berkeley in a subsequent interview.

The burgeoning of the biotech industry was in part because California is very imaginative, and it has very good universities and a way of spreading the usefulness of that technique [recombinant DNA]. The venture capital community was very alert to how important it was to connect with industry and the advanced scientists. I think the combination of those factors was the reason that biotech took off so quickly.

Hughes: But why not Berkeley?

Koshland: Just because the leading people in recombinant DNA were in those two other areas [UCSF and Stanford]. I'm not sure that the people outside Cohen, Boyer, maybe Berg-- Kornberg didn't go into biotech very much at that time. Later on he did, and he was very close to [Alejandro] Zaffaroni. There were only a few people that started [companies]. The Berkeley people did start [companies], but we had fewer people. You're right about that.

Hughes: I'm wondering about the climate at these three institutions. Berkeley prides itself on being an elite basic science institution. UCSF is a medical school; it's implicit that there's going to be a tie-in between basic science and medicine. Stanford has the reputation of being, next to MIT, probably the most entrepreneurial university in the country.

Koshland: What you're saying is correct. I think it's maybe a version of what I was saying. Stanford is entrepreneurial because Hewlett-Packard and the computer chip developed there, and so then Silicon Valley attracted venture capital. It attracted people who were willing to invest in a totally new thing. Many of those businessmen really didn't understand the science at all. But they talked to professors who weren't all-out nuts, and they became very successful. And then they said to their colleagues, "You'd better really listen to these guys." And then they put more money in. I think you're right that Berkeley was slow, and our slowness one of the main reasons I pushed the reorganization of biology at Berkeley.

I think there was also maybe another factor--I'm saying this very tentatively. The first people, of whom Rutter was one, and Cohen and Boyer and so forth, were heavily criticized for blurring the line between academia and industry. I think they're probably still bitter. It was really, in my opinion, dishonest criticism. I'm sure some of the people voiced it honestly; some of it was just jealousy. The university had long experience with chemists consulting for industry. Lawyers flew to Washington all the time to get paid as consultants for the government. Architects were having little businesses off campus.

Sometimes, in my opinion, the criticism was correct, and people were spending too much time on [outside business]. But there were really good [university] rules, if enforced, that could have prevented abuses. Biochemists had been an impoverished group; this was not an area like chemistry or physics. Physicists, with the bomb projects and nuclear power, were also big consultants. I think they just expected biologists to be the poor cousins. Not only were the biologists making money [in biotech], but very big money, because they were involved in patents and venture capital with large amounts of money.

Partly because of that, there was a question of how much [intellectual property] was transferred from the university, from an NIH contract, to industry. Was unfair advantage being taken? But if you think that over--and I think what's being done now--that's just a matter of quantification and negotiation. NIH contributed a certain amount, the university contributed a certain amount, the investigator contributed a certain amount--and now what they're doing is dividing [patent royalties] up in some relatively fair way. It wasn't a question of ethics. It was really a question of dividing it up correctly.

I think Berkeley, being one of the most liberal and radical places and very open to people who are criticizing others, which I would say happens very often-- The humanities, which have no stake in it, are always taking big stands about how Lawrence Berkeley Lab shouldn't be identified with the Atomic Energy Commission because atomic power is bad. I have very little patience with people like that. They rarely thought through the problem. There is a certain point where it's dangerous--academic freedom and so forth--but they weren't saying that. They were just sort of saying you [UC] don't want to be involved with the nuclear power industry.

Of course, [the humanists] were not suffering anything. If the Lawrence Berkeley Lab shut down, it would have a big effect on the chemists and biologists and physicists and no effect on somebody studying English literature. The pipers never mentioned that kind of thing. If [scientists] had said that there was no point having library support for English because it was so unimportant, [the humanists] would have been very annoyed. So I considered it very peculiar.

The papers, as a result of the sixties and everything, would report protests even when they had no intellectual substance, in my opinion. I think probably because Berkeley was a hotbed of that kind of thing, it may have inhibited people from doing [recombinant DNA research?]. They may have thought, well, I'll get a lot of criticism from my colleagues, and I'm not sure [recombinant DNA is] that important; I can do something else in my research. I think Berkeley became a little behind, and that's one of the reasons the reorganization of biology was done.

Scientific Rigor

Hughes: You wrote a note to Peter Reichard of the Karolinska in 1984. I want to quote--

Koshland: You've been reading my mail.

Hughes: [chuckling]. I think it's very useful; I have to put in a plug for your papers collected at the Bancroft Library.

Anyway, quote, writing to Reichard: "You needn't apologize for going into cell biology." He had just given a seminar for the biochemistry department. "We are all going in that direction, but enzymologists apply an element of rigorous thinking to the problem, which makes the work more believable." I'd like you to elaborate. What is the rigorous element?

Koshland: It's sort of why I went into chemotaxis. What you're constantly doing is developing tools and then applying them to more complex problems in society, usually because human illnesses in almost every case involve enzymes. But they involve enzymes at a complicated level, and they interact with others.

Reichard--he was an enzymologist--probably said something to me which implied that he had applied enzymology to cell biology. The problem with lectures like that is that sometimes people talk about, "The exciting work I'm doing with this muscle...", and, "We have a pure enzyme in the test tube..." Then they extrapolate and say, “Well, this explains why, when you have tetanus, you get very exhausted; you're over-using your muscles.” Sometimes it is very glamorous to hear that an enzyme is being used in a complicated problem, and sometimes the logic can sound very good in a lecture like that.

But when you really sit down and think it over, it doesn't work out. [A muscle is] a very complex system in which lots of things [enter] in. So then the people who are really rigorous say, well, cell biologists are not so rigorous as us, and therefore you can't believe everything they say. So then the field of cell biology gets a bad reputation. It really isn't fair because it means that what you're saying is that cell biology is more complicated than enzymology, and if you get into it, you've got to be just as rigorous and careful of what you say. A cell interacts with certain things which catalyze a certain enzyme. The enzymologist is more interested in the individual steps and therefore is likely to be more down-to-earth. That's what I was saying.

Self-definition

Hughes: As a scientist, how do you think of yourself?

Koshland: You mean, am I any good?

Hughes: [chuckling] I guess that would be an interesting question, but that wasn't quite the meaning I intended. However, you brought it up. So, are you?

Koshland: I got tenure.

Hughes: You also got a Lasker award.

You've done a lot of things. You could call yourself a biochemist. You could call yourself an enzymologist. You could call yourself a protein chemist. You could call yourself a physical chemist. Probably you could call yourself other things that I haven't thought of.

Koshland: Jack of all trades, master of none.

Hughes: [laughing] What do you call yourself on your passport, for example?

Koshland: I probably just call myself "scientist" or maybe "chemist."

The facts are that biology really is the chemistry of life. The thorough understanding of biology really involves chemistry. You can talk about DNA base pairing; you're really talking about hydrogen bonds between chemical atoms. So it's really chemistry, but you can package it in a little different way.

An atom is a complex phenomenon of a nucleus and an electron and a proton and so forth. You can break these things down further and further. But you refer to them in packages as, say, the copper atom or the hydrogen atom. So when physicists say, "Well, it all comes down to physics in the end," they're right. But the Heisenberg equation is a long equation that takes several pages to write. When you're talking about a copper atom being oxidized to CU^{++} from CU^{+}, that's a lot easier to remember than the total Heisenberg equation.

What I'm saying is, the simplification that you can handle about living materials is chemistry. I think the constant theme of my life has probably been chemistry. But because I was a physical chemist, and then in the war did almost physics, I've always liked mathematical and chemical and physical approaches to research. Therefore, I've been less afraid of going into research areas that involve those techniques. I always liked quantitative science. Problems of chemotaxis, which involve memory and behavior, really involved experiments with a fair amount of mathematics and logical thinking. Enzyme catalysis involved math. I like to solve mathematical equations.

So it's a little hard to say what I am. I follow my nose into problems that are of interest. But I am not deterred if a problem gets mathematical and complicated, whereas a lot of other scientists once it becomes very mathematical would say, "Okay, somebody else can do it. I want to go off in a more descriptive way.

Hughes: Do you have a philosophy of science?

Koshland: Yes. I gave a talk at the University of Uppsala. Or Stockholm. I've forgotten which, but I think it was Uppsala. One of the very well-known professors introduced me saying, "I've always liked Koshland's work because Koshland is so childish." What he meant: I had a childlike curiosity. I really just like to do problems. But his word was "childish." Afterward, the distinguished head of the department came to me and said, "I want to apologize for Professor [Jerker] Porath. I hope you weren't insulted by the introduction." I said, "No, I was flattered by it. I knew exactly what he was saying, and that's exactly the way I feel."

I just enjoy doing science. It's why I won't retire. I just enjoy solving problems. I guess that's the key characteristic of a scientist. I think the best scientists I know just enjoy solving problems. When I was a kid, people would try to make a mathematical problem more interesting by saying, the budget of the United States is $10 billion and therefore what would half of the budget be? They tried to relate numbers to important things. But to me, a mathematical puzzle was always a wonderful puzzle. Nobody had to bother telling me what it related to. I didn't want to hear about the budget of the United States. I've always felt that.

I think there is something about a scientist that enjoys an interesting puzzle, and the idea that you have to make it practical is unimportant. If I am working on enzymology and I can use it to solve Alzheimer's, I want to do that. When any number of problems are interesting, I might as well work on one that's very useful. But it doesn't really require it being useful to make me interested.

Scientific Collaboration

Hughes: One last question for today.

Koshland: You're way over your time limit, but go ahead.

Hughes: [chuckling] Give me an inch, and I take a mile. Have there been important collaborations in your career?

Koshland: You mean with people in my own lab?

Hughes: I mean outside the lab.

[End Tape 11, Side B. Begin Tape 12, Side A.]

Koshland: [Albert] Goldbeter from the University of Brussels is a really fine scientist. He is very much a mathematician and a theorist. He really doesn't do experiments. He visited my lab several times, and we wrote a number of papers together, a couple which turned on a very important phenomenon, which we called zero order ultra-sensitivity. Those in part combined our love of mathematics and experiments that I was doing at the time. We used the math to explain it, and I would say my mathematical skills were important in getting us going. Goldbeter was a better mathematician than I am, and so he could carry it further than I would have been able to carry it. So that was an important collaboration.

Later on, I did some collaborations with Robert Stroud and later with Kim, who are crystallographers. They really taught me a lot about crystallography and helped the people in my laboratory. I've gradually learned a fair amount myself, so I could start to do it without collaborators. But they were very important in helping me to that.

Hughes: Since you mentioned the term, please give me a quick definition of zero order ultra-sensitivity.

Koshland: We had a purely theoretical idea. We were solving mathematical equations and found this situation. To explain to you roughly: if two reactions are going ninety miles an hour in the opposite direction-- Let's say you're delivering corn from New York to Boston by a train that's going ninety miles an hour, and you're delivering corn from Boston to New York by a train that's going ninety miles an hour in the opposite direction. The net transfer of corn is zero, right? You're delivering just as much corn to New York--assuming the size of the trains is the same--as you're delivering to Boston. That's an equilibrium.

What you would do in an enzymatic reaction would be to measure two enzymatic reactions that are going the equivalent of my ninety miles an hour. Now, if one of those reactions goes eighty-nine miles an hour and the other goes ninety, that's a very small difference. That's one percent change. But in a very little time, almost all of the corn is going to accumulate in, say, New York. It's going to all be depleted in Boston. The faster they're going, the faster it's going to be depleted in one place. If it's going at one mile an hour, it's going to take a long time to get from Boston to New York, anyway.

Basically, what zero order ultra-sensitivity pointed out was that a dramatically different result could occur by a very small change of two things that are very close to the same value and operating in opposite directions. That may sound very esoteric. But what we said was that it was going to be very important in some phenomena because it was a way of changing something very dramatically, the equivalent of, let's say, burning up all the stores you have in your body or building up all the stores.

If you wanted to change [metabolic rate?] dramatically, like having a hormone influence depleting your store [of glucose] so you could run fast, then zero order ultra-sensitivity was a very useful kind of thing to [use]. We developed the theoretical idea and published it, with no application in mind. And then we found one in *E. coli* and did it. Zero order ultra-sensitivity stayed in the literature for a while, and nobody mentioned it. I wrote several reviews on the same subject. Then recently [James] Ferrell at Stanford found out it was very important in cell cycles. How your cells recycle, duplicate, in cancer and in [normal] replication is important. Several people have found it important in other reactions, too. So it has sort of caught on and it's becoming very exciting.

Hughes: Thank you.

[End of Interview]

Interview 9: March 4, 1999

[Begin Tape 13, Side A]

University-Industrial Relationships in Biotechnology

Academic Consulting for Industry

Hughes: Dan, last time we talked about your views on faculty relationships with industry. I want today to return to the topic because I found a letter in your correspondence that was written to a Dr. Howard Simmons at DuPont.[22] Do you remember him?

Koshland: Yes, I got to be friendly with him.

Hughes: I was interested in the fact that you were obviously writing as a consultant.

Koshland: Yes, that's correct. They paid me as a consultant.

Hughes: You wrote quite a long letter to him. [provides letter]

Koshland: Really? I'd totally forgotten. He retired, so maybe I ruined him.

Hughes: [laughs]

Koshland: Oh, yes. The DuPont Company was considering converting a number of its laboratories to bioengineering and biotechnology, which was an enormous change. The DuPont Company probably has the biggest industrial organic chemistry lab in the world and hires more people. And, of course, the famous [Wallace H.] Carothers invented nylon there. DuPont was going to do chemistry but use recombinant DNA. So the fact that they found that recombinant DNA could get products for them cheaper than their classical methods, where they had worked out the techniques probably better than anybody else in the world, was <u>really</u> a revelation.

Hughes: It was true that DuPont could do it more cheaply using recombinant DNA?

Koshland: They must have. I've never checked on what finally happened. But they were considering how to do this. They had me on a committee-- I've forgotten who was on it, but a fellow named Darnell at Rockefeller. I'm not sure whether Jim Watson was on it, too. They had people from all over the country, and we were on this committee to advise them. That's what this letter was about.

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[22] Daniel E. Koshland, Jr., to Dr. Howard Simmons, Du Pont de Nemours & Co., September 17, 1971. (Koshland papers, carton 6, folder:1981 chronological file, Bancroft Library).

Hughes: Did you go to DuPont?

Koshland: We flew in. I remember we got an enormous amount of money for staying there for about a day. I thought to myself that if the scientific community charged that amount of money for its consultants, most of the classical scientific journals would go bankrupt. The National Academy of Sciences, which gets all this free advice, all would be out of business. I mean, only a big industry would do this.

Hughes: Was it usual for biologists to consult?

Koshland: I think it was usual because DuPont was considering a big, big step. Then they proceeded to have [recombinant DNA become a long-term manufacturing approach].

I tended to turn down consulting offers. I did very little consulting, as you've seen from my curriculum vitae. A lot of my colleagues did more. That was really for two reasons. At the beginning, I really didn't need the money, and I didn't want to bother with consulting, whereas a lot of other people, for whom the money was useful, did consulting. Later, when I became editor of *Science*, I turned down all consulting because I felt it would cause, if not actual conflict of interest, the appearance of conflict of interest.

Hughes: You of course had come out of chemistry, where consulting is routine.

Koshland: Yes.

Hughes: Did your colleagues in the biological sciences, where consulting was a little less common, have any hesitation?

Koshland: I will tell you my impression. In general, chemists consulted for years, and the rules I would say were lax. When I was a postdoc at Harvard, there were complaints that some of the professors spent so much time consulting, they weren't around very much. Most universities have some rule, like you're not supposed to spend more than one day a month consulting. They feel that a professor's intellectual interest in learning how industry is doing things probably is an advantage for the students. Consulting increases the professor's horizons and at the same time doesn't take away from his teaching that much. And I agree with that.

Chemists did it. Physicists did it probably even more in the war effort, consulting for government agencies. And then, of course, economists do it, lawyers do it. Architects at the University of California and I think at other universities have sort of separate architectural firms where they are consultants part of the time and here on campus part time.

Impact of Industrial Biotechnology on Academia

When the recombinant DNA thing broke, biologists, who were considered the impoverished little kids who never did anything worthwhile, all of a sudden became big stars. The difference--if you want my honest opinion--was it involved much more money than anybody else in other sciences had gotten, partly because the whole venture capital world had changed due to Silicon Valley. I got something like six thousand dollars from DuPont for a day's work. That's a lot to an academic. But these guys [biologists] were getting millions for being co-founders of a company, and they were being paid in stock options, which might turn into nothing or might turn into a lot of money, but they were turning into a lot of money.

I always questioned the people who raised big ethical issues. I think there really were some ethical issues, and there were some people who seriously and correctly questioned that we had to set up machineries to do it. But some of it, I think, was just pure envy. They were just mad that the biologists were making so much money, when they were getting so little. Having said that, I think there is some legitimacy to the criticism because some of these people were getting paid by NIH to develop, in this case, recombinant DNA applied to various vaccines or new hormones or things like that. Then they formed a company with what they found out. In a way, the taxpayer wasn't gypped because you couldn't do all the practical stuff at a university, so it was good that you applied it to a practical problem.

The question was, really, how much money should the NIH get out of it, to pay the taxpayers back; how much should the university get out of it; how much should the individual person get out of it; and how much the new company? I think now we have a lot of machinery, and apparently there's a fair amount of negotiation by the university. I've not been involved in any of this, so I don't know, but I have a feeling it's pretty fair. That is, NIH is going to sponsor this research, and then NIH doesn't know which of these various projects are going to be useful, and we're sponsoring it for the good of the taxpayer because if we end up with a cancer drug, everybody is going to benefit. And then the university says, "We're giving our grounds [facilities] and our tax-exempt status, so we're providing a certain amount of research support." And then the final person who's going to apply this says, "Okay, we've learned all of this for the taxpayer's advantage, but we're the ones that are spending all the money to develop it into a real drug, conduct a clinical trial, and go on market with it."

I think wiser people than I are now involved in it. What they've done sensibly, instead of just getting mad and jealous, you sit down and say, "What is the reasonable, fair amount that each of these people should get?" I think they're working that out now, and I think the university has a biotechnology committee or ethics group.

Hughes: It seems to me that biotechnology represents an intermingling of university and industry at a level that no one had previously anticipated for academic biology.

Koshland: Well, yes and no. What I was saying is the following: Some of these people were already consulting and sometimes consulting too much, in my opinion, for very classical companies, like Standard Oil and DuPont and so forth. Most of the time it was done very fairly. But where people did it too much, the university probably wasn't as wary as it should have been because in fact it was done very rarely and very few professors wanted to consult that much.

I think the big difference really was scale. I don't think it's fair to say biotech was first; it was really the computer companies that were first. Physicists or chemists at universities who did the early work on computers then had these big venture-capital [-supported] computer companies.

Hughes: The difference there, I believe, is that computer scientists by and large left the universities completely to found companies. That hasn't always been the pattern in biotechnology, where professors kept their feet in both camps. That is what particularly caused problems.

Koshland: Yes. I don't know enough about the history. I think you're probably right; that is, that probably more of the molecular biologist and so forth types have remained in the university. For example, Robert Tjian formed a company, Tularik, and he's still a professor at Berkeley. He hired a bunch of people who formed that company, and some of them are full time there. Well, I know some people who are full time there and don't have any university connections. He's sort of like chairman of the board; I mean, he's not a CEO. Knowing Tij, he spends at least fifty or sixty hours on his university work and maybe twenty or thirty hours on Tularik. I mean, he works very hard.

Peter Schultz is probably a similar type. He left the university recently to accept another appointment, and everyone in the university was really very upset that he was leaving. It was clear the university was getting a very full share out of his use.

Hughes: Why did he leave?

Koshland: To join a big foundation. The Novartis Institute is giving the money for it.

What I'm saying is that a number of people have left, but I think in no case that I know of was the university reaction: "Phew! He hasn't been around here very much. We're glad to get rid of him." But I think you're probably right that biologists are different than the computer people; more of them wanted to stay around [academic] biology but have this company on the side.

Let me just say, I think there are abuses. I know of a case, fortunately not at this university, of somebody who has a biotech industry on the side. There have been accusations that some of the students have made inventions in his lab, and instead of publishing them in the open literature, he's taken them over to his company to develop them. So there are these possible conflicts. I think we have to watch it, and I think that's something we do.

Industrial Application of Recombinant DNA Technology

Hughes: Getting back to the DuPont issue, as you were implying, it was quite a step for a company of this size and history to take on recombinant DNA technology, particularly when it had existing technology that worked. What do you think is the place of big companies in the early acceptance of recombinant DNA? The pharmaceutical industry is mainly located on the East Coast. What does that mean, if anything, about how biotechnology first got located?

Koshland: I'll give you my guess about what goes on. In terms of the validation of the method and the usefulness of recombinant DNA with practical problems and to make medicines and vaccines, I would say big companies have practically no role at all, partly because DuPont got in after it was obvious to everybody that recombinant DNA was very useful. What happened was, the early fledgling companies, mainly being Genentech and Chiron and Amgen--they were the three big successful companies. One of the early ones also was Cetus, but it never really did that much.

Hughes: And Wally Gilbert's Biogen.

Koshland: Yes. And [Mark] Ptashne had something called the Genetics Institute. But it was mainly a West Coast phenomenon. It was mainly these biotech companies which really validated the technique and got it useful and got going, number one. And it was really after they got going and were successful that the big companies, of which I think Merck was really ahead of DuPont-- I'm trying to remember what other--

Hughes: Well, Eli Lilly.

Koshland: Eli Lilly was another one. Hoffmann-La Roche did a little.

Hughes: Schering-Plough.

Koshland: Schering-Plough got involved with DNAX. But basically, these early little [biotechnology] companies were very successful, and they started to get bought out. I don't think the big companies did very much in validating the technique.

I think the second thing was that the big companies involved in making big quantities of chemicals--sulfuric acid and things like that--were all big eastern chemistry companies. I think a great deal of the success of biotech was at western universities-- Stanford, Berkeley, UCSF--and also the fact that a lot of the venture capital people saw how much money all these people were making in computer companies and were beginning to get bored with one computer company after another. And all of a sudden, biotech was a refreshing new idea [for investment].

Since I know a fair number of people in the financial world, they would phone me up and say, "Is this [recombinant DNA] a good idea?" They were really fascinated by it because it was so new. They were favorably disposed towards venture capital because the computer industry had been so successful. But they really liked the idea of something totally new, and medicine was known to be a winner.

I think that venture capital really made the biotech revolution go fast. Many of these investments in the early days were, I think, really risky. I mean, investors went in for the idea without the company having any real drug or other product.

Hughes: What did you in general say to investors when they called you up?

Koshland: I generally either said yes, on the basis that the company had very good scientists, and I knew they were going to do it. Say, Peter Schultz formed Affymax; I just knew he was good. I know Tjian is good. Or they had some product, say the way Genentech had growth hormone, which I thought was going to be very useful to have. Genentech had insulin and Eli Lilly. So they either had a pretty good idea or they had a drug or they had people that were very good.

Hughes: One of the things that you read nowadays is that the investment community had really no appreciation of how long the process to make a marketable drug would take.

Koshland: Correct.

Hughes: Did people who consulted you about investing in biotechnology seem to have any appreciation of how long drug development takes?

Koshland: Yes. First of all, people like me warned them about this. But if a company gets a big blockbuster drug, they make up for everything, all the mistakes they made, so it really is understood that's investment in drug development is a very good thing to do. I think investors sort of took that into account, but they thought biotechnology was really something new, whereas making new automobiles wasn't that new. It was very hard to make an automobile that was so much better than any other automobile. But when you make something totally new, like a new drug, that was going to open up a whole new market.

I think that some people went into it without thinking, but the smart people really knew it was a pretty big gamble. But they felt it would pay off with large amounts of money, sort of like hunting for oil. By now you've drilled a lot of holes, and you know the chances of hitting oil are very low, but if you hit, it's a big deal.

Hughes: And, of course, some of those early investors did hit it very big.

Koshland: Of course.

Recruiting Biologists to Industry

Hughes: One of the things that you stressed in that letter to your friend at DuPont was the need to find top scientists to lead the company's various research endeavors. You were writing in 1981. Was it likely at that time that a top biologist would take a position at DuPont or any pharmaceutical company?

Koshland: I think the really top people wouldn't. DuPont never had large research groups. They never had eight or ten people working for one scientist. They generally had one scientist with a couple of helpers, which was very classical for organic chemistry. We warned them that is not a way to do it for biotech. Molecular biology professors usually had eight or ten people in their laboratories. So they were unlikely to leave a university to work with just one person.

Probably they were selecting for the kind of people to whom fame was more important than money. It was really a different world. My own impression is they didn't get anyone. I'd have to go over the list, but I think DuPont didn't change. They took some of our recommendations; they didn't take that one, and they didn't get [molecular biologists].

Monsanto, which was smarter about giving biologists a large group more similar to the kind of environment they had at a university, was much more successful in getting big-name scientists. Even they didn't get very many.

Hughes: Why is it important in molecular biology to have a larger group?

Koshland: It wasn't necessarily that important. A tradition grew up of the way you did things. But there was a second factor: As the research gets more sophisticated--this was true of organic chemistry, too--then a professor can have many more ideas than he can carry out himself. So it was very desirable to have students. You always have to think it over with a student and write calculations, but sometimes that's straightforward, and the actual carrying out of the work takes a lot more time. In that case, it's really a big payoff to have a number of people working with you on a problem.

If it's, say, a very abstract physics problem where it's very complicated math, and the professor has to sit down and work his way through the equations with the student, then, of course, it doesn't help that much to have a lot of people. But, on the other hand, if you have to set up a gel or attach electrodes for electrophoresis and do the kind of long, tedious experiment that biology requires, then having a number of hands is really a very useful thing.

Hughes: So DuPont was working on a model derived from the physical sciences?

Koshland: Organic chemistry. That's a good model if the scientist has only a limited number of ideas and the time it takes to carry out that idea in the laboratory is short with respect to the time it takes to develop the idea.

Hughes: But isn't there something else operating here? Namely, what it takes to do the science. Biology requires many kinds of expertise. Maybe you need somebody with expertise in crystallography. Maybe you need somebody with expertise in electron microscopy. Doesn't molecular biology require more technologies to do the science than would, say, physical chemistry?

Koshland: No, I don't think that's quite true. There is some very routine biology. For example, sequencing the genome. That is a very repetitive business. It's a little different because there's a little different sequence at one end of the chromosome than the other, but the way you go about sequencing is sort of automated. But I would say as the science gets developed, it almost doesn't matter what science it is. There are more standard procedures, and you have to do them, and probably you can always use more people.

Industry has caused a great deal of what I call the democratization of science. In the old days, organic chemistry flourished, particularly in Germany because they paid a lot of money to have big laboratories with lots of Ph.D. students preparing new compounds.

[End Tape 13, Side A. Begin Tape 13, Side B.]

Koshland: The Germans provided a lot of hands to provide support to the big German professors. A [professor would have a] student make a lot of Compound A to make Compound B. The Germans dominated classical organic chemistry for a long time because they had this structure, whereas the Americans were much more individualistic. Nobody could build up a big group, so a professor in the United States with his own hands had to make a lot of Compound A in order to make Compound B. That stretched out the time a lot. Nowadays, since we have a fair amount of money, industry makes a lot of these compounds and enzymes available. It really means small labs can compete with big labs because they just buy the stuff.

Hughes: Getting back to DuPont, why were they wedded to this system of small lab groups?

Koshland: [Management thought]it was bad enough that they were going to put a lot of their money, not into classical chemistry, but into biotechnology. But then if the people they brought in were much more privileged and could run big groups, whereas the organic chemists were kept to small groups, that would cause a lot of friction in the company. So I think there were a lot of forces for inertia to have them keep the old system.

Hughes: DuPont is a chemical company as opposed to a pharmaceutical company. Does it present a different model from that of a pharmaceutical company?

Koshland: Yes. I would say there's a different model, although the new biotechnology companies introduced lots of new principles that the other companies learned from. For example, the big pharmaceutical companies were notorious for secrecy. They practically never told you what they were working on. They kept their ideas very much close to the vest. It was traditional that sometimes they'd send company scientists to things like Gordon conferences and [they would] never relax, even off-hours. After the conference was over, they wouldn't sit down and tell you what they were doing.

The biotechnology companies, on the other hand, got their scientists and basically let them publish. What they lost in secrecy, they gained in the quality of people they got. See, the old people in, say, Lederle or Eli Lilly, essentially never published when they went to the company. They got much bigger salaries than they got in the university, but they couldn't publish or become famous. What Genentech and Chiron did is they let their scientists publish. They applied for a patent ahead of time, and sometimes they even didn't, and let them publish, so they got really good scientific reputations. Some of the scientists actually came back to universities after they had gone to industry. Their gamble paid off.

Generally, bright young people turned down the DuPonts and the Lederles and went to the Chirons and the Genentechs. Now Eli Lilly allows its scientists to publish. They found they weren't getting any good people [if the firm prevented them from publishing]. So in many ways, the biotech industry influenced the big companies.

Hughes: On the other hand, biotech companies were virtually forced to emulate certain academic standards. In the late seventies and early eighties, most of the expertise was still in the university. Well, how are you going to get a university scientist to join a risky, new company? You had to recreate a quasi-academic atmosphere or a top academic scientist was not going to look at an offer from a biotech company.

Koshland: What you're saying is absolutely correct, except for one thing. All great ideas are obvious after they're formed, right?

Hughes: [chuckling]

Koshland: Some of Einstein's most ridiculous ideas--that light rays bend and so forth--if it's so obvious, why didn't everybody think of it? The facts are that if the very brightest talents could have been lured by this method, then it was really silly for the conventional pharmaceutical companies not to try to get some of these people that way. It was only when these venture-capital companies started doing it that they recognized this [biotechnology] was really worthwhile. If, let's say, the venture capital companies had been wrong and this didn't pay off, then the pharmaceutical companies would have been right and would say it's a dumb way to do it.

Hughes: You could say that some of the pharmaceutical companies, such as Eli Lilly, hedged their bets because they didn't immediately take on in-house genetic engineering; they contracted with the Genentechs and Chirons of the world.

Koshland: They got some of the people inside, but you're right. They dipped their toe in the water slowly.

Hughes: Well, another thing I found interesting in that same DuPont letter was your advice to, quote, "Set up an ongoing relationship with a number of universities." Why did you say this?

Koshland: I thought some professors would not want to leave the university and would be willing to spend a limited time consulting and that that would be very good, particularly when the DuPont effort in recombinant DNA was starting up. I lost track of them when I became editor of *Science* in 1985. I had been on the board of the Hoffmann-La Roche Foundation. I resigned from that when I became editor of *Science* and severed any even informal relations I had with DuPont at the time. But I do know that basically what we recommended there was something that Monsanto did, and that was very successful. [interruption]

Hughes: You used the term "clone by phone" in the DuPont letter. I think that is an interesting insight into the state of recombinant DNA science at that time. The implication is that things were changing so fast that you didn't go to the literature; you pick up the phone?

Koshland: That's exactly right. I thought for industry, which tends to be more ponderous, that if they had connections with scientists in universities who were in the forefront of [the new genetic technologies], who were interacting with students, with other professors, were going to meetings of the various societies, that was a quick way of getting a lot of expertise rapidly.

The Department of Biochemistry at Berkeley

Koshland's Arrival in 1965

Hughes: I'm switching topics radically, leading up to the chairmanship. But before we get there, I want to go back to 1965 when you arrived at Berkeley and ask you what you found when you came to the Department of Biochemistry.

Koshland: I agreed in 1964 to come to Berkeley, as I remember. Maybe you read about how I came to Berkeley in the *Annual Reviews of Biochemistry*?[23] My wife was not in favor of moving to the West Coast. We went back and forth. I said, "Darling, if you really don't want to go, I won't go, even though I prefer to go." And she'd say, "Darling, if you really want to stay, I'll stay, although I don't want to."

Hughes: You're telling me that the Koshlands are indecisive?

Koshland: We are very indecisive.

Hughes: [chuckling]

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[23] Daniel E. Koshland, Jr., "How To Get Paid For Having Fun," *Annual Reviews of Biochemistry* 1996, 96:1-13.

Koshland: I told you the way my wife finally decided. She woke me up in the middle of the night and said to me, "I made the decision." I--heart pounding--said, "What is it? And she said to me, "Well, either we stay on the East Coast and I spend the rest of my life making it up to you, or we go to the West and you spend the rest of your life making it up to me. We move." That was it. I always claimed that she drove a Mercedes and I drove a Volkswagen, and that was the indication of what happened. But anyway, we moved.

I had been at the university as a graduate student and a postdoc, but not as a professor, so I had to learn. First of all, I had to start teaching. There were a lot of new things, but they weren't totally foreign to me. The biggest thing was that it was the sixties, and I moved to Berkeley at a time when all the excitement over the Vietnam War was going on, and Berkeley was in the headlines every day.

I remember the chancellor [Roger W. Heyns] spoke to me and said, "Most university presidents are desiring to have their university in the headlines and sound important. Berkeley is the only campus I know where I'm just desperately trying to stay out of the headlines." It was a really turbulent thing. But interestingly enough, that was one of the attractions to me. I loved it. There was turmoil when I was an undergraduate--all sorts of protests; it was just the atmosphere I knew about. I thought it was carried a little too far, but it was fine.

At one point, when Ronald Reagan ordered the tear gas, I thought, "Well, this is really the end of the university." I remember asking a friend, "Am I being stupid? Is this university going to collapse?" He said something which I've never forgotten. He said, "Dan, if you really want to talk about stability in this world, universities are it. If you want to talk about longevity, universities are more likely to last than countries are." Nobody would have foreseen at that time the breakup of Russia, the breakup of Yugoslavia. People were already talking a little bit about the breakup of Africa. But he was saying John Harvard, a very obscure little person, formed a university that is Harvard. The French empire has collapsed, the German empire has collapsed, and Harvard is going right along. He said, "Don't worry. A university is going to survive." And, of course, it has.

By the way, I should tell you, since this was 1965 and I had just moved, there were various people in the East who phoned me and said, "Dan, things are really turbulent out there. If you want to come back to the East Coast, we've got a job for you" at X university. I got a number of these offers.

Hughes: Did you participate in any of the politics?

Koshland: Oh, sure. There's no way to avoid it. I would say I was a conservative faculty member, not very different, I think, from most of the faculty, but very different from-- The Far Left fringe was having protests all the time. I didn't participate in those. I felt it was sort of silly about Vietnam, but I thought, well, I came from the World War II generation that fought in a war that we all thought was a very good war in the sense that it was a necessary war. We didn't like war, but we just felt you had to fight Hitler, or we all would have been in terrible shape.

The idea that you defied the country-- I felt it wasn't really for the individual citizen to say, "No, I'm not going to go to war." You did everything you could politically to say we shouldn't go to war, if that's what you felt. But once the country decides on war, if every individual says, "This is a war I don't want to go to," we never would have beaten Hitler or we never would have done a lot of things.

Secondly, I was against some of the protests. Some of the students thought if they shut down the university, Lyndon Johnson would then change his policy. Well, they did get a certain amount of publicity. But I said Lyndon Johnson couldn't care less whether the University of California closed down or not. The ironic part of it was that during World War II, the emphasis was always that it was very important that universities stay open, that you maintain scholarship, that if the university collapsed, then Hitler really would have won a victory, even without invading us-- or something like that.

The whole psychology was totally different.

In fact, I would say one of the things I liked about the typical Berkeley protests, nobody was ever rude to me, ever. I remember distinctly in that Vietnam period that the students came around to me and said they would like me to devote a class hour to discuss the war in Vietnam. I said to them I didn't think that was appropriate. I said, "I'm no expert on the war in Vietnam. I'm really an expert in biochemistry. That's why you come to me. I have, I think, very intelligent feelings about the war in Vietnam, probably a lot smarter than some people who think theirs are important. But I'm objective. The world I know will not say that I'm smarter; it will say, 'He knows biochemistry. He should shut up about Vietnam.'"

Anyway, there was some day that they called Vietnam Day on the campus. I got to the place, and there were students with placards. They said they wanted me to discuss Vietnam. I said to them very nicely, "I don't think that's appropriate." You couldn't tell how many students really supported them because there was a lot of noise and there were placards and things. I said, "You're maybe a very vocal minority, but most of the people who came here want to learn biochemistry, and they paid their tuition. I'm going to talk biochemistry. But I will be glad to talk to you about my opinions on Vietnam if you're interested, and I'll do it Saturday morning. Anybody who wants to come around Saturday morning can hear my opinions on Vietnam."

I said, "And then I'd like to go on and give my normal lecture in biochemistry. At the end of the class, those of you who want to will come up, and you can sign up for the lecture I'm going to give on Vietnam on Saturday." That happened. The vocal ones didn't like it very much. I gave my lecture in biochemistry, and at the end I said, "Now we'll discuss Vietnam. Class dismissed." Only one student came up. He was a student of mine, a very nice kid. I think his name was Stuart

Rosenblatt. I still remember. He was crushed. He was mainly crushed because nobody else came up. To him, that was an indication that students of his generation lacked any ideals and didn't do anything. I said to him, "Stuart, you're really silly. That didn't say they don't have ideals and they don't care. They just say they're not very interested in hearing me on Vietnam."

Every newspaper I knew had editorials about Vietnam. *Science* magazine, *Time* magazine, *The New York Times Magazine*--everything had editorials on Vietnam. "It isn't because of lack of knowledge. They just don't care to hear the opinion of Dan Koshland, professor of biochemistry, on Vietnam. They couldn't care less about it." So he felt a lot better about that. It was humorous because I was sort of reassuring him.

Hughes: You have described the political situation when you arrived. What about biochemistry itself? What state was the department in in 1965?

Koshland: The biochemistry department at Berkeley was excellent. I think it was number one or two in the ratings, with Harvard, so it was an excellent department. It had very good people, and it had really strong emphasis on protein chemistry, which is exactly my area, so it was great for me. I remember in the early days I was put on a couple of search committees for new faculty. Against--not all, but a fair opposition--I said, "We've got to have some nucleic acid chemists." Because the whole field of nucleic acid chemistry was becoming much more important. We hired a couple of students who had gotten their degrees at Stanford. Arthur Kornberg had been one of the leaders. He converted almost his entire department to DNA work, and he said that. So it was a center of DNA work. But I said I didn't want to convert our entire department to DNA work, but we ought to have some, and so we hired some people.

Hughes: Do you remember whom you hired?

Koshland: I remember one was Mike Chamberlin. Another was Stuart Lin. I'm trying to remember who else. A guy named Greg Milman, who actually didn't get tenure but is now a professor at Hopkins or something like that. We hired, among others, Ed Penhoet, but he was not in the DNA area. He was protein chemistry, protein virus. He was a student of Bill Rutter's, so you'll think this is a small world when this is all over.

A Schism in the Department

Hughes: Wendell Stanley was brought to the campus by [UC President Gordon] Sproul to unite biochemistry in one department. But for a variety of reasons—some of it due to scientific approach, some of it due to Stanley's personality--that didn't work very well.

Koshland: Yes.

Hughes: By the time you came, the biochemists had left the Virus Lab, had left what is now Stanley Hall.

Koshland: I'm not sure all of them were ever here. What happened is that [Horace A.] Barker and Hassid were considered by a number of people as old-fashioned protein chemist types, because the Virus Lab was much more focused on nucleic acid, although it wasn't exclusively. Stanley isolated the protein of the tobacco mosaic virus. They were doing both protein chemistry and nucleic acid chemistry. But in general, the molecular biology department was very glamorous. It had [Melvin] Calvin in it; it had Stanley. Calvin was a Nobel laureate. So was Stanley. The biochemistry department was considered more stodgy. But it was doing very good work. Among the biochemists, it was still considered one of the top departments in the country. And then I heard gossip that there were hard feelings. Particularly Barker and [Michael] Doudoroff and Hassid, who were sort of the leaders in the biochemistry department--they had been there a number of years--resented Stanley coming in and creating this new department.

But when I got here, I found out it was really a great exaggeration and not really true. There was a split in the department and a little bit of competition, but as far as I knew, there was no hard feeling. We kidded about it. I still remember the kids had a skit, with a version of *Romeo and Juliet*. Romeo, from the department of biochemistry, was interested in Juliet, who was a member of molecular biology, and their parents didn't want them to get together. It was really a take-off. They had a song, where the father says to the girl, "If I've told you once, I've told you ten times, don't marry a boy who crystallizes enzymes."

Hughes: [laughs]

Koshland: I had no trouble collaborating with people or talking to people, so it wasn't really much of a split.

Hughes: Where were you located?

Koshland: I was located in Barker Hall, which was called the Biochemistry Building at that time.

Hughes: What about the geographic distance from Stanley Hall?

Koshland: It was one end of the campus to the other, but that doesn't matter.

Hughes: No?

Koshland: Well, it means you don't drop in every day. One of my generalizations about life is you can only talk to a certain number of people every day. At small universities--the Haverfords and Sarah Lawrences and Bryn Mawrs--professors say, "Well, I know a lot more of the faculty. It's much more *Gemutlich*. At Berkeley, there are a thousand professors, and you know fifteen or twenty. At Haverford, I know a third of the faculty."

I was interested in this one point. When the students were exaggerating the value of liberal arts colleges, I asked people how many people they actually talked to in a day. I then talked to my colleagues and thought about myself. And the basic answer is you talk to the same number of people. But if you have a very small university, that's a much bigger fraction of the total university. But in fact, if you want to get anything done during the day, you can only talk to a limited number of people. So that, I think, is really the difference.

A 1966 Citation Classic

Hughes: What should we say about the years between 1965 and 1973, when you became chairman?

Koshland: Those were very hectic years for me. In 1966 I published a paper--Koshland, Nemethy, and Filmer--which was a citation classic. That's what [Eugene] Garfield called papers that have over a thousand requests for reprints or something. Anyway, it was in 1966, which is one year after I landed here, so I probably wrote a large part of it at Brookhaven. It was rejected the first time I submitted it to a journal. It actually appeared one year later than I had wanted it to appear.

Hughes: Did that bring you fame?

Koshland: Yes, well, I was already pretty well known for the induced-fit theory and some other things. But that [1966 paper] was the theory of cooperativity, which was in direct conflict with [Jacques] Monod's theory. As a result, it stirred up a lot of fuss. I was invited to talk at a lot of Gordon conferences and other meetings, present my side of the case, and Monod presented his side of the case. It was a lot of fun. It was big arguments. It was a very exciting period.

It's pretty well over now, although it still is an important theory and has turned out to be largely correct. Monod's theory, I think, was too simple. Mine was a little more difficult to grasp because it was more complicated, but I think now it has turned out to be largely true. But at that time, it was really fun because Monod was a very fine scientist. He had very good arguments for his theory, and I had thought of pretty good arguments for mine. So we presented those back to back at scientific meetings, and then people would argue with us, and we'd talk about it, so it was lots of fun.

[End Tape 13, Side B. Begin Tape 14, Side A.]

Teaching

Koshland: I really enjoy teaching. I am basically a ham. I like to have three hundred students listening to me and having to laugh at my jokes. Actually, when I first came here, you're supposed to have a year off from teaching, to set up your lab and do all those kind of things. It's traditional with any new professor, even a young assistant professor. A professor was murdered by a student, who was mad about his grade. So they asked me if I would teach one of their elementary service courses. I felt I could be a good guy, so I did. That really rushed things even further.

Hughes: Did you step into an established curriculum?

Koshland: I had to establish the curriculum for the course. Because I had been a scientist and certainly hadn't read broadly the way you'd have to do as a professor, I was reading a chapter ahead of the students some of the time. It was a hectic year. But I learned a lot, and I really enjoyed it.

Hughes: Was it introductory biochemistry?

Koshland: Well, there's no such thing as really introductory, because a student who enters biochemistry usually has to have two years of chemistry and physics and math as prerequisites. Students begin biochemistry their junior year, so the course is introductory in that it's the first time they're doing biochemistry, but they're not beginning students.

I remember I was teaching from something like eight to nine in the morning, and Professor [Clinton] Ballou was teaching a class right next to mine in Dwinelle Hall. We walked out at the end and frequently walked back to the Biochemistry Building together. He would look just absolutely dragged out. Just said he was exhausted. He didn't know what he was going to do the rest of the day because he was so tired. And I was just exhilarated and ready to go. I just loved dealing with students. I didn't consider it was much of a job. I thought it was mainly fun. So it was clear he was much more conscientious. Every sentence was much better prepared than mine. But I just liked to do it.

I remember that when I became chairman, it affected my idea of teaching. Basically, when you're giving undergraduate courses, any professor at Berkeley, in my opinion, should be able to teach the course. It isn't very specialized. You're giving a broad view of the subject. I decided that the way we select professors is not because of their knowledge of certain subjects but rather for their personalities.

Professor [Horace] Barker, for example, was really a bad lecturer. On the other hand, he was wonderful in the lab. He was very conscientious, took care of everybody, always was very careful to see that everything was well prepared, and was very courteous and generous of his time and helpful to students. The students used to report to me that he was everybody's grandfather. They just loved him in the lab because he took so much care.

I decided, well, you don't rotate professors around; you pick those professors for the big lecture courses who are sort of flamboyant characters who love to talk to three hundred people. You pick people like Barker for the labs, and then you take the specialists, who really enjoy their own specialty, for the graduate courses. In the other words, the way we selected people was much more for their personality than for their expertise.

Hughes: And that was a new way of selecting teachers?

Koshland: That was sort of different. They certainly did that for a number of years after I was finished being chairman.

Hughes: Did the faculty in general like the system?

Koshland: I think they generally liked the courses I assigned them to. But I never articulated it very much; I just did it. I was a benevolent dictator. I didn't believe in very much democracy.

Hughes: You talked about your enthusiasm for teaching. Would you say something about your general approach and what you hoped would happen to students in your class?

Koshland: Well, I really got pretty good student ratings. I was a very conscientious teacher. I taught for thirty years the Biochem 100 course, which was the major introduction to the majors in biochemistry. There was a service course that was biochemistry for people who weren't majors. It had lower prerequisites and was more of a survey course. I didn't teach that. I taught the main course, which was the higher-level course. Well, they were both about equally attended. I enjoyed putting on a performance.

It was considered a very tough course. It was listed as one of the toughest courses in the university. We not only covered tough material, but we covered it very quickly because we wanted to cover a lot of material, and the majors at the University of California have a limited number of units. You can only require a certain number of units [for a major]. Since biochemistry required chemistry and physics and math as prerequisites, we couldn't require that many additional units for the major. This course was listed as three units, and, compared to any other course in the university, we were really asking for five units of work. Finally, very reluctantly, we had to increase it to four units.

It was known to be a course that you really had to work very hard in. That wasn't just me. That was others, too. I really wanted the kids to learn a lot. I tried to be as entertaining as I could be, but I really liked them to be real excited about biochemistry. I was lucky because when I started, there was no really good textbook in biochemistry. Then Lubert Stryer wrote a book--he was a professor at Stanford--which was a very good textbook, and I could use that in the course, and that was a big, big help.

What I found when you lecture is the best students really take very good notes, and the poor students don't take as good notes. Then it really accentuates the difference when you give exams. You find the good students are really learning. The students would come in and ask me questions, and if it was, say, a C student, I would look at their notes, and I was utterly appalled. They really had missed points. I thought there was something terrible about my teaching, and then I'd look at the good students' notes, and they were very good notes. When I switched to a very good textbook, then it was much better. The students sometimes didn't grasp everything, but at least they got the basics down much better.

Hughes: What about graduate students and postdocs? What can you say about teaching or mentoring them?

Koshland: I don't take all the credit, but I think I taught well, and I think the other professors I taught with taught well. As a result, we had a lot of students that went to other places. Most of them, when they came out, all said their undergraduate training in biochemistry at Berkeley was very good.

Oh, I did do one other thing: We had a big argument in the department about lecturing in the course. There was a professor who dealt with, say, carbohydrates, and gave three or four lectures in his own specialty, whereas really you should only give one. We thought we'd get together and all agree how much time should we spend on each area of biochemistry. When I met with the group, we found we were all arguing about how much time. I said, "This is fruitless. We're spending a lot of time, and you can't really decide this. We're going to take a textbook, and we're going to agree that the amount of time [per lecture topic] is determined by the amount of [space devoted to it in] the textbook." Professor X spends the first five weeks and covers chapters one to six or something like that; Professor Y covers seven to fifteen, and so forth. I said, "We're not going to have big arguments about how much time. You're expected to cover your chapters, and how you give your individual lectures is up to you. But we expect you to cover the areas that are in the textbook." And so we did that. That was a good principle, I think.

Hughes: Did that continue?

Koshland: That continues. That's what they still do today. I don't consider that very innovative, but it was useful.

Biochemistry Chairman, 1973-1978

Hughes: It was a rotating chairmanship?

Koshland: Yes, five years.

Hughes: How was it decided who came next?

Koshland: The tradition was, the dean would write the department and say, "Who do you think should be the next chairman?" And each person would write a totally confidential letter saying, "I think so-and-so and so-and-so should be chairman, and so-and-so and so-and-so should <u>not</u> be chairman." The dean would get all of those suggestions and then pick somebody. It was not a democratic vote.

On the other hand, if everybody said so-and-so was really bad and you shouldn't take him, and the dean picked that person, then there's enough gossip in the department that people would say, "What's going on?" Or if everybody said so-and-so was the right person, and the dean felt that was the wrong person, he didn't have to do it, but it would cause a certain fuss.

Usually you did a little canvassing ahead of time, to find out who would be willing to be chairman because it's silly to write a letter and then the person refuses to do the job.

What was the year I became chairman?

Hughes: Nineteen seventy-three.

Koshland: So I had only been here six or seven years. And there were a number of older professors who had not been chairman. Anyway, a delegation made up of Bruce Ames and Esmond Snell and a few of the people in the department said, "Dan, we want you to run for chairman, and we're going to write letters." I said, "I don't want to be chairman. I've just got my research programs going very well, and there are a lot of people who are older who should be chairman." They said the department needed some rejuvenation. There needed to be a bunch of changes. They felt I was the person to do it. Anyway, they talked me into it.

Hughes: What changes did they have in mind?

Koshland: Well, it had to be more modern in the teaching, and they had to be better at recruiting, not just do what we've been doing all the time. We weren't getting as good students as they felt we ought to. They felt a malaise. I forget what all their arguments were.

The logical person to follow me should have been Bruce Ames. He was very reluctant. He was the same way [I had been]. His research was going very well. I had recruited him, by the way, from NIH. He started to act as though he didn't want to do it, and I reminded him that he had been in a group that had asked me to be chairman, so he accepted.

It was a really important tradition in our department that frequently the person who may be almost always the person who should be chairman doesn't want to be chairman. It was sort of a duty you did for five years. That took a lot of time, but everybody did it very conscientiously. Once you said okay, you said, "I've got to be a good chairman."

The job was made much easier because the biochemistry department has a lot of subcommittees--the admissions committee and the library committee and the grounds committee and the various things. All those people did their job well. It was considered that you should do well whatever job the department wanted you to do. Well, that made the job of the chairman much easier.

Hughes: How much did being chairman interfere with your research, or did it at all?

Koshland: I published--I found out at the end--just as much when I was chairman as when I wasn't. What was sacrificed was that I didn't go to very many movies. I would say it took 20 percent of my time to be chairman of the department.

Hughes: Did you have a particular way you partitioned your day?

Koshland: No. You just had to be very efficient. In those days, they didn't give you time off from teaching. Later on, they decided the chairman's job was sufficiently big, you've got to decrease teaching load. But I got added secretarial help, I remember. There were some perks to the job. It ended up, I spent a fair amount of time, but as a result, I was more efficient about other things. I did get off university committees. The chancellor asked me to be on the board of directors of the art museum, and so I got out of that when I was chairman.

Hughes: You have said that you were a younger man in the department. It was a prestigious collection of faculty members. Was there ever any question of your authority?

Koshland: I would say no. First of all, remember, I was recruited as a full professor, so I already had a pretty good reputation. I was younger than some of the people. They were all very nice people, and basically the minute I became chairman, I had that responsibility, and they all pitched in to help out. People liked to be chairman; it was good recognition. And some of those people became chairman later. But they weren't dying to become chairman. It wasn't a matter that we all had to run for election. They were signed letters [of recommendation to the dean], but nobody ever revealed what anybody said. So it wasn't that anybody was turned down because of me, so there was no animosity that way. Sometimes people disagreed with things I did. Remember, this was the seventies. I was not chairman during the worst of the sixties, which was a good thing, because I had too strong opinions.

Hughes: Was there anything that you particularly set out to accomplish while you were chairman?

Koshland: I was really upset with the quality of the students we were getting. The best students were not coming to us. Some of them were going to Harvard and Stanford, which is normal attrition, but I felt we should do better. And we did improve that area. But that in part led to the whole reorganization of biology at Berkeley because other departments were suffering much more than we. It was sort of endemic with Berkeley, but of the Berkeley departments, biochemistry was one of the best.

Hughes: I guess you wouldn't have needed the chairmanship to become aware of the problems at Berkeley.

Koshland: Oh, no.

Hughes: But did the chairmanship give you any insight that was later useful when you become involved in the reorganization?

Koshland: No. If anything, the chairmanship kept me very busy, and I felt maybe I had to be on a committee with other departments so I knew a little more about other departments.

Biochemistry Graduate Students

Hughes: Then talk about graduate students.

Koshland: The graduate students gradually improved. We did get better students. I got some really excellent students. [pointing] Those are the theses.

Hughes: Two shelves of theses.

Koshland: Yes. So I got very good graduate students. But it's sort of typical of a new young professor in a pretty hot area. We limited graduate student admissions to one or two students per lab per year, so I ended up with five or six students in my lab. I liked them a lot. Now I don't get nearly as many. You know, when you're older, they don't go to you. But I found out the same thing happened to Tij [Robert Tjian], who's fifteen or twenty years younger than I am. He complains that the young professors are getting the new students. I think that's sort of typical. You've just got to face that as you get older, students think you're less important.

Hughes: What do you look for in accepting a graduate student?

Koshland: One thing which everybody agrees on is good grades in college. You really have to be pretty much an A student. Secondly, we look for research. Students should mostly have done some research as an undergraduate or had a job. And in a small liberal arts school, even now they're allowed to do research--not as much as they can at a big university. The inclination to do research is considered very important by most of my colleagues, maybe a little less by me because I feel, okay, it doesn't matter if you're not doing that much. Then letters and statements about originality and things like that. Sometimes the straight-A student is not that versatile and a little rigid, and a B+ student might be as good. But I think most people don't think so.

Hughes: How possible is it at Berkeley for an undergraduate to do research?

Koshland: Oh, they all do.

Hughes: Anybody who wants to can get an undergraduate research position?

Koshland: Not anybody who wants to, but if you have a very good record, you certainly can. Some students who don't have a very good record even volunteer, and some professor really wants them as a pair of hands. I think to get into the very good labs, it's harder and you have to do better. But the students generally are very good.

Hughes: How much mentoring and contact do graduate students have with you?

Koshland: Oh, you have a lot of contact. I would say you don't talk to them every day, but maybe every two or three days you go over how they're doing and help them out with their problems. Even the undergraduates. Frequently the undergraduates work with a postdoc. I talk to them.

Hughes: You talk to the postdocs?

Koshland: I talk to the postdoc or to the postdoc with the undergraduate.

It is a nice system. In a place like Harvard, let's say, the selection principle means that almost anybody who gets in is very, very good. At Berkeley, the top third of the class is probably just as good as Harvard, but then you have two-thirds of the class which isn't as good. The system at Berkeley is that after you get here, if you do well, you end up getting the kind of personal attention you would get at Harvard. I think it's a reward system for the bright young students. They then get in the lab and get a lot of personal attention.

[End of Interview]

Interview 10: March 26, 1999

[Begin Tape 15, Side A]

Editor-in-Chief, *Science* Magazine, 1985-1995

Appointment

Hughes: Why did you accept the editorship of *Science* magazine?

Koshland: I always liked to write. I was from a large, Jewish family that made a big fuss about birthdays and things like that. I was good at writing poems. I'd write poems for my parents and my sisters and so forth. I got so I could do them pretty quickly. In large Jewish families you don't celebrate only fiftieth birthdays and sixtieth birthday parties; you have fifty-fifths and fifty-sixths and fifty-sevenths. If you have a large family, you're going to birthday parties every week.

Anyway, I always thought that someday, when I retired from science, I would like to do something different. Being editor of a small-town newspaper is what I thought would be a good career to try to taper off with. When I was sixty-five, I got this phone call from *Science*, a very prominent journal, saying would I consider being editor of *Science*, which of course I knew about. The way they offered it, it was a full-time job, and I would have to give up my lab and go to Washington, D.C. So I said, no, I really wasn't interested. But if I could do it half-time, I might be interested. I really hadn't thought very much about that; it was fun to say over the phone [I would do it] half-time. They said, "Well, thank you very much, but we're not interested." So that was it.

About three months later, they called me up and said, "We've been thinking it over, and we really considered your doing it half-time." I was actually out by the swimming pool at my house, and my children were there. I hung up the phone, and my children said, "What did you say?" I said, well, I really haven't thought about it that much, but I had gotten interested in a lot of university activities, so I didn't think I'd do the editorship.

My daughter-in-law, May Porter, Douglas's wife, a very cute, attractive young lady, said, "Oh, you'd rather be provincial than global." I didn't like a thirty-year-old telling me I was provincial, so I thought it over overnight again. I phoned *Science*, and I said, "I'm ready to consider it. I've got to come look at the job more seriously and see could I do it by going back, say, a week a month, which is what I would consider doing."

Hughes: Who was making these calls to you?

Koshland: Then chairman of the AAAS board, David Hamburg, now president of the Carnegie Foundation. He said fine; he would arrange it. And so I went back and talked to a lot of people there. At the end of it, I thought, well, I could do it. I would have to go back a week a month, because you really have to interact personally with the people on the staff. I told them it would probably take about 50 percent of my time, which is about what it did. And so I said yes.

They had never had somebody with that kind of a schedule before. But my feeling was it worked out pretty well because when I left the next editor [Floyd Bloom] was given the same arrangement. He could keep his lab and come back to Washington, D.C. one week a month. So it really worked out very well, and I could keep doing my science. I felt it was good for the magazine that I was really a scientist; I had to have grants; I had to publish papers, so I really felt like I was in the scientific world as well as being the editor of a scientific journal. Inevitably, as editor of *Science*, you're a spokesman for science, so it's good that you don't get up there in the administrative realms but are really a working scientist.

Hughes: Do you know why they wanted you?

Koshland: Yes, now I know more than I did then. They really wanted me because I was a very prominent scientist. I was a member of the National Academy of Sciences; I had gotten a bunch of honors; people knew that I was a very distinguished scientist, and I had shown, by being on various committees--of the National Academy and others--that I was interested in politics; I was interested in global issues of science, not just my own research. So that's the kind of person they wanted. The ironic part of it was they didn't know anything about how well I wrote. So I agreed in something like July of one year, maybe 1984, that I would do it the following year, starting July of 1985. I said, okay, I'm going to do it--it's going to be a big, interesting challenge--and then I didn't worry about it very much.

A reporter for the *San Francisco Examiner* called up and asked why was a man of sixty-five taking a new job at this point? I've forgotten what I answered. But he also called up my wife and children, which I thought was enterprising and different. So Bunny said, "Oh, Dan comes from a family where they work right up to the last minute and then just drop dead. His uncle worked until ninety and then dropped dead. That's what I expect will happen to Dan."

I came into the lab the next day and told them that my plan was to live to be a hundred, but my wife had ruined my whole schedule. Everybody was going to have to work much harder because I had ten years less time to get everything done than I had planned before. Anyway, that is one of my memories of that incident.

Writing Editorials

In about February or something of that year, I started to think about writing editorials. I thought I'd better start looking at the way Phil Abelson, who was the previous editor, wrote editorials and how I should do it. I had a terrible time. I couldn't really do it very well. Fortunately, I had a friend named William Keast, who was chairman of the English department at Cornell. I told him about this, that I was going to have big trouble doing editorials like Phil Abelson. He said, "Dan, you never should try to imitate somebody else's editorial. You should write in your own style." That's what I did, and that saved my neck.

My first editorial was sort of humorous. I think some of the editors thought, my God, we really made a mistake. In fact, they sent it back to me with a statement that it wasn't appropriate for a scholarly journal to have a humorous editorial. It was on a serious subject, but nevertheless it was humorous. So I said, "Well, you're going to have to learn, because I can't write editorials without having a little humor." Then they all gradually accepted it. It was quite useful. I think my editorials became quite popular.

Hughes: Was Abelson a model?

Koshland: No, he was helpful to me but not a role model. *Science* and *Nature* were the two international [scientific] journals and were very different from the scientific journals whose editorial boards I had been on previously. *Science* and *Nature* had big news columns as well as scientific articles. When I took over, compared to *Nature* magazine, *Science* really had gone downhill. *Nature* was considered a great deal better.

Phil Abelson was very nice to me, really an ideal person because he was very helpful but didn't get in my way. I changed a number of things that I knew he would probably not like. For example, one of the people he used was a lady--very nice lady--who did the composition [layout], and she knew nothing about computers. The modern world was just beginning to have computers. Everybody knew that computers were going to be important in setting up type. So I essentially demoted her and put Pat Morgan in charge who really could do things like that.

There were things like that which anybody, even if they are very well-meaning, is going to resent. You have to make big decisions like that that could be implied as [unintelligible] of my predecessor. Phil was <u>wonderful</u>. I never heard one word back to me, "Phil Abelson thinks Dan Koshland is doing a bad job with the journal." Whatever he felt, he was quiet, or he said it to me. He didn't even put much pressure on me to keep *Science* the same. He knew I had come in to improve it, and he was all behind me and really helped me a lot. Because I was away [in Berkeley] and he was there [in Washington, D.C.], he would frequently warn me. If there was some kind of a palace revolution, he'd say, "Dan, when you come to Washington be sure to go to the AAAS meeting. There are people there who are criticizing you." There's an antagonistic relationship between the editor and the director of the AAAS, who was my boss. Because the editor of *Science* wants more room for science, and the board of the AAAS wants more money for [unintelligible]. The AAAS runs a big establishment, and they really make a lot of money from *Science*. My editorial changes and a good financial decision by the director of the AAAS resulted in *Science* making a lot more money. *Science* became very, very successful financially.

Hughes: By increasing circulation?

Koshland: Increasing circulation, increasing advertising. The net result was that then he could think of new things to do with the AAAS, and I could think of things I wanted to do with *Science* magazine. So we always had big arguments about how the budget should be spent. We had a very friendly relationship, but still we had some fairly strong arguments. Abelson would always warn me about things like that. He was very helpful.

On the other hand, various people did say to me, the one thing you want to see is that Abelson has nothing to do with the magazine; you can't have the former editor around because it will cause all sorts of trouble. I thought that over, and I decided, well, I'm the boss, and I shouldn't be afraid of a strong-willed person who is willing to be helpful. It's perfectly all right with me people saying things, as long as they know I'm the boss. I decided I didn't want to write an editorial every week. Every other week I thought was okay. Abelson wrote very thoughtful editorials in a different style from mine, so I thought that would be a very symbiotic arrangement.

Hughes: Abelson was more closely allied with the physical sciences, wasn't he?

Koshland: He was. But that didn't make that much difference. He wrote about general subjects, the same way I did. He was a real scholar; his editorials were very good. He tended to be interested in geophysics and oil production and things that I wasn't that interested in. His editorials were very serious, and mine frequently had a lot of humor in them. It was a good mixture. I would say 90 percent of the editorials were split up between my writing half and Abelson writing half, and then we had about 10 percent where I invited people from the outside. It worked out very well because it really relieved a lot of pressure on me to not have to write an editorial every week.

Hughes: Did Abelson have other responsibilities as well?

Koshland: Yes. He was sort of consultant to the AAAS, but he didn't have a lab to go back to the way I did. So he was glad to have the editorial job and to help with the journal. I did it because I thought it would be very helpful to the journal, but it also was very nice for him. He behaved superbly and we became very good friends. I never felt I deserved any gratitude because I was doing it just because it would make my life easier.

On the other hand, I did ignore the people who said you couldn't have Abelson around because it would cause all sorts of trouble. I guess that's part of my philosophy of life. If you feel something is right, then you deal with the trouble if it arises. Sometimes it's pretty obvious that you shouldn't take one alternative. But I felt the chances it might work out were pretty good, and if it did cause trouble, I was going to have to cope with that when the time came.

Koshland's Priorities for *Science*

Hughes: What priorities did you set for *Science* when you took the position?

Koshland: I really wanted to make *Science* as good as *Nature*.

Hughes: What do you mean by "good"? In terms of circulation?

Koshland: Well, circulation was one, yes. The most important was having equal quality across the sciences. *Nature* and *Science* were probably the two most prestigious journals. If you were a biochemist, you put your article in a journal like *Biochemistry;* a physicist put his in the American Physical Society journals. But if you felt there was something that was very general and very important that all scientists should know about, then you published in *Science* or *Nature*. But of those two, *Nature* really was the first choice of almost everybody, including all the people at Berkeley. What I set out to do was to make *Science* as good as *Nature*, so the two were equal. I think I really succeeded in that. That took time. *Science* became a competitor and is today, I think, considered equal if not better than *Nature*.

At the beginning, I had to plead with people to send articles in--frequently friends of mine who were either at Berkeley or other places. They were going to send them in to *Nature,* and I said, "Please send it in to us." I got them to do it. And then, at the end, we were so successful, I was turning these same people down because we just didn't have enough space to publish all the articles we could have had in.

Then I had to improve the editing. The news articles, I thought, were not well enough written. They were boring. Some of them were much too long. If you're going to read about a subject that is not right in your field of specialty, then you'll read about it if it's fairly short and interesting, but you won't read it if it's a lot of hard work. I said most of the stories had to be made shorter, and they had to be written better. I hired a new news editor, Ellis Rubinstein, to improve those stories. And I changed a little the philosophy of what's called "Research News," the stories about research. I used the same argument, basically, that if you're a physicist, you're vaguely interested in what's going on in biology but not enough to really spend a lot of time. If you sit down after dinner and can read the article fairly easily, you'll read it. If not, you won't bother to read about biology.

Hughes: One of the things I understand you did in that regard was to make the abstract of scientific articles comprehensible to a general reader.

Koshland: No, that's a mistake. That was something I thought I was going to do at the beginning. But the rules of international scientific journals are, abstracts must say what has happened in the article in terms that are appropriate for the specialist in the field. They have to be short, and scientific accuracy requires scientific wording so abstracts could be easily read by them. When I found that out, I introduced a new feature called, "This Week in Science". I picked the five or six articles in the magazine that I thought were the most important articles or the most far-reaching articles and explained those in layman terms. *Science* is still doing that.

Hughes: Did you write those yourself?

Koshland: No, I hired Ruth Geyer to do it. That was what we did because I couldn't change the abstracts. That was one page in *Science* called, "This Week in Science." You could read a short, say about one paragraph, abstract in layman terms. Then, if you wanted to read the details, you turned to the article to get the more scientific. It turned out to be a very popular feature. I did it really to allow scientists in different disciplines to read what was going on in other disciplines. It turned out the newspapers loved "This Week in Science" because they picked up those stories. So it had a lot of other benefits. Sometimes you do a thing, and it turns out to have all sorts of benefits you hadn't thought of.

Hughes: Did you find that reporters based stories only on the synopsis?

Koshland: No. Something very important, a new cystic fibrosis gene, any good science reporter will realize that's a big thing; that's a disease that affects many, many people. So they would be attracted to the story by the layman version that was easy to read. But if they were good, they then read the scientific article. Now, the chances would be that we would have an abstract on a discovery like that. But journalists probably would have picked it up anyway, without the abstract.

Hughes: When there's an important breakthrough, do science journalists read the scientific article?

Koshland: Yes. *Science* magazine and *Nature*, which is our main competitor, one week ahead of publication time always release the contents of the article to a designated group of reporters. You don't send it out in general. Moreover, for that list, we make the article available, if they want it. We don't print the whole journal for them. And then we list the authors and their addresses, where they can be reached. Because the way journalism operates, they like to have it on the same day. So if you provide this courtesy, they can phone the authors. The story is embargoed. That means the journalist can't release the story till the day the journal is published, and everybody is in the same category.

Hughes: Was that system in place before you became editor?

Koshland: The embargo system is widely known.

Hiring Editors with Advanced Science Degrees

Hughes: I understand that your brought in editors with not only expertise but also higher degrees.[24] There hadn't been many Ph.D.s on the editorial staff before you arrived.

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[24] Telephone interview with Richard Kerr, geochemist and *Science* news writer, April 1, 1999.

Koshland: What I found when I first came was that the editors were largely people who were, say, English majors. They were people who wrote well, who could help edit the manuscript and make it sound a little better, but they really weren't scientists that could understand it. I said the quality that's most important is picking the most exciting new scientific advances. Most scientists are not English majors. They don't write iambic pentameter. But they generally can write pretty comprehensible English. The important thing was to select the best scientific articles, not to improve the quality of the prose. Improving the quality is part of the job, but it's not the main one. I gradually replaced the editors with people who had Ph.D.s, so all the editors now have Ph.D.s.

That was one of the difficulties when I first started because I really felt that the people whom I was displacing were being displaced for no failure of their own. It's just that I changed the philosophy of the journal. The managing editor whom I hired was Patricia Morgan. I told her I wanted to be able to get jobs for all these other people, that I really felt badly that they all had to leave. But it was to their advantage as well as *Science*'s because they really had no future at *Science*. If I brought in a few Ph.D.s and kept the other people on, they would really have nothing to do. It would be very expensive for me. It was much better for them to go off to a journal they were appropriate for where they would have a chance to move up and become important people. Pat Morgan and I got almost all of them jobs. We kept all of them on the payroll till they got another job.

The only person that was any problem was a chemistry reporter. We kept getting him offers, and he kept turning them down. Finally, I had to come to him and say, "Now, look, I want you to have another good job, but you may not get the absolutely perfect job in the perfect city that you've always wanted to be in. The next good offer, you better take it; otherwise, you're going to be out on the streets." So he took it. I give Patricia credit. It was my philosophy, but she had to do most of the spade work of finding other jobs. But most of the people were pretty good. We told them that we gave them a year so they could get another job. They would read advertisements in various journals, with a great deal of help from her and some help from me.

Hughes: Presumably you were trying to spread out the expertise and recruit people who had specific training in the scientific fields that the *Science* staff lacked.

Koshland: We picked some physicists, a chemist, a biologist, and so forth.

Hughes: How did scientists with Ph.D.'s feel about working in a field that wasn't laboratory science?

Koshland: I think that's a big problem. The people who were willing to be editors were probably largely people who weren't that good as scientists. If you're good enough to do science, you really want to do science. There were a few people who went through and really decided, "Science is not for me; I think I would rather be an editor." Most of them probably had completed their postdoc and then recognized they probably weren't quite good enough to compete in the first range of science and that it would be more fun to be an editor. They could be pretty good editors because that selects for a different quality. But it does mean in some cases that that they were not as good at ????. Some, however, were very good at it. They were the best editors. One editor, Eleanor Butz, as a star in that ?.

Hughes: Were you successful in the people you recruited?

Koshland: Yes, I generally got a very good group.

I had published in both *Nature* and *Science* before I became editor, and so I knew the gossip. They were the journals I would send articles to. The people at *Nature* had Ph.D.s, but they didn't go on in science. They were rather arbitrary; they didn't really understand the science in some cases. *Nature* was a very prestigious place to publish. It gave you sort of an instant reputation.

Some people complained bitterly that I was making decisions about tenure, because accepting or rejecting an article for *Science* was all a person needed to get tenure or not get tenure. Then they [*Science* editors?] got a little bit arrogant and started treating authors--"I know best." Of course, authors would argue that really the article was as good as the one they had seen last week, and so it should be published.

The Manuscript Review Process

I set up something called the Board of Reviewing Editors. That was a group of people that I thought was a little more general in their knowledge. They were all distinguished scientists, members of the National Academy of Sciences--although membership was not a criterion; some of them were members of the National Academy, and some weren't. But that caliber of science is what I wanted.

Hughes: The board represented the full spectrum of science?

Koshland: The full spectrum--a physicist and an X-ray crystallographer and a chemist and a biologist. An article would come in, and we'd say, This is [an article on] X-ray crystallography. We have [on the board] an X-ray crystallographer who's a professor at, say, Johns Hopkins. Or it's X-ray crystallography of a hormone, and we have a hormone chemist. He's at University of California. So you could use either of those criteria to select the reviewer.

[End Tape 15, Side A. Begin Tape 15, Side B.]

Koshland: I found out that before I came all the [submitted] articles went out for review, and sometimes it took nine months to get an article back. Well, nine months is a long time. I said that's ridiculous. People will not send good articles if they think they're going to have to wait that long to get an answer. I wanted a very quick review--to say, "This article is in the category that we think is worth publishing."

And it would then go for an in-depth review by specialists in that area. That should take a few more weeks, but the chances of its getting accepted at the second stage was about fifty-fifty. Either you heard your article wasn't going to make it and you got the article back to send to some other journal, or else you were told you have a fifty-fifty chance of making it. If you wanted to yank it out of *Science* then, you could, but if not, it was going to be a month or so more. [Dr. Koshland retrieves a current issue of *Science*.] This is a list of the Board of Reviewing Editors, all these people.

Hughes: It's extensive.

Koshland: He's a crystallographer at Cal Tech. Martin Raff is a well-known hormone person at University College, London. Gottfried Schatz is a very-well known yeast expert in Basel, Switzerland. So I had people from around the world because I wanted people to feel it was an international journal.

But anyway, these people reviewed the submitted articles quickly, and they were picked to be generalists, but very good in their own field. So they would recognize an important paper, but were not enough of a specialist to know whether it was really done well enough to publish.

Hughes: Did reviewing editors receive guidelines?

Koshland: Yes. The rules were, they got the manuscripts, and they had to return them within forty-eight hours and rate them on a basis of ten to one, ten being absolutely very good, we ought to take it; and nine and eight being not quite as good but we certainly ought to take it; and seven being a little more questionable, and so forth. Anything below five was generally something we didn't consider for publication.

I was astonished. I thought, my God, this review system is tremendous. Can you imagine getting five or six manuscripts every week and you're supposed to read them quickly? You didn't have to write a long analysis; you just gave them a rating--ten, nine, eight, seven or whatever it was. They had to return them within forty-eight hours. And they did it! Not only that, but they liked to do it. It was considered quite an honor. You were listed on the masthead as one of the special people. But I thought they'd all get tired and quit it.

Mike Brown got the Nobel Prize, and so I thought well, he's going to say he doesn't want to continue as a reviewing editor. He said he was very busy. (When you first get the Nobel Prize, everything descends.) He said, he would like to take a vacation for a couple of months. But he wanted to go back on the board of reviewing editors as soon as he was back. He did, and he's still on.

Hughes: Isn't it a good way for a scientist to keep up with breaking research?

Koshland: Oh, certainly. That's what they like. They also really liked that they didn't have to fill out a long, detailed questionnaire. They could just give their feelings for the submitted paper. That was a very successful venture.

Hughes: The second review stage was more traditional, in which there was a close reading of the submitted paper?

Koshland: The [reviewing editor] wrote back and said this is really worth publishing. Then the editors in Washington--that's why it was important that they be Ph.D.s--would send it out to specialists, who would then look at it and say, is this really a good paper [for example] in crystallography?

The first guy [reviewing editor] would say, "This guy [author] has done the X-ray structure of a heart muscle protein. That's going to be a very important protein. It has to do with heart attacks; it has to do with all sorts of things. This [other paper] is on the X-ray structure of the hind left tooth of the nematode. Who cares?"

Hughes: [chuckling]

Koshland: "So that can be published someplace else." That's the kind of decisions [the reviewing editors] were making. Before, they were evaluating all the papers equally, and they'd say, “This is an excellent paper, and it came back on a subject we didn't give a damn about.” I said, you should first weed out most of the submissions, and only send out for review a limited number. So it made much better [use of editors' time].

Hughes: Did you have any model?

Koshland: No.

Hughes: This was a new system for a science journal?

Koshland: Yes.

Hughes: Is it still being done that way?

Koshland: Yes.

Nature imitated "This Week in Science," but we imitated *Nature* in some things, so I don't say we had all the ideas. They have not imitated the board of reviewing editors. Their editors make all the decisions. In the long run, my feeling is *Science* will make better ones, and I think it <u>is</u> making some better ones.

I don't know how many manuscripts a year *Science* gets. We get thousands. I as editor of *Science* couldn't go through every one every week. But I would set the standards, and there was consistency as far as we could get it. I think the main inhibition was time. By going through this extra category [in the review process], it took longer than just having the editor do everything himself, but I think it improved the quality. We had to constantly keep our eyes on how long the review process was taking.

Hughes: In one of your initial editorials, you established that papers submitted one week would not be held over for possible publication in a later issue of *Science*.

Koshland: I said that right at the beginning. I didn't want editors to say, well, this paper is really pretty good; we hate to turn it down; we'll hold it over a week. The danger of that is you get a backlog very quickly. Every week we could accept twelve of these short articles and no more. Every once in a while, we would take one left over from the week before, and then I would say the following week we had to take only eleven. Otherwise, pretty soon you get a backlog and you stretch out publication time. It's much better to tell the author, no, your paper is not going to make it. Send it to another journal.

But that was a disadvantage: If you were unlucky enough to send a paper on a week when we had a lot of other excellent articles, we might have turned it down; if you sent it in the following week, you might get in. I think that's unlikely in most cases. But I put that in the editorial, sort of as an ego problem assuager: people whose articles were rejected could say, I just sent it in in a bad week.

Coverage Skewed Towards the Biological Sciences

Hughes: As we mentioned, Phil Abelson is a physical scientist. Yet *Science* during Abelson's tenure as chief editor had apparently favored the biological sciences. You came in as a biologist and wanted to give more coverage to the physical sciences. Why was that?

Koshland: I was a biologist--biochemist, really. But remember, I was pretty chemical. Since the war, I've been a chemist, almost a physicist. I knew a lot of those people. We leaned over backwards because I wanted to get more physics and make the journal more general. It was still heavily biology.

Hughes: Why?

Koshland: I saw it, and I said to myself, there's got to be a structural reason. We're doing everything we can to encourage more submittals from physicists, and it's not working. Why is it? So I looked a little at the finances of biology, the finances of physics. The answer is the following: First of all, there was much more money to support biologists, much more than for the physicists. The National Science Foundation, which gives money across the spectrum, was of the order of $3 billion when I left. The National Institutes of Health was $10 billion. That's a big disproportion, number one. Some of the $3 billion, remember, was going to biology, but it was more to physical sciences. But even if all of it had gone to physical sciences, it still wasn't equal. The physicists were getting money from the

Defense Department and others; the biologists weren't. But even so, that total amount of money was small compared to what the biologists were getting.

Number two, biology is largely little science. By little science, that means people like me who are among the bigger of the little scientists--I get grants of $100,000, $200,000 a year. Physicists were doing things like the super collider, which is a $1 billion project. There were lots of physicists together on one project. Then every five years they come out with some big paper, with a hundred and seventy-six physicists' names on it. Whereas little D. E. Koshland, who is struggling to get his grant renewed, wants to publish as much as he can. So I publish eight to ten papers a year from my own little laboratory, and that's what all the other biologists do.

Then, of course, they're [*Science* was advertising?] selling equipment. They're not just selling, say, a generator that's going into this big, big thing. They're every week selling chemicals, pipettes, all this kind of thing. So the big advertising and the big publication thing was in the biological sciences. It was just totally different from the physical sciences in terms of the [numbers of] publications and people publishing. That's what I realized was happening. No matter what we did, *Science* was skewed heavily towards the biological sciences.

Hughes: Isn't there another factor? It's a cliché that World War I was a chemists' war; World War II was a physicists' war. The current era is dominated by biology.

Koshland: You're right. But that, of course, is reflected in the financing. Biology is in a very exciting phase, and public health has become a very big deal, so biologists get more support.

Changes in Format and Logo

Hughes: You made some little changes--little compared to what we were talking about. One of them was moving the authors' names to the beginning of the articles.

Koshland: Yes, that was important. When you're looking over a number of articles and you come across an author: Oh, Westfall; I know him. He always writes good stuff. I felt you shouldn't have to turn over a page to find out who wrote the article, then turn back again and read it.

My second argument was I always wanted the table of contents all on one page so you could look at everything. I said most of the people reading *Science* don't browse. They will browse a little. *Nature* felt that science was the most important; science was up in front, and the news was always in the back. I changed the news in *Science* to up in front because I felt the news was the kind of thing you browsed. You sit down in the evening, and you want to read about whether NIH got more money or whether the head of Rockefeller was going to resign. That's sort of easy going. When you really wanted to get down to the science, then you looked at the table of contents and said, well, this article is really interesting to me; I'm going to read it.

Hughes: What was the controversy about the dot over the "i" in the *Science* logo?

Koshland: Oh, we changed the logo on the cover of *Science*. The other I thought was very drab. I got a designer in. There are professionals who design covers of magazines. [Displays a current issue of *Science*.] This is the new editor's [Floyd Bloom's] cover, which uses a lower case "i".

Hughes: I forget what the previous logo looked like.

Koshland: The *Science* logo was in caps with a dot over the "I". It really made a very catchy title. It's important because "science" is in the title of so many science journals--*Neuroscience*, *Biological Science*, everything.

Bill Cary was theoretically my boss. He was the executive director of the AAAS. I had a bunch of different designs. He picked out this one right away. I had the logos in my office here. I tried them out on my students and professors who came in, a cross-section of the community, and then I chose that one. That's the kind of thing the editor has to do. You can't have a committee doing that. When the new logo appeared, *The New York Times* denounced it. They said it's really disgraceful that a scholarly journal has a dot over a capital "I", which is incorrect. Well, rules of grammar don't apply to logos. Bill came in to me and started to hem and haw about changing it. I said, "Bill, you liked it before." Anyway, that didn't last more than thirty seconds. I told him I wasn't going to change, so that was it.

[Displaying a copy of *Nature*] Notice anything?

Hughes: Well, the logo's in small letters.

Koshland: Correct. You picked it out right away. The logo's totally incorrect. This is a proper noun, right? So they did something distinctive by making it in lower case letters. This became a famous case. Everybody quoted it.

Hughes: I read something to the effect that the dot over the "i" was a balloon, symbolizing the ascent of *Science*, or some such.

Koshland: That's right. The light at the end of the tunnel.

Hughes: Was that a little tongue in cheek?

Koshland: Of course. I wanted to throw the challenge down.

Introducing the Feature, "Policy Forums"

Hughes: You also added the feature called "Policy Forums."[25]

Koshland: Yes. They didn't have any of those before. They had articles on issues like global warming. But I deliberately put in Policy Forums which could be short, one-page or two-page arguments. That gave me a lot of freedom because then, if I didn't want to take a position on, let's say, the super collider, which a lot of physicists wanted and a lot of other physicists didn't want, I could have a Policy Forum by somebody who said we ought to build one, and it'll cost about $10 billion; and by somebody else saying, it's all very well, but that's too much money to spend on any one project. It wasn't worth having a whole article on it; there wasn't that much new physics in it.

Hughes: Those two counter viewpoints would be in one Policy Forum?

Koshland: Sometimes they'd be in one, and sometimes I'd write one on one side, and then I would say, if somebody else wants to write a rebuttal, send it in; we'll evaluate it and if it's good enough, we'll put it in *Science*. It provided a way for people to argue.

Hughes: How did you choose topics?

Koshland: If it was a new subject nobody had thought of or a controversial subject that people were talking about. At one point we were discussing AIDS research. Remember, it was a politically proactive group. But the number of people dying of AIDS was trivial compared to the number of people dying of cancer. Should we put all this money into AIDS? Well, you can argue that most people with cancer are older, so if you talk of years lost, you could say a disease that strikes younger people involves more years lost. You could make an argument both ways, so that was a good thing for a policy forum.

Hughes: How did your readership take to having *Science* expand beyond science?

Koshland: It had a number of features like that. But still, most of the pages were devoted to science. I think they liked it. People read *Science* to learn about the whole science community. We had many more articles like that than *Nature* did. *Nature* then decided they would imitate us, but their news stories were all very short.

Hughes: Does this reflect a philosophy of yours? That scientists have a responsibility to be informed about the implications of science?

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[25] Telephone interview with Richard Kerr, PhD, *Science* news writer, April 1, 1999.

Koshland: Yes, sure. I would say even more than that. I felt if you're a really good scientist, you ought to know what's going on in other areas. You're not at all sure that it's going to do you any good. But how do you know? The fact is, in the modern world there are a lot of things like neural nets, where physics computing has learned from biology, and biologists have learned they've got to use physical tools to really do good biology. My feeling is that in the modern world, as scientists are becoming more specialized, it is good to have some journal which constantly keeps you in touch with other fields.

Hughes: Your point in two early editorials was that you were very interested in having a multi-disciplinary journal and facilitating the links between the disciplines.

Koshland: Exactly right.

Exerting Authority

Hughes: Did you have a firm line in mind between what you hoped *Science* would accomplish and where the specialty journals should take over?

Koshland: A firm line would be hard to say, but I had a line; I just wanted the best of every field. My feeling was twofold. I said this in one of the early editorials, I think. If there is an unbelievably exciting development in physics, which has almost no use in any other field, I will publish that. But if it isn't quite that dramatic, then, for example: NMR [nuclear magnetic resonance] is a tool that is very useful to chemists as well as physicists. An article on NMR doesn't have to be absolutely, unbelievably smashing in physics. But if it's something that's very useful in chemistry and biology, then it really is appropriate in *Science* magazine. In other words, we would publish a very abstruse article in math that really advanced math a lot.

Hughes: And you got your reviewers to accept that philosophy?

Koshland: I was really the boss. I got along with people pretty well. But there was no question that when I decided something, I decided. Sure, I wanted to persuade them because they were good people. They would argue with me, but they knew if I decided I wanted it this way, they had to do it that way.

Hughes: You would change decisions regarding the acceptance and rejection of papers?

Koshland: Well, on papers, I didn't overrule my editors very much, but I did on occasion. There were just so many articles that came in, there was no way I could read them all. They'd get one, and it had to be set up in type and had to go. There's a lot of pressure at a weekly magazine. We operated *Science* with a smaller staff than *Time* magazine. It's a much more complicated journal than *Time* magazine, with all the science and everything in it. And it comes out every week, the way *Time* magazine does. Just to get it out is physically a feat. You can't possibly have one person reading all the articles, so you have a staff doing it.

If you start overruling them pretty arbitrarily, they'll eventually throw up their hands and say, "Dan, if you delegate it to me, you've got to give me a little respect for my judgment." Every once in a while there would be an article where I read the title and said it was really pretty good or was by Professor X, whom I knew was a very good scientist. I'd say that we ought to consider publishing it.

[End Tape 15, Side B. Begin Tape 16, Side A.]

Koshland: Professor Y is a real authority on the subject. We'll ask his opinion; we'll write him and see what he has to say. So then we'd do that. Sometimes the reviewer said the editor was right and I was wrong, and sometimes he would say I was right and the editor was wrong. I never arbitrarily said, "Even though you think the article's bad and are going to reject it, we should put it in." But I did say, "Think twice about this."

Hughes: Were you subject, with all your connections in science, to pressures to publish?

Koshland: Very little. Frankly, it was very surprising, and I don't know why, although I would get kidding. Every once in a while, at a board meeting of the AAAS, they'd get mad. I wrote an editorial, and they really just didn't like the point of view, or *Science* had accepted an article which was very one-sided, in their opinion. I overheard, "We ought to do something about this," and someone else said, "Oh, you know Koshland. There's no way they're going to get away with anything with him." And that was true. It was partly because I was doing very well. First of all, we were making lots of money. I always said if I had been the best editor in the world in terms of writing English and we were losing money, I would have had a hell of a time. I said, if I'm a lousy editor and we're making money, I'm going to be pretty secure.

International Expansion

In fact, we expanded a lot internationally. I partly wanted to do that for the prestige of the journal but partly just for money. Our circulation at the end was four or five times *Nature*'s--partly because the United States is a much bigger country than England. We're pretty even with *Nature* in the other countries. We started out way below them, but I built it up to about equal.

I really switched because of an advertising manager. All of a sudden, Beckman Instruments, one of our big advertisers, was going to reduce Beckman Instruments' advertising in the journal. They had had five ads during the year, and they were going to have two instead. I said, "Why?" He said, well, he wanted to switch to a more international journal, like *Nature*. "Our business is going more global these days. We're not just an American company." When I heard that, all sorts of little bells went off in my brain. I said [to myself], if he thinks that way, other firms are going to think the same way, and we'd better get more international. That's why I increased the board of reviewing editors. We made a big effort to expand internationally. We opened a bureau in England, and we've since opened one in Japan.

In addition, we did surveys, and practically every [science] Ph.D. in the United States was subscribing. We were about at the limits. If *Science* was going to grow in circulation, it would have to be international.

Hughes: You did two things in 1993: You started the Europe office and you added fifteen new reviewing editors, and fourteen of those were Europeans. Had you been moving in this direction before then?

Koshland: Sort of. Cary was replaced by a guy named [Richard] Nicholson [as AAAS executive director]. I wanted to increase our circulation. That meant we had to put all the new money that was coming in in the journal. The AAAS wanted some of the money, so I had to argue with Nicholson. He was theoretically my boss, as I said. When I say "theoretically," I mean I really was quite confident--maybe incorrectly, but I'm pretty sure my interpretation is right--that if I had ever had a knock-down, drag-out fight with Nicholson, I would have been supported. In other words, I would have won the fight.

I was much more famous as a person, and the journal was going very well, so it was very unlikely that somebody would say, "This is a dumb idea; you can't do it." On the other hand, Nicholson's job was to keep charge of the finances. I really couldn't do it without his approving out of the budget the money I needed to go abroad and open up offices. If I didn't get the income and advertising to cover the expenses--it was going to be a lot more expensive to fly the magazines over to Europe--then the whole thing would not work.

I had to argue with a lot of people to get them to do it. Then you have to get all the figures together, and then you have to make the case, so finally it gets done. We really started, I would say, at least three years ahead of when we finally implemented the European office.

Hughes: And the same was true of the Japan office?

Koshland: That was easier because once the thing was very successful in Europe, then it was easier to argue we ought to be opening in the Far East, too.

Hughes: It's an obvious observation, but it seems to me that *Science* reflected what was going on in science. Science has been international, but I think never to the degree that it is nowadays.

Koshland: On the other hand, there are real financial considerations. *Life* magazine got to its biggest circulation ever, but it went broke. Why did it go broke? It's because they were subscribers from an income level that the advertisers didn't care about. If you got an enormous increase in *Science* subscribers from the homeless population, it wouldn't work because 50 percent of our revenue comes from advertising.

Advertising

And part of why *Science* gets such good advertising from which it makes tons of money is, the companies which make goods for the various laboratories know that when they advertise in *Science* they deliver to an audience that reads it every week and goes through these ads and says, "Aha! That's a new centrifuge. I'm going to buy it from them." If it's a bunch of people who have no intention ever of buying a centrifuge, the advertiser doesn't want to spend money on an ad. Advertising in *Science* is very expensive. It costs much more than in an average journal. A company makes a big decision in investing a lot of its advertising dollars in *Science*. It's a very good audience because it spreads over the whole field, but nevertheless, it's a lot of money.

Hughes: Do scientists look upon *Science* as a source for the latest in equipment and services?

Koshland: Sure. They look at other journals, too, but the ads in *Science* are very good. Moreover, we use an argument with the U.S. government that the advertising is in part education, and it is. It really helps the scientists who read it to say, "Oh, gosh, this is available. I didn't know there was--." For example, the computer program which makes it much easier for my secretary to arrange bibliographies is something called "Endnote." I ran across an ad for it in *Science*. The same thing is true with a centrifuge. There are new centrifuges that work better than old ones. There are some air-cooled ones that work on a desktop. You don't have to hook them up to big water coolers. So the advertising is a form of educating the scientists to what's available.

Hughes: So consequently you were asking for tax relief?

Koshland: That was related to how the taxing is done.

Publishing Speculative Articles

Hughes: In your review article in *Protein Science*,[26] you said that in other editorial positions, you had an eye out for the unusual paper or the diamond in the rough. Did you carry over that approach to *Science*?

Koshland: Yes. I overruled my editors much more on the side of those speculative articles. They would say, "This is too speculative. They've got to do more to prove it." And I would say, "No, that's a very exciting article. I want to publish it, even though I'm not sure I understand everything in it, or I'm not really sure it's totally right." Let's say, if you show peas and corn are good food, and then somebody makes a slightly bigger pea and somebody makes a slightly more advanced corn, you could almost

[26] D. E. Koshland, Jr., "Recollections: The Joys and Vicissitudes of Protein Science," *Protein Science* 1993, 2:1364-68.

be sure that they're an advance and it's worth publishing. But it isn't anything dramatic. Somebody comes along with something called a grapefruit that nobody had ever had before and you just wonder, is anybody going to eat it? This guy ate it, and he didn't drop dead.

Hughes: [chuckling]

Koshland: I'm saying, "Take the article." I definitely was on the side of being a little more adventurous.

Hughes: What about grapefruits that twenty years later are found to be mutagenic? Did you ever get burned?

Koshland: I don't think we did. I'm trying to think of one that turned out to be wrong. I remember one paper, which I'm very proud of, which was really sort of nutty. This guy used DNA to solve famous mathematical problems, like the three traveling salesmen. Have you heard about that?

Hughes: No.

Koshland: If there are, say, six cities just taken at random in the United States, you can go to every city once, and you have to end up back where you were when you started. You have to go to every city one by one. What's the shortest route? You have to go to Boston and New York and Atlanta and New Orleans and then back to San Francisco. You probably go to Boston and then New York and then down around the South. That's pretty obvious. But now you throw in a lot more cities. Now you have Boston and Chicago and Dayton. You need to go to Cleveland, which is almost all the way to New York but pretty far from Chicago. In what order do you go? Can you put some formula down and calculate it? Nobody has been able to solve that. It's one of the famous unsolved problems of mathematics. You can do it by computer; you can do it by trial and error. But as far as getting a mathematical equation to do it, nobody has done that.

So this guy figured out a way of programming DNA and then selecting the DNA so it solved the problem. I didn't really thoroughly understand it myself, but I said, "This is such an original twist of mind, we're going to publish it." And we did. And do you know what it led to? An entirely new field called molecular computing, where people generalized even more greatly than that. That's really fun. I'm trying to think if there were any that turned out to be wrong; I don't think so. I think what happens is, if the article turned out to be not as useful as I thought it was, then it just disappeared.

More on Exerting Authority

Hughes: Have we said enough about the relationship between the board of reviewing editors and the editorial board?

Koshland: No. My experience will be useful to anybody who ever reads these interviews. In various activities, including some I'm doing now with the university, various people are always saying, "We should consult everybody." Sometimes [pause] you really just have to make decisions and go ahead. You have to listen to people. If you're a good listener, you really get it, and then you make a decision. But everybody can't be in on everything because it just involves too much time to explain to them. *Science* is a very complicated thing.

For example, one of the criticisms of *Science* is a lot of people pick it up and say, "They're discriminating against my field." We were criticized at one point that we had too many articles on AIDS. Well, in fact, *Science* magazine, before I came--I don't deserve any credit on this--had a couple of smart editors who saw the rise of this new field called AIDS and realized it was going to be a big disease. They had articles on AIDS long before the great medical journals, like the *Journal of the American Medical Association*, so *Science* became very famous in this area. And partly because it was viewed that way, it got the best AIDS articles.

So then you get a very good article on AIDS, and you get sort of a mundane article on geophysics. Your decision is, "We'd better take this article on AIDS. This is really a much better article." And then you get the journal too over-weighted towards AIDS. Then you have at some point to say, "This is a super article, but we've got too many articles on AIDS. We want to publish this one on geophysics." That's where the editor-in-chief has to step in.

The decisions are very complicated. For example, when we went global, I never wanted the journal to be very much bigger than it is now. This current issue is about 30 percent bigger than it was then. But I wanted a journal you could take on an airplane with you or sit with at a table. That was my goal. That meant, if we went more global, 30 percent of the articles could represent European work, because I figured about 30 percent of the total scientific literature across fields came from countries outside the United States.

Hughes: Keeping the number of pages the same?

Koshland: No, we had to allow for 30 percent more pages. If I did that, I could take 30 percent more scientific articles. But I wanted to have 30 percent of the news, then, reflect European events. It wouldn't be right to have all news of American science; I had to have a little news about what was happening in Germany and England and so forth.

Hughes: Your European office told you that?

Koshland: Correct. I had to coordinate all of that. This is a criticism I have: sometimes you can have too much democracy. There's no point in having a whole bunch of people second-guessing you, if they don't spend at least enough time to get as much information as you have. That doesn't mean my judgment is always right, but it means that it's silly for me to go into a meeting with a whole bunch of people who have spent much less time than I have on it and have them say, "No, Dan, you don't want to do it that way." In my heart of hearts, I know they don't really know what I know. Therefore, if I'm really going to run this well, I'm going to make my decisions anyway.

Hughes: You held the position of chief editor.

Koshland: Right. You may say it's sort of obvious, but it isn't so obvious. This university sometimes requires or sometimes they're pressed into it: you've got to have the students on university committees. Well, the students are here to learn. In our department, we have the students on committees that deal with admissions of students because they're at that age when they're very helpful, telling what you're really thinking when you're a young undergraduate and choosing an institution. But to have the students on the library committee, when most of them haven't read nearly as much--some of them are very conscientious and helpful, but on the average it probably is less useful.

My reaction is, if you want to have a committee you're going to consult, you'd better staff that committee with the caliber of people you really listen to. A lot of people, in my opinion, in an excess of democracy, want all sorts of people on committees. But then when they get there, the committee members are not making much sense, so they just ignore them. That makes everybody mad. "Why do I waste my time on that committee?"

Hughes: I had a long conversation with Monica Bradford, Managing Editor of *Science*, who told me that you hired a number of in-house editors.[27] Names that she mentioned were Phillip Szuromi and Barbara Jasny, and then John Brauman and Thomas Chech as deputy editors. She thought that was an important step.

Koshland: Those were very important additions, right. You see, *Science* magazine roams all the way from social science to mathematics, the most abstruse to the most general. I knew I couldn't do it all, and so I wanted to have really high-caliber people to come in as editors. Monica was very helpful with that. The person who preceded her was Pat Morgan, who also was good. They really understood that we were really going to make a big effort. In other words, a big fraction of their day was going to be devoted to getting good new people. If you get good people, you can delegate a lot to them. If they're not that good, you're always second-guessing them and wasting a lot of your time.

Hughes: Give me a flavor of what you actually did when you went back to Washington for that week a month?

[27] Telephone conversation, January 4, 1999.

Koshland: Let me just say, I didn't do all of my *Science* work there, and I didn't do all of my research here. In other words, sometimes I'd go back to *Science* and I'd take with me on the plane a manuscript I was finishing, and then when I finished my day at *Science* I'd go back to my hotel room and work on a manuscript. And sometimes when I was there, I had to write a journal article and take a little time out from the day, but it was never really that precise.

When I went to *Science*, I tried to save up those things that were difficult to do on the phone--let's say, having a conference with three or four people. Suppose we were going to do a whole journal devoted to AIDS. We wanted to get a bunch of science articles from people who were doing research on AIDS and some newspaper articles on development, how much Congress was going to appropriate for AIDS. I could phone the news person or the editor and so forth, but it was a lot easier to get them all together and say, "We're planning this issue. How do we do it?" I'd take people out to lunch. You can't be a disembodied spirit. People just respond better, they work harder if it's a human being that takes you out to lunch, rather than some voice over the phone. I think part of it was the rapport of the group in general.

A lot of my work in the early days was to get people to send an article to *Science*. I did that right up to the end because I really wanted to get very good articles. After I left, some of the editors said to me, "Dan, we tried to solicit articles ourselves, but we found out how much time you really spent on it." That was very important because, you see, it makes a much bigger impression when you phone someone directly. If I call a very prominent scientist, like David Baltimore or Mike Bishop, if I'm the editor of *Science* and say, "Mike, I really want you to send us an article. I don't guarantee I'll accept it, but I guarantee I'll review it very quickly. So if we don't accept it, you can send it to another journal very quickly, but we'll probably accept almost anything you send because I know how good your judgment is." He's much more likely to do it than if some assistant editor calls. The chief editor has to do a number of those things himself.

Important *Science* Articles

Hughes: Can you think of specific papers that were published in *Science* during your tenure that you consider to be particularly important?

Koshland: There were some scientific articles and perhaps some non-scientific. I'll pick a couple, just because they're easy to describe; they may not be the best. I would say an article we published showing that there's a gene that makes you gay. I had always believed that being gay was something you were born with. I never knew whether it was inherited. Sometimes there's a combination of genes giving you certain physical, social, or psychological characteristics. I always felt it was innate in the sense that the evidence was pretty strong, and it was being developed in the psychological literature. It was always the minority opinion, at least when I first read about it, that this was something that people were born with; it seemed to be such a basic urge. My own instincts, from what I knew about biology and protein chemistry, supported that opinion.

But I didn't think it would be inherited because I felt it would be selected against in evolution because you can't have any children. But then there's this guy in Los Angeles who discovered what he called the gay gene. There was a gene which did make people gay. I remember when people first came to me with the manuscript, I was asked, "Dan, would you accept that paper?" I said, "Why not?" They said, "It will cause a lot of controversy." I said, "Well, first of all, I don't agree with you on the controversy. But regardless of that, if it's good science, we'll take it. We're not here to second-guess what is good for the populace. We're here to publish science. A lot of gay people wrote me that they were really pleased to read the article. Gay people said, "From the time I was a little kid, I felt I was different, but I couldn't say it then."

Hughes: Was there also negative reaction?

Koshland: We didn't get any real big response.

I wrote some editorials about DNA as useful for trials, which was a big support of it at the early stages.

Hughes: Fingerprinting?

Koshland: Yes, DNA fingerprinting as a source of identification. As in any political situation, if the FBI comes out with it first, then a certain group of people will automatically hate it, and a certain number of people will like it. If the ACLU [American Civil Liberties Union] says it's a good thing, then a certain number of people will say it's terrible; a certain number of people will say it's good. I said, it's just like personal fingerprints, maybe even more powerful. It has turned out to be, if anything, more powerful in acquitting people who are not guilty than it has been in implicating people who are.

We were also one of the early advocates of the Human Genome Project, which has turned out to be very successful. There were a number of people in the scientific community who argued against that.

[End Tape 16, Side A. Begin Tape 16, Side B.]

Koshland: There are some people who felt it would be bad because insurance policies would be turned down and kids will apply to medical school and get turned down and so on. I really considered those pretty bad arguments. I never have very much patience with them. I think they're real problems, but I think they're easy to solve.

Hughes: You're extrapolating from the possible outcome of the Human Genome Project?

Koshland: Yes. A lot of people will say that you'll know ahead of time if somebody has got Hodgkin's disease, and therefore they're probably going to live to be only forty-four, and so a woman wouldn't marry. Well, that is a possibility. On the other hand, they would be able to say, "My mother had Hodgkin's but I don't have any trace of it, so I'm going to live to be ninety-three." I think it's going to be such a trivial use of the genome project data that I'm not very concerned. You can make all sorts of rules.

Immunity to Criticism

Hughes: Gretchen Seiler, with whom I also spoke--

Koshland: What did she think of me? I had some arguments with her.

Hughes: She told me that you loved a good argument.[28]

Koshland: Yes, I did. And she was a good arguer, too. She was very loyal to the boss. That was the reason for my main arguments with her at times.

Hughes: The boss being?

Koshland: The boss being Nicholson, who was theoretically over me, as I said. At the beginning she was the secretary of the guy before him, who was also executive officer. Remember, I was hired by Cary. By the time they came [to the AAAS board], I was really more senior than they were. It's sort of like having a new chancellor. The chancellor is my boss. On the other hand, there's only a limited amount he can do with Dan Koshland.

Hughes: Who is pretty ensconced.

Koshland: Pretty ensconced, correct. I was much more ensconced at *Science*.

Secondly, I was immune; I had another job; I never resigned from Berkeley. Remember, when I got the offer, I went to Mike [Ira Michael] Heyman and said, "I really figure I should cut my salary in half, and you should pay me half of my salary." That's what happened. "But I'd like to keep my lab." He said, "Fine," and that was it. So the facts are if I ever got into a big row, which never happened, I would have just said, "Fine, I'll go back to Berkeley."

When somebody said, "I don't like your editorial" or "I'm going to go to the boss and complain about you," I said, "Go ahead. It doesn't bother me at all." I never even spent much time worrying about it. I think it was pretty obvious that they couldn't do it [fire me], and then, as I said, I was in a pretty strong position, so it

[28] Telephone conversation, January 4, 1999.

really never came up. But I will be fair: nobody ever threatened me very much. People disagreed with me, and they got angry, but nobody ever said, "Dan, I'll get a bunch of people and we'll--"

Some of my friends wrote me at times. We published a lot of letters, some letter denouncing certain things I had written or published. One of my friends would write in and say to me, "Dan, I saw that letter denouncing you. Do you need a letter saying you're a good guy? Because I really like what's going on." I wrote back, "No, don't worry. I am not threatened with losing my job. It never worries me when people disagree. When they write they're canceling their subscription, then I'll start worrying."

That was one of the measures of success. We had one of the highest rates of journal renewal of any magazine. *Time* magazine and publications like that keep a record of [subscription renewals] because financially it's a lot easier to get renewals than it is to get anything else [new subscriptions?]. You'd have to send out lots of letters. The statistics are, one out of every twenty people accept an advertising campaign. With renewals, you're not spending any money on advertising. If you put in any advertising, it goes out with the magazine anyway, so it doesn't cost you anything.

Renewals of scientific journals in general are pretty high, but *Science* and *Nature* are really way up there. They have 90 percent or more renewal, so that's a pretty good test of whether people like them.

Koshland's Contributions to *Science*

Hughes: What do you consider to be your major contribution to *Science*?

Koshland: I think probably the single most important was improving the quality of the scientific articles. I think the whole credibility of the journal depends on that. But I think I also made the journal much more readable. A lot of people told me they read *Science* in preference to *Scientific American* because the articles were so easy to read. I felt there was no diminution in quality, so I'm really pleased with that. I think probably going international was very important.

I think the single most important thing was probably getting *Science* up there with *Nature* as really being a journal publishing first-rate science. When I first came there, various people said, "Are you going to emphasize the news? There are rumors you're going to let the science part wither away." And the scientists would say, "I hear you're going to do the science but let the news part go to nothing." The two are related to each other. The news is treated very seriously because the science is very good, and we get a bigger circulation because the news is good. It's a perfect example of two things helping each other. I think you can't say any one thing is more important.

Hughes: Thank you.

[End of Interview]

Interview 11: April 1, 1999
[Begin Tape 17, Side A]

Editor-in-Chief, *Science* Magazine, 1985-1995 (continued)

***Science* Editorials**

Koshland: I think all of my previous experience was useful. *Science* magazine and *Nature*, which is its counterpart, really have no exact counterparts in the scientific world. So you learn a lot when you're head of a magazine in the sense of meeting deadlines, how you evaluate articles. The big difference in *Science* and *Nature* is you have a big news reporting function. In most of the scholarly journals, the news report, if you have it at all, is a minor thing. Most of your job is evaluating and editing manuscripts.

A big part of the job at *Science* and *Nature* is evaluating manuscripts. But another half of the job is reporting the news of science all around the world and what Congress is doing and what reporters think. For example, the fraud issue became very important when I was editor. There were issues of how much money was going to be spent on the supercollider. It's really quite a different experience [from editing a scholarly journal].

I would say my experience as editor of the *PNAS* [*Proceedings of the National Academy of Sciences*] was important, but my experience as chairman of the department of biochemistry here at Berkeley was also important. Probably my experience in the reorganization of biology at Berkeley was important.[29] They chose Phil Abelson and me--I'm pretty sure, from the gossip I heard--pretty much because we were prominent scientists; we were members of the National Academy of Sciences; we were regarded well by other scientists. Floyd Bloom, who followed me as chief editor, was a member of the National Academy.

As far as I know, nobody checked whether I could write. In fact, *I* never really thought about writing editorials. I thought, well, I'm editor of *Science*. I'm going to decide various things *ex cathedra*, like the Pope, and tell everybody [through my editorials] what I thought about science, and everybody would roll over and accept whatever I said. Well, of course, that isn't what happens. But making the editorials amusing was an important feature, something that I did, which has been done less since then. But the idea of finding out if I was a good writer or could even write an English sentence was not something anybody really thought about before I got there. And *I* didn't even really think about it.

Hughes: Had you been in the habit of regularly reading the editorials in *Science*?

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[29] The oral history volume, “The Reorganization of Biology at the University of California, Berkeley,” in the Bancroft Library series, contains interviews with three participants, including Professor Koshland. http://digitalassets.lib.berkeley.edu/roho/ucb/text/reorganization_biology.pdf

Koshland: Yes.

Hughes: Do you think that your colleagues routinely did and do that?

Koshland: This has turned out to be something very conceited. My editorials were considered to be very amusing, so lots of people read them. You always have a select audience. A lot of people said, "I read your editorials," and a lot of people have since said, "I miss your editorials." I just had lunch with the president of Haverford College, a liberal arts college. He was a scientist before becoming president, and he always read my editorials, and he knew [my fictitious character] Dr. Know-It-All. People have to say something like that so I can really believe they read them; otherwise, maybe they're just flattering me.

But the present editor of *Science*, the guy who followed me, basically did something that I didn't do, which is he made it more of a policy forum. He invited the president of MIT to write an article, invited the head of the National Science Foundation, the president of the National Academy of Sciences.

Hughes: He invited the President of the United States.

Koshland: Is that right?

Hughes: Yes!

Koshland: I invited the Emperor of Japan.

Hughes: Did Clinton write one?

Koshland: Yes, [Bill] Clinton wrote one.

Anyway, I didn't do that. I did it at the beginning, but it was a pain in the neck to get them. *Science* has a big audience. It's estimated something like, I believe, 800,000 people read it a week. That's a lot of people. That's as big as some of the biggest newspapers.

Hughes: What is *Nature*'s circulation?

Koshland: About a fifth of that. The two of them are very widely read, all over the globe.

Anyway, my feeling was, the president of MIT--his constituency is not all the scientists all over the world. His constituency is the alumni and members of MIT, so he's not that interested in writing for me, for *Science* magazine, so he would not spend much time on the editorial, and then it would not be very good. I'd look at it, and I'd send it back to him and say, "Could you fix this up?" Well, then he wouldn't get around to it. I designed that editorial for March 5th, and on March 3rd I realized he wasn't going to deliver it on time, and so I had to write an editorial over twenty-four hours, which is a pain in the neck. Having done this a few times, I decided it's not worth doing all that. Every once in a while, I'd try somebody and say, "Send it in whenever you can."

You want the editorials to be topical, so you invite a guy because he's president of Princeton and Princeton has a big new nuclear reactor, and that's in the news. Then he doesn't write anything for two years, and then he writes about something maybe you don't want to put in the magazine at all. It really wasn't very helpful. As a result, I arranged this scheme which turned out to be really smart, but I didn't realize it at the time. I didn't want to write an editorial every week. So I asked Abelson to write editorials maybe every other week, and then we'd get a certain number of guest editorials.

Hughes: Dr. Abelson told me that he figured that in a given year, you wrote twenty editorials; he wrote twenty editorials, and then there were ten written by others.[30]

Koshland: Correct, that's a good guess, and that's exactly what happened. So the net result was that Abelson always wrote very thoughtful editorials, and he spent a lot of time on them, and then they were excellent. That scheme worked out wonderfully for me, and I liked it very much. The net result is we did get a few guest editorials, but we didn't have to depend on them.

What happened with Bloom, to be very honest, was what I also observed: you think, well, these guys will write something really interesting and novel. But since it isn't their primary audience, as I said, the most novel thing they're going to save for what is going to be their big day. If you're going to preach to the Catholic church, you save your best ideas for Easter Sunday, right? Or if you're a Jewish rabbi, you save it for Yom Kippur. So the idea that *Science* was going to get their best ideas I found out wasn't true. So my reaction was, well, okay, I'd invite them, and if they got around to doing it, that would be a plus, and that would be the ten a year that Abelson and I didn't have to write. But I wouldn't count on them. When they did write, they tended to be things that were in favor of motherhood or against sin or something really dramatic like that. It was so boring. I couldn't stand them. Most other people said the same thing. They had these very prominent people--the head of the NSF [National Science Foundation]--but it wasn't his priority. He was not asked to write an editorial on a specific topic, so it tended to be pretty boring stuff. I really felt the editorials should be interesting.

Abelson didn't write humorously, the way I did, but he wrote real content. He discussed, say, a big thing that was coming up on the gas bill and usually discovered things that nobody knew about the gas bill. He did his homework. You wouldn't see it in your local papers. I thought he really did a very good job, and it sort of complemented mine. My editorials were frequently more topical, partly because I made fun of things.

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[30] Telephone conversation, March 3, 1999.

Hughes: Abelson told me that he decided very early on that it was not a fruitful approach to tell his colleagues, other people with Ph.D.s, how they should think. He thought his editorials would serve better if he provided the information--

Koshland: Right.

Hughes: --and then people could use that information to come to their own decisions. Did you have a similar approach?

Koshland: No. I basically let him write the editorials that he wanted. They were quite different from mine. I didn't do that. It was pretty clear what I thought when I wrote my editorials. But I thought that was good. You see, I thought the more different Abelson's were from mine, the better off it was. First of all, I thought he was very smart. I liked his approach. And the fact that it was different than mine I thought was really good because it provided contrast.

Hughes: He also considers you much more a political animal than he is.

Koshland: Correct.

Hughes: Your editorials tended to have a more political slant to them.

Koshland: Correct. His were much more educational than mine were. What he said to you is accurate. That's exactly what it was.

Hughes: I also talked with Richard Kerr, who was brought in as a news editor in 1977, before you were editor-in-chief. He said that you were "definitely an activist editor, no doubt about that." [31]

We talked last time, you and I, about how you hired editors with Ph.D.s.

Koshland: He had a Ph.D., I think.

Hughes: Yes, in geochemistry. One reason you were able, he thinks, to attract people with PhDs was because you hired copy editors who took over the mundane functions that editors had to do before.

Koshland: Yes, that's what I did do, yes.

Hughes: Dr. Kerr also said that there was a feeling in the news department when you started the Policy Forums that there was some overlap with the news department, that you were treading in their territory.

Koshland: I don’t remember that one.

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[31] Telephone conversation, April 1, 1999.

More on the Manuscript Review System

Hughes: We talked last time about how you revamped the review system. I didn't get a picture of the role of the in-house editors. He gave me the idea--and I want to verify it with you--that even though the board of reviewing editors may have suggested publication of a given manuscript, there was still some choice left for the in-house editors.

Koshland: Big leeway.

Hughes: Did they make the final decisions?

Koshland: No. The system we had when I was there was modified from the previous one but was not too different. I refined it. I set up this board of reviewing editors that was designed to cut down on reviewing time. Supposing somebody said in an article, "I think the moon is made of green cheese." In the old days, they would have sent that out to review. Probably got a couple of reviews back, saying, "This is ridiculous." That's an extreme, but it will give you an idea. You could tell this was pretty ridiculous.

The board of reviewing editors would get on the average of eight to ten manuscripts a week. That's a lot. In one of my first two editorials, I said I was going to [streamline the review process] because it was taking nine months to complete. Part of it is they were just getting too many articles to review.

The idea was that those people on the board of reviewing editors was to provide advice for cutting the number down to, say, about one-third of what they had before, maybe less. Why they liked it is they could review rather quickly--they didn't have to review in detail. A reviewing editor would rank the article, ten being the best and one being the worst. Usually, an article went to at least two of the board of reviewing editors. They would then decide whether or not it went for in-depth review.

The in-depth review meant now it's really a good subject. It's something we're likely to publish, and therefore we'll go pick a couple of good physicists who are going to review it. The reviewing editors were just supposed to decide whether this was worth going on to review. But we also encouraged them, because they were experts in their fields, to suggest possible reviewers. That was a big help to people in house. They liked it.

A lot of times, one of the board of reviewing editors would give it, say, a ten, and the other one would give it a four. Generally, six and below meant you didn't review it, and ten meant you automatically reviewed it; seven was in between. Okay, so if somebody gave it a ten and somebody gave it a four, then the editors had to make a decision. They decided we're going to send it out to review.

Hughes: Or not.

Koshland: Or not, right.

Hughes: That's why you had to have--

Koshland: Ph.D.s. And not only that, but if they decide to send it out to review, whom do they send it out to? They had to read the references and call up somebody and decide Professor X at Illinois or Professor Y at San Francisco would be the two people to review it. Then they'd send it out. Some of the reviews would be just terrible. They'd say, "This isn't worth considering."

We had what was called a space meeting once a week. It was called that because we had a limited amount of space in the journal. All the [in-house] editors got together--remember, we had editors who specialized in biological article, some in physics, some in chemistry, some in social science. We all sat down, and then we went around the table. I attended those meetings whenever I came to Washington. So when he said I was a hands-on editor, I was. That was wonderful for me because I learned how they thought, and I learned how good they were.

I wanted to keep the journal small. These were the best articles of that week, okay? That meant that we could really only accept twelve little articles and about two or three big articles in the front of the magazine. That meant that of all these excellent articles, we had to pick the best ones. So the space meeting was where the decision was made.

Hughes: And then, of course, you had to choose which sciences are going to be represented in the issue. That must have been a consideration, right?

Koshland: Oh, it was. It was a big one. When I didn't feel in any one issue if we didn't have any chemistry, it wasn't terrible. But over the long haul, if we had no chemistry, I would feel that was bad.

Hughes: You must have been getting more submissions in the biological sciences because they were booming. Therefore, it was harder to publish in that field.

Koshland: Oh, yes. You're very smart, madam. The people in the other fields would say, well, Dan Koshland favors the biological sciences. He's turning down excellent papers in my field, and I'm dealing with anthropology. In fact, the competition in biochemistry was much greater than in anthropology. We were getting many more papers in biology. They were competing with each other, and it was much harder. And the fact of the matter is, there were just many more people in that field. The amount of money that was behind biochemistry was just so much greater than in anthropology.

Power and Argument

One of the things I learned, I really had absolute power as editor-in-chief of *Science*. The University of California--if I didn't like a professor in my department, I didn't have very much power. The department chairman has quite a bit of power. He can make life pretty unpleasant for people he doesn't like, but only to a limited extent. In the case of *Science* magazine, it's pretty clear. It's like any business organization. You'd get a lawsuit if you just go up and say, "I don't like the way you part your hair. Get out of here." But within that limitation, I pretty much made the rules. That was an interesting feature because I found people were very, very polite to me at the beginning, which is not anything I was used to. In fact, it was not something I liked. I gradually got around--somebody would say they agreed with me, and I said, "You don't really agree with me on that." And they'd say, "Oh, yes, Dan, you're really right." "Come on! I know what you really think. Tell me." Well, they gradually got to learn that I really liked an argument. They knew I just thrived on having big fights with people.

[End Tape 17, Side A. Begin Tape 17, Side B.]

Koshland: I remember there was one great incident in my office. The advertising manager, whose name is Beth Rosner, was very good. She really made the amount of advertising in *Science* just zoom. She was just making tons of money [for the journal]. She kept coming up with ideas for the magazine. She never asked us to take this article or not take that article, which would have been stepping over the line between advertising and editorial content. But she wanted to provide some timing so the advertisers could correlate with editorial content. Let's say the Smith-Kline-Beecham Company, a big pharmaceutical company, would like to have their ad appear in an issue that was going to be devoted to biology because then more biologists would read it. Some of the editors would say, "That's really bad. Dan shouldn't even be talking to the advertising editor, let alone have her dictate policy. It's really dangerous." I'd say, "Come on! If a company tells you what articles to publish, that one thing I would oppose. But to say they'd like it in an issue that has biology in it because of articles we accepted with no input from them, that’s not so difficult for us to do. That’s not a lot of extra work for us, and it will help Beth do her job.

Barbara Jasny, who was one of my very best biology editors, was very passionate on the subject. She was against helping advertising in any way. I had her and Beth Rosner come into my office and present their cases--Barbara saying that she was impinged upon, and Beth saying the editors had to learn to be a little accommodating if we are going to get enough money to pay their salaries.

The two of them came to my office. We shut the door, and they gradually got so mad at each other that they were shouting. People could hear it through the closed doors, as I later heard. They were at the door, listening to this tete à tete. When they left, I went back to my desk and started working, and the outsiders came in and said, "Dan, weren't you upset?" I said, "It was a great meeting. Those two people care passionately about the good of our journal." That's the kind of staff you want. But the outsiders said, “They were shouting and very angry.” I said, "It doesn't matter. They were arguing strongly for their point of view, but I'm sure they're still good friends." And that's one generalization I have: I never let an argument become *ad hominem*.

I never was bothered by arguments like that. When I was chairman of the department here, I did the same thing. If someone started to get angry--every once in a while that happens--someone says, "I'm a member of the National Academy, and I know more about this thing." I always said, "That's the end of the discussion." I found that people really don't resent disagreeing with you. They really resent it if you say, "You're not good enough, and my opinion is better, just because I'm a smarter person."

Instituting the "Perspectives" Feature

Hughes: According to Dr. Kerr, there was friction over your idea to have a place in the journal in which scientists wrote perspectives on science.

Koshland: The idea I had was that a lot of the news people would write articles about science, and frequently the articles were superficial. I had gotten some criticism. *Nature* magazine had something called "News and Views," where they would get scientists, probably because they didn't get much funding so they couldn't do much research, who enjoyed commenting on other people's science, so they got a higher caliber of people.

I wanted to have something like that. I introduced something called "Perspectives," where I'd invite scientists. Say, we had a paper on some new virus--let's say, the hanta virus, which is a new virus which was discovered recently. I would want to publish an article that scientists in general--meaning not just biologists--could understand, which would put the discovery in context. So I would invite David Baltimore to write a perspective: this discovery is really very interesting because we've never had a new category of virus like that. Or it's very interesting because it looks like it's lethal. Or whatever it is. Say whatever was important about it.

The conflict that Kerr was talking about: When I first proposed "Perspectives," they thought it was taking away from the news department, that these would be among the most exciting articles. Barbara Culliton did have a fight with me about that, but then we just did it. I didn't spend an age debating it, and I didn't put it to a vote. I just was going to do it, and we did it. Did Kerr think I fired her?

Hughes: No, he didn't say that, but he did say that she left.

Koshland: She did leave. In fact, I hired a new news editor, a guy named Ellis Rubinstein.

The "Research News" Feature

Hughes: You, as a scientist, were probably first and foremost interested in publishing a journal that appealed to your science audience.

Koshland: Right. That was number one. There's no question.

Hughes: But was it also a consideration to make *Science* understandable to the lay public?

Koshland: That's an excellent question. This is a case where I got credit for what I didn't deserve. "Research News" was designed to explain science to people in a different scientific field; in other words, to try to explain, say, something in physics to the biologists. Those articles, when I read them when I became editor, I felt A) were too long, and B) were often difficult to read. My feeling was that I as a biologist was not going to read an article about physics unless it was really easy for me to read. I said the articles should be shorter, and they should be made much more readable. That's something I really did.

Hughes: It seems to me that if you're a physicist, you're not going to bother with the synopsis in “Research News”; you're probably going to go to the article itself.

Koshland: Correct.

Hughes: So why would you write the synopsis for the physicist?

Koshland: You're right, most of the time. But on the other hand, it turns out all the areas are specialties. In other words, modern science has gone so fast, a high-energy physicist is no longer an expert in low-energy physics. A virologist doesn't know that much about biochemistry. A biochemist doesn't know immunology.

It turned out--that's why I say I got credit--it turned out that laymen can read and understand those “Research News” articles. *Scientific American*, which is supposed to be designed for the layman, was getting more and more complicated. They were not editing that well, and they were getting articles where the people kept trying to write a good article about physics for the physicists, rather than for the non-physicists. So lots of people who were laymen told me they read *Science* all the time, and they didn't read *Scientific American*.

We looked over a list of *Science* subscribers. We had stockbrokers who were reading it because they felt they had to be up on the latest developments. I really did it to make it easy for scientists to read, but it ended up being good for science for the layman. I was proud of that, but on the other hand, it isn't what I started out to do.

Hughes: You mentioned Ellis Rubinstein, who came to *Science* in April 1989, almost midway through your tenure. Did you hire him?

Koshland: Yes.

Hughes: Why?

Koshland: He was editor of another journal--what was it called? I think *The Scientist*. He was doing a very good job at it. It was not nearly as big a job as being the news editor of *Science*.

Hughes: A good job in what sense?

Koshland: It was something that people didn't read very much, and he was making it very readable. There were a couple of other people I also thought about. I actually called them up and interviewed them and didn't like them that much. Ellis I thought would be very good, and he said he would like to take the job, and so I hired him.

Hughes: What changes did he make?

Koshland: Oh, he made big changes. Ellis got rid of the people who weren't good editors, and he really edited articles. Editors knew their articles were going to get edited and told if they weren't doing very well. And then he recruited some very good young people. Ellis really improved the quality of the news section.

Hughes: Dr. Kerr said after Ellis Rubinstein came in that there was a more consistent writing style and more focus on design and appearance. I have to be careful here because he wasn't meaning his comments as criticism of what had gone on before. He thought some of the pointed and controversial journalism had dropped out. He described a rather complicated editorial process in which an article was often considerably changed during the editorial process. I think he was saying that over the years he had seen a shift; a personal style which was rather controversial and opinionated gradually became blander. He missed some of that, knowing where an editor stood on issues.

Freelance Reporters

Hughes: I understand that under Rubinstein freelance reporters began to be used substantially. Kerr thought that up to one-third of the articles were written by freelancers.

Koshland: Correct. The freelancers were brought in because we [at *Science*] couldn't really counteract the fact that the reporting was too Washington oriented. Our stories were too much about space science and NASA and things like that. I felt *Science* was missing a lot of local stories. We opened a bureau in Massachusetts and one in California because they are centers where there are a lot of scientists. "Bureau" means that you have somebody permanently hired out there. But there were other areas, like Texas and Washington [state],which were building up scientifically. We couldn't have bureaus all over; that was too expensive. But there were freelancers. There was a good science reporter on the [*San José*] *Mercury News*, and we'd encourage her to write articles for *Science*. And the same thing with somebody in Texas.

[End Tape 17, Side B. Begin Tape 18, Side A.]

Expanding Circulation and Advertising

Hughes: We spoke last time of the increase in the circulation of *Science* while you were editor. But Kerr pointed out that the American readership didn't increase much.

Koshland: It didn't, no. That's really one of the reasons I went to Europe. Some advertisers wanted to be more global, and *Nature* was pictured as being more global than *Science*. The other reason was we had saturated the readership. Practically everybody [in science in the U. S.] took *Science*. It turns out when you really look into it, almost every American scientist either got *Science* or had easy access to it. The lab got it or the lab across the hall got it; things like that. So the need for global circulation became obvious to me, and the only place we could really grow was in Europe and China and Japan.

Hughes: We talked about the explosion in advertising when you were there. Prior to your tenure, a New York advertising agency had been handling *Science* advertisements, and you got rid of it.[32]

Koshland: I had a role in it, but the main person who did that was the executive officer. He runs the whole AAAS, which has a division related to arms control, a division which watches the federal budget, and then a division which is concerned with Africa and other developing areas. One of the divisions is called *Science* magazine. Well, as you can imagine, this is like having elephants and a chipmunk and a rabbit. Most of those divisions were very small things, and almost all of them cost money, whereas *Science* brought in a lot of money. Essentially all the income came from *Science*. The [AAAS] meetings, I think, didn't make money; if anything, they lost money. So *Science* was the big dog as far as money is concerned.

The executive officer was in charge of all of these things, but he didn't do very much in *Science*, although theoretically my budget had to go through him. I had a big argument with every exec because I always wanted more money for *Science*, and we were making all the money. This is an interesting thing, where understanding structure is very important, and that is, the executive officer was almost invariably hired to run the AAAS and incidentally *Science*. But in fact, there was not much he could say to *Science*. If there ever would have been a knock-down drag-out fight, I'm sure I would have won. I was secure: *Science* was written very well. I was a lot harder to replace than the executive officer.

It's not worth having a fight like that. But I got pretty angry occasionally at the budget. For example, when I wanted *Science* to expand internationally, that meant

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[32] Telephone conversation with Richard Kerr, April 1, 1999.

spending money abroad. We wanted to open a bureau in England and so forth and so on. The executive officer was very resistant. I said, "It's ridiculous. I'm requesting a tiny amount of money, and the journal really needs to expand globally." I won finally, but it took me much more time than I thought was worth it. But he was theoretically the boss.

What was the original question?

Hughes: I asked about getting rid of the advertising agency.

Koshland: Getting rid of the advertising agency was his responsibility, not mine, because it was on the business side. We really had a big influence on the advertising; it was quite clear. So I was involved in choosing the person that was hired.

Hughes: Who was Beth Rosner?

Koshland: Yes, Rosner, who is very good. The previous executive officer had signed some really bad contracts with the advertising agency, which made it very difficult to fire the advertising agency. The executive officer, Bill Carey, who preceded Richard Nicholson, didn't read those clauses. Those clauses were really devastating. To Nicholson's credit, he finally decided to get rid of this agency. It was very good for *Science*. I really wasn't responsible.

Hughes: Kerr said that within a couple of years, having a much more efficient in-house advertising unit made up for any money that had been originally lost.

Koshland: That's right. We made tons of money [for *Science*].

Hughes: Abelson singled out Beth Rosner for doing a good job.

Koshland: She was the person.

More on Comparing *Science* and *Nature*

Hughes: When you were chief editor, how well do you believe that *Science* stayed in sync with the scientific enterprise?

Koshland: I think very well. I don't think there's a criterion. I think we probably even did a better job than *Nature*. They were the big competitor. They did a very good job. Most people would say it was pretty close. *Nature* never had the system that *Science* has of long, two- or three-page news articles on a subject. *Nature* almost invariably had articles that were only a column or two columns long. They covered the panorama of science more comprehensively. They routinely went to Yugoslavia, Russia, Italy. But sometimes nothing very much happened in, say, Italy that month, and they felt they had to cover the fact that the minister of something resigned. Well, you know, here from the United States you didn't give a damn if the minister of something in Yugoslavia resigned. We had much more interpretive articles, which would cover Italy, say, once a year or once every six months. In many ways, we weren't covering it as well as *Nature*, and in many ways we were covering it in a way that non-Italians would understand better. It depends on where you're looking at it from the point of view of an Italian or a non-Italian.

But I would say we were very much in tune with scientific developments. The science was clear. That's very competitive. It was a lot of prestige to publish in *Science*. We'd get articles from all over the world. We had to be very careful because people would be very upset if they didn't get published. In Italy they'd jump to the conclusion we didn't want articles from Italians. Just the way American physicists were upset because they didn't get an article on physics published. They said, well, Koshland is only interested in articles on biology.

Science magazine, when I left, was accepting one out of ten articles. See, people would send their absolutely best articles to us. Of those best articles, we took only one out of ten. My friends from Berkeley would say, "Dan, I sent you the best article I've published in ten years, and you turned it down." I said, "You know, everybody else who sent one in said that was their best article in ten years." It's a very small magazine. Only a fraction of it is biochemistry.

Hughes: Can you think of instances when you believe that *Science* magazine shaped contemporary science?

Koshland: Not in the sense of the conscious direction of the editors. We pushed science all the time because we published the best new science. Then people could read that. For example, the famous PCR [polymerase chain reaction], which you hear a lot about in biotech. We published that paper, so it was very important that paper get published because everybody did it. We accepted it just as a very good paper. It wasn't because I brilliantly decided PCR would be very good for everybody to have.

News Embargoes

Hughes: Do you want to comment on the tensions around news embargoes?

Koshland: Yes. *Science* magazine publishes very hot science. Newspaper reporters want to publish exciting science. They've learned that *Science* and *Nature* are two of the best sources. To make a long story short, when *The New York Times* wants to cover an exciting article, they like to have an in-depth story where they not only report the science which is there but they can also call up the author and find out what he says about it and get a little more background. Journalists don't want the detailed science that we have in a *Science* article; they want the implications and the concept.

It is convenient for them to write a story ahead of time, to get this background, so that when the story comes out, it will appear in the papers. So *Science* and *Nature* generally publish the table of contents a week ahead of time, and then we generally publish in addition the phone numbers and addresses of the scientists who have written the article. That means that a week ahead of time, journalists know what's going to appear in *Science*, and they can phone the people and really get a good story.

The tradition is that the news stories are embargoed, meaning that nobody can publish until the journal appears. Everybody is equal. Every once in a while, a paper breaks the embargo. We get very angry at them. The minute they do that, they're crossed off our list. We don't send them information in advance of publication. People who don't know what they're talking about say the embargo system holds back information. Well, it's a week at the most you can't let the story out. By doing it in this orderly way, you don't play favorites.

Suppose somebody breaks the embargo. Then what do you do? Do you hold firm with other publications? Sometimes they come around to me and try to explain. I say, "There's absolutely no excuse. If you got the story another way, then the minute it came across your desk, you should have phoned me up and said, 'We didn’t violate the embargo; we've got the story from another source.' But you don't tell me after the story's released, 'We got it another way.’" I was very, very tough on that.

The second type of problem concerns the scientists publishing the articles. Let's say there's a story on a cure for cancer. We say we're going to release it to the press, and it will be covered by *The New York Times*, but we can't have you releasing it from your own university ahead of time. If the university wants a press release on it, that's all right with us, but it has to have the same embargo date.

A scientist goes to the American Cancer Society meeting and gives a paper on a discovery. In the past we said, "If there's an enterprising reporter that goes to the sessions on cancer and is smart enough to understand them, we're going to take that chance. It rarely happens. Occasionally a news article will appear on a *Science* article in press because an author has given a report at the Cancer Society meeting. We didn't want to be in the position that dirty old bosses like Koshland just want to increase the subscription of their magazine and so they prevent people with cancer from being treated expeditiously.

Hughes: Well, that is a point that some of the AIDS activists made.

Koshland: That's right. At most, the delay in publication would be a week.

Hughes: Dan, I'm at the end of my time and I'm sure your patience, but is there anything in summary that you want to say about your ten years at *Science*?

Koshland: I really enjoyed it. I had a great time. It was a big challenge. I liked the people there. I argued with the executive officer about the budget--I had some pretty strong fights—-but we ended up friends.

Hughes: Do you think your science suffered?

Koshland: Oh, I'm sure. I kept my lab the whole time, and we published, I would say, half as many articles as I normally publish. I think it's clear that I would have published more if I had not been editor of *Science*. On the other hand, it was fun. It was a good vacation. I'm probably more enthusiastic about doing science now because I took the time off. So it was a good episode.

Hughes: Well, I thank you. [End of Interview]

Interviews 12 and 13 are appended at the end of this volume as they appear in the oral history volume “The Reorganization of Biology at the University of California, Berkeley.”

Interview 14: May 20, 1999
[Begin Tape 23, Side A]

Approach to Scientific Research

Hughes: Please comment on your philosophy of science.

Koshland: I'm not sure I have any well thought out philosophy, but in terms of looking back empirically at what happened to me, I basically am an experimentalist. On the other hand, I always liked theory a lot because I am mathematically inclined. I would say something like a tenth of my papers are pure mathematics or mathematical theory. This is a little unusual for biologists and probably was caused by the fact that I started out liking math and then, because of the Manhattan Project, ended up in chemistry and physics, which has much more mathematics than biology. So then when I eventually got to biology, which is really what I was intending to do if the war hadn't come in between, I had done enough math that I really tended to use it as a tool, whereas a lot of other biologists didn't or shied away from it.

Hughes: So the war shaped--

Koshland: The war did probably influence that aspect of my career. I really like math, and I would think of research problems in terms of trying to get a theory for them. That permeated a lot of my thinking because almost invariably, when I design experiments, I have some pretty good idea of what I expect the results to be. I tell my students. "You must not get your ego involved in the answer." In other words, it's really good to have a hypothesis because it helps you design the experiment. But you recognize that you're going to be wrong a fair number of times [about what you expect to find]. So you've got to be open-minded if the experiment turns out differently from what you expected.

I did a lot of research on the edges of science where you're about to step over the precipice. Induced fit was really a big leap in the dark at the time I proposed it. I had done a number of things from the theoretical point of view that indicated to me I was probably likely to be right. But a lot of people didn't think so, and there were some arguments. In order to establish the theory of induced fit, we had to demonstrate it experimentally. In recent years, I have been doing some work proving a theory of orbital steering, which is something I proposed entirely based on mathematical deduction and calculations. It was very controversial at the time it was proposed and has turned out to be correct.

I would say [experimentation] is 90 percent of my activity. But I've always been very much guided by my theory of how I think things work, either chemically or biochemically. I was saying [to someone that I based my experiments on] theory, and they said to me, "Dan, that's probably why you've never had to retract anything." It probably is true, because I have a background in theory. When I've said controversial things, I've always had a theoretical background for them. So when I do experiments, a sort of general understanding has been helpful. It tells me, this experiment [I'm considering] really sounds crazy. It doesn't fit in with any of my theories, in which case I just do the experiment a different way or do it over again or double check. And then it usually warns me, the first experiment wasn't right. Contrary to what most people think, you can goof an experiment as well as you can goof a theory.

There are a lot of experiments that are just routine. If you want to lay down a road over the Appalachians which is similar to the road over the Rockies, that's an experiment. But basically, it's a very standard experiment. The road may be over different mountains, but it involves just the standard way of building a road. On the other hand, if you want to make a suspension bridge across Golden Gate harbor and it's the longest suspension bridge in the world at that time--which it was--then you're straining the limits of what everybody knows about engineering and suspension bridges, so you're really taking a chance in not doing something that's routine. What I'm saying is, when you're applying new theory or new experiments that are very complicated, it's really good for the experiments to augment the theory and vice versa. So I think that has been very close to the way I operate my research almost on a day-to-day basis. I almost always have some kind of theory behind what I'm thinking about.

I'll give you an illustration. In the early days, when I was working on chemotaxis, a man named Adler, a very fine scientist at the University of Wisconsin, and one of the students, Parkinson, had done a little genetics, and they showed there were four genes that were identified with chemotaxis in bacteria. I really had no training in genetics and had very little knowledge of genetics; I was a biochemist, and my own instincts were, this system is far too complicated to be controlled by four genes.

So in spite of the fact that everybody accepted that finding, I said to myself, we'd better find out if there are more genes. I had a postdoc who was, like me, a biochemist, a very smart person but with no genetics training. We said we've got to do this genetics. Bruce Ames and several other people in biochemistry at Berkeley were really knowledgeable about genetics, so I asked them. They gave me some articles to read on what I should do. We proceeded to do the genetics, and we just had to learn our own way. We used classical genetics and very well-known techniques. We ended up finding eight genes, which struck me as much more likely as the answer. Using an analogy: Columbus has an idea that the world is round, so he keeps going, instead of going the first five miles and saying, "I'd better turn around and go back." Sometimes I've been spurred on because I really thought I knew the answer, and I'd better not give up at the first indication that I'm not getting the result I want.

Hughes: The idea that there might be more than four genes, was that a hunch or were you basing it on some theory?

Koshland: I don't know what you call it. It's just that of all the biochemical pathways I knew, very few had [only] four enzymes. A gene generally codes for an enzyme, so when you say four genes, you mean four enzymes. Most of the pathways that I knew about had more then four steps, although there are some that have four steps.

Induced fit--I really felt there were a bunch of anomalies that didn't fit with the old theory, and then when I proposed the induced fit theory, it all fit in with my own ideas about how proteins work, you see. I knew a lot about proteins and therefore could apply this [knowledge] to the new situation. So that's where the theory comes in and where it's more than a hunch. But, on the other hand, it's not really solid. I mean, other people hadn't perceived that. So you're taking a jump in the dark to some extent. I tend to extrapolate from very little data. People kid me all the time about how little data there are in my articles; I jump to conclusions.

I come from a very secure family and had a very good marriage. That gives me an enormous amount of security, and that did affect the reorganization, where a lot of people were very angry at me. My parents expected me to do good things, but if as a result a lot of people were angry at me because of something I believed in, my parents wouldn't desert me. I knew that. And the same thing was true in my marriage. That gives you a lot of extra courage about taking on difficult problems. That is where the intersection of scientific philosophy and what you actually do in your life becomes important.

Philanthropy

Father’s Philanthropy

Hughes: The next subject is philanthropy. I want to start with your father because a colleague of mine, Eleanor Glaser, told me that he had a philosophy about philanthropy. I wonder what it was and whether it was passed down to you.

Koshland: That's difficult. My father was not articulate, but he was an absolutely wonderful role model, so it was passed down to me--whether it was passed down in words, I don't think so. I have his oral history,[33] and I don't remember reading anything about his philosophy of philanthropy. But I will tell you what it is.

He was an extraordinarily philanthropic person, just because he had an unbelievably warm feeling for everybody. There were people who said, "You ask Dan Koshland for something, and he just won't say no." Which wasn't true. My father really had some pretty good standards, and there were a lot of people he said no to, but he was very reluctant to say no to anybody who had a really good cause.

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[33] Daniel E. Koshland, Sr., "The Principles of Sharing," an oral history conducted in 1968 by Harriet Nathan, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1971.

We grew up at a time when Levi Strauss [& Co.], which is the firm he was in with his brother-in-law [Walter A. Haas, Sr.][34], was a good but struggling business. In fact, there were four overalls companies in San Francisco at the time of Levi Strauss. It was during the big Depression, 1933. At the end of the Depression, three of them had gone bankrupt. So it was a very competitive and tough business. I mention that only because now Levi Strauss is a very big firm and very successful, and lots of people today think it was always successful and always very good. The net effect was that I lived comfortably all my life, but it wasn't a big fortune. I knew we were moderately well off. We had more things--two cars--and a lot of families only had one car, and things like that. But I wasn't really sophisticated about the ways of the world.

My father was very generous with his money. But the most important part was he always really gave of himself. I'll give you two examples. We were on a picnic once, and my father said, "We've got to get back by five o'clock" or something like that. I said, "What's going on?" He said he was meeting an author who wanted a little money to finish his book. He didn't have enough money to survive without having some money. I asked my father, "Why do we have to get back at five o'clock?," when this guy was coming at six. We were all having a good time at the picnic. "Oh," he said, "I've got to finish the book. I've read a good part of it." I said, "What do you mean, Dad? You're going to give him money, aren't you?" And he said, "Of course, but I want him to feel he's earned it because he wrote a very good book, and I've got to read the book to be sure it is." I knew the amount of money he was going to give would not have upset his standard of living very much. Moreover, my father was very generous, and I knew he would give it to him.

But that taught me a lot. If you want to talk about handing down a philosophy: my father felt that it would give the author confidence in himself, and it was sort of a compliment that my father had read and really liked the book. My father gave to people just totally freely, never made a quid pro quo stipulation--you're supposed to give it back. He had the most incredible record of people either giving the money back or giving it to somebody else.

I remember some very poor kid who was the son of one of the garage mechanics my father met in San Mateo, which is where we lived. He put this kid through dental school. Then, when the kid finished dental school, he came to my father and said now that he was earning a lot of money, he'd like to pay him back. And my father said, "I don't want you to pay me back. Give it as a scholarship to the university or something like that," which the person did. There were all sorts of incidents like that.

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[34] Walter A. Haas, Sr., "Civic, Philanthropic and Business Leadership," an oral history conducted by Harriet Nathan in 1971-72, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1975.

Hughes: Does the term "federated giving" ring any bell?[35]

Koshland: A lot of people give to the Jewish charities or the Catholic charities, and those are standard kinds of things. But then there were a lot of things, like Boy Scouts and Girl Scouts, which in those days--this is now a long time ago--didn't have big arms to raise money; didn't have priests and rabbis who would go out there and get money. My father thought of having all such organizations lumped together as a group, which was called in San Francisco the Community Chest and also called the Jewish Federation of Charities. So those people went out and got money.

In the case of the Jewish Federation, there's the Jewish home for boys, and there's the Jewish home for elderly people, and there's the Jewish home for immigrants. The Community Chest did something similar for the Boy Scouts and the Girl Scouts and the Red Cross and things like that. My father decided it would be better to have one unit that went out and raised money and then distributed it to all these other organizations. And so that is probably what is meant by federated giving.

The Community Chest was a big success, which then later turned into United Way. I wouldn't want to say my father started it for the whole country because there probably were people like him that started it in other places. But certainly the San Francisco one I know he started, and it developed into a much bigger thing. My father also started the Council for Civic Unity. He perceived in World War II that there were going to be a lot of blacks moving into San Francisco--

[End Tape 23, Side A. Begin Tape 23, Side B.]

Koshland: --and he got a lot of business and labor leaders and social workers to welcome blacks to the community. That became a very successful group.

Hughes: When did he start the council?

Koshland: Probably '41 or '42.

Hughes: During the war.

Koshland: During the war, because that's when the build-up of industry started, so it was around the forties, I guess. He was a very prominent businessman by that time, and he lent his name to this organization and was a very prominent figure in it. That, of course, gives courage to more timid souls. They can always say, "Dan Koshland is doing this, and I'm a minor official in not quite as big a firm. It means that I'm not being an idiot and sticking my neck out in supporting the Council for Civic Unity."

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[35] Phyllis Koshland Cook suggested that Mr. Koshland used to discuss the concept of federated giving at the family dinner table. (Telephone conversation with Sally Hughes, April 2, 1999).

During the sixties, when Berkeley had all the riots and the left wing--the anti-Vietnam people--was denouncing the government. My father appeared with my uncle [Walter Haas] and one or two other people, and they were the main ones who appeared in Sproul Plaza to defend the university. I know the chancellor [Clark Kerr] was very pleased with that because he was worried a lot of the wealthy donors to the university would decide they didn't want to be associated with such a radical organization.

Hughes: Your father's motivation was to dispel that concern?

Koshland: Exactly, that was it. So they appeared, and it was in the headlines. My uncle was also a very loyal supporter and perfectly willing to have his name [associated with the university]. That's probably related to this whole family [solidarity]. It was a very close family--there were one or two fights, but mostly we liked each other And so there was a lot of security in it. What really stood out for me is my father felt a very great obligation: we were very lucky to be as wealthy as we were and that we ought to pay it back to the rest of society. By that he meant not just money but also time and effort and understanding.

We went to New York once when I was very young, about ten years old. (My mother had a number of friends and relatives in New York.) My father said, "There's something we're all going to go to on Tuesday morning." He wouldn't tell us what it was. Tuesday morning, we all got dressed up. We didn't know if we were going to go to the zoo or the Statue of Liberty, and my father announced that he was going to take us to the ghetto in New York City.

Hughes: Harlem?

Koshland: Not Harlem--I think the Lower East Side where the poor Polish, Jewish, and other immigrants lived. The main point was to show us very poor people. He was teaching us a lesson, that we were living in very fancy hotels and eating out every night, and here were people who had to worry about the next day's meal and clearly didn't have good clothes. He was just reminding us that we were extraordinarily lucky, and he would expect us to do something with our lives.

Hughes: He wasn't any more specific than that?

Koshland: No. In fact, he didn't say anything. He just wanted us to see it. That was the whole lesson; we never got a lecture. So that, I think, was his philosophy. He just lived a very fine life.

My mother was probably more articulate than he was in many ways. She was much more of an abstract thinker. Probably I get that from her more than I got it from my father. He was a Phi Beta Kappa. He was not dumb. But he was not as articulate as she was. On the other hand, he made it clear what he felt.

Personal Philanthropy

Hughes: When I talked with Diane Portnoff [of the American Committee for the Weizmann Institute of Science] today, she said that you have a reputation for being an independent donor, meaning that you don't necessarily follow along and support the charities that other people are supporting.[36]

Koshland: That's correct.

Hughes: What are your criteria?

Koshland: That's a good question. Some of these things I haven't even thought of before you asked me. I give to things that are not that different. I give to the Jewish Federation, which is an organization my father gave to, and I think it's good. I give to the Red Cross, which is a very standard kind of thing. So I don't really think I'm very original.

On the other hand, my wife [Marian “Bunny” E. Koshland] and I set up a fund with the San Francisco Foundation, which has turned out to be very successful and which I'm really quite proud of. It was my wife's idea. She was reading in *The New York Times* about this young kid who came from a very poor family and had dysfunctional parents. And this high school kid went out and got a job and was bringing up his two little brothers, providing the money and the supervision for them. And so this kid was not only going through high school but supporting these two younger siblings. Bunny and I were discussing the situation, and she said, "We ought to do something. There are a lot of college scholarships, but I don't know of any scholarships for high school kids, and I'll bet you there are a lot of kids like this." So we gave a fair amount of money to the San Francisco Foundation. When I went there, they assigned a very nice person [Adrienne Klug] to me. We originally sent a letter to the various high schools which described this article we had read, and asked, were there students who were holding their family together?

My reaction at the beginning was that the social workers assigned to me were all trying to rescue kids who were marginally on drugs. I said I wasn't interested in that kind of person. I was interested in a kid who really had it all together but had shouldered a lot of responsibility that he didn't need. The social worker who was working with me finally recognized what I was saying. I shouldn't say "finally"; she was a very smart person. She kept saying, "Well, maybe we ought to pick so and so." And I'd say, "This person has a low grade-point average and is never going to be a leader in society. And this other kid has put it all together, and he's getting good grades. You know he's going to make it." We picked a certain number of minority kids. I really wanted kids who were going to be leaders, who would then go back to the ghetto and be the leaders in the black community or the

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[36] Telephone conversation, May 20, 1999,

Mexican community. I said, "That's going to be a lot better than rescuing a kid who was going to be on drugs." I think it's worthwhile that you save him from drugs, but he's never going to amount to anything anyway. It's much better to help these other kids.

I interviewed the first people myself, with her. These kids were so unbelievable, you can't imagine. There was one little girl whose mother was mentally ill, totally wasn't doing anything, and she was raising money for her mother and putting herself through school. She was planning not to go to a university just because she was going to have to take care of her mother for the rest of her life. Anyway, we gave her money. And she wrote the most unbelievable letter you've ever seen--it brought tears to my eyes--saying that it was the first light she had seen in her life. She for the first time saw that she could go to college, and she wouldn't just have to take care of her mother for the rest of her life. And then there was a little kid who came over with some of the Vietnamese boat people. The parents didn't speak English, so she had to handle all the bills and everything for the family, in addition to raising money and all sorts of things. I mean, unbelievable. I was going to give one scholarship a year, and I gave three because there were so many good kids.

Hughes: For a year of education?

Koshland: I think each of the children get five thousand or ten thousand dollars. My condition on the money is, they have to use it to further their own education. All of the kids are so nice; they immediately want to use it for their family problems. It's administered by the San Francisco Foundation. Now that other people have heard about it, they're contributing added money. That's what I'm doing independently.

I'm very tough about the money having to be used well. I give a fair amount to the Salvation Army, which is tied up in some ways with the Christian church, and I'm Jewish. But I really think they run their organization very well; money goes to the people who need it. I think the Red Cross is just a superb organization. They're there when they're needed, and I like to give to them.

Hughes: How do you determine that the funds will be used well?

Koshland: Oh, I read their brochures and I know a little about the organizations.

I've given a lot to the University of California more recently. I didn't do very much charitable giving when I was younger; I was concentrating on being a scientist. So I've done more charity since I've gotten older. I've said to my children, they should not worry about charity till they're not good for anything else.

The Jewish Federation came around to me about giving an endowment. I asked them what kind of control they have. They give to various organizations--Jewish Home for the Aged, the Jewish camp for underprivileged kids. I said, "How do you check up on these institutions? I'm not going to give an endowment unless you have an institutionalized procedure. If I'm giving an endowment, that's forever."

Anyway, they set up procedures. So now you can see a pattern: I'm not a really generous person; I'm just so unpleasant about [my philanthropy].

Giving to the Weizmann Institute of Science

Hughes: The Weizmann Institute of Science is also one of your interests. What inspires you to continue to support it?

Koshland: The Weizmann Institute is a very prominent institute in Israel. I was originally invited over there to give the Weizmann Memorial Lecture [1971]. They have one usually fairly prominent scientist give a lecture a year, so you're invited to come to Israel and give the lecture. I went over and gave the lecture, and they were all very nice to me. They were very good scientists, too. It and Hebrew University are <u>the</u> big intellectual centers in Israel. It's a very small country, but Jewish culture is very much identified with intellectual life. They were in a very poor country that needed help.

So when I came back to San Francisco, I said, "We ought to organize to raise money for the institute." There were a bunch of other Jewish organizations that had units in San Francisco, and the Weizmann Institute didn't. So I helped them organize it right from the beginning. I arranged to have luncheons where we had famous scientists who were visiting here from Israel give lectures. I set it up so that we weren't to ask for any donations because the people were going just to learn about science. This really got the paid directors nuts. They said you don't get people together without asking for money. I said, "We've got to deliver a service for a while, so anybody who wants to come, comes. Once we've got them hooked, then you start asking for money." Then gradually we did ask for money. People thought this was a good idea, and so they started [fund raising for the Weizmann] in other cities around the country. I was asked to be on the board of governors of the Weizmann, and so I became more and more involved.

Hughes: The Bay Area Committee for Weizmann was founded in the 1970s, and you were the first chairman.

Koshland: Right. There was probably nobody else who'd do it! It wasn't a big honor. I'm cynical about awards. I think they give you awards because then they can have a dinner where they invite a lot of other people who they ask to raise money. But the Weizmann is a very good organization. It's run very well, and I've been very pleased, so I keep giving to them.

Hughes: Do you have a special place in your heart for science when it comes to charitable contributions?

Koshland: Yes. The Weizmann combines science, Jewish things, and Israel, which I think is an underprivileged nation that needs help. It's a good combination, so I continue to give to them.

Hughes: Diane Portnoff told me that you're particularly interested in supporting young scientists.

Koshland: That's pragmatic. Diane knows what I've given at the Weizmann Institute. the Weizmann Institute needed support for young scientists. There were older scientists who built up big groups; they had worldwide reputations. A lot of the young Israeli scientists would want to go back to Israel after they'd finished their postdoc abroad. But then there was no money, so they had to work for the famous scientists in order to earn their salary. I said that was really a bad feature of the institute, which I'm sure they really didn't like themselves, but they didn't have enough money.

I gave some money to provide a fund so young scientists could work independently. Young scientists could learn a whole new field that wasn't being done in Israel at all, and the Weizmann could support that. Moreover, giving in that way would set a standard so that Weizmann could go to other donors and get more money for that [purpose]. And that has happened.

Giving to UC Berkeley

I've given a lot of money to Berkeley in recent years. Part of the reason I give as much to Berkeley as I do now--and I've given a fair amount--is they named that building [Koshland Hall] after me for work I did. I gave no money for that building.

Hughes: You mean the work in the reorganization of biology at Berkeley?

Koshland: The reorganization. The chancellor named the building after me, which was really so surprising.

Hughes: That's unusual, isn't it?

Koshland: <u>Very</u> unusual, particularly because I was alive! A bunch of professors went to the chancellor, and then the chancellor said it was okay. I found this out afterward. They didn't say a word to me before they told me about it. I thought that was really very nice. And I really had spent a lot of time on the reorganization. I hadn't given much money to the university before that.

Hughes: Was there a reason?

Koshland: Well, there was a quasi-reason. It would be nice to say I didn't go into my father's business because I wanted to see whether I could succeed on my own. Right from the beginning, I really loved science. I didn't undergo any sacrifice by giving up the business. I was really concerned that it had hurt my father's feelings that I didn't go into his business. He was wonderful; he said it didn't matter at all. I don't know whether it did. I think he never would have said it to me if it had. But certainly I was under no pressure whatsoever to go into business.

My mother wanted me to break out of the family, for the reason that my father and mother were first cousins. There are still some people who think that marriage of first cousins is bordering on incest. There's no incest in California [law] for first cousins; it's only for brothers and sisters. My father and mother fell in love, and they decided they were going to get married. They went to the chairman of the genetics department at UCSF--they told me this later--to ask whether or not they should have children. They said they were going to get married anyway, but if it was really bad to have children, then they would adopt children.

My parents investigated the family history and, in fact, there was no evidence of genetic defects. So they had three children--myself and my two sisters. My younger brother, who died at birth, died from Rh [factor incompatibility], which had really nothing to do with heredity; it has to do with the immune response. Anyway, my mother felt strongly that she didn't want it to happen again. We have a big family, and there were a lot of cousins my age. So she was really delighted when I married totally outside the family. She wanted me to break out and do something different.

Endowing a Science Museum in Memory of Marian E. Koshland

Hughes: In memory of your wife, you are giving a science museum at the National Academy of Sciences.

Koshland: Correct. What I've done recently is give where I thought the gift would advance something really original, and particularly something that I'm able to evaluate. I thought that was a little bit following in my father's tradition. I mean, he gave in areas like the Council for Civic Unity because he knew a lot about social work; I've given in the area of science.

I was really very upset when my wife died, and I wanted to do something to make me feel that her life was not in vain. It was a great marriage. I was very much in love, and it was very traumatic. I was on the council of the National Academy. That's the governing board. Bunny had been on many committees there, so they knew her very well. She was a very good member of the Academy.

One of the things the Academy was concerned about was the public understanding of science. There was a committee on the public understanding of science, and she was on it. It was an area that I knew she had been prominent in, and I was really involved in. I thought she was also an interesting role model for young women scientists. So I went to the president of the academy [Bruce Alberts], who's also a friend of mine and my wife's, and said, "Do you have anything to which I could donate to perpetuate her memory?" Bruce said, "Well, we've always wanted to have a museum for the public understanding of science, where tourists would be exposed to how science works." I said, "Fine." And so we're still working it out. I promised him I'm giving the money. I kid him all the time: a man gives a ton of money to the academy, and then I have to work like a dog. It doesn't seem fair. [laughter]

[End Tape 23, Side B. Begin Tape 24, Side A.]

Koshland: I'm on the [building planning] committee. The building will be on the Mall [in Washington D.C.]. The National Academy of Sciences is on Constitution Avenue, which is on the Mall where the Lincoln Memorial and the Vietnam Memorial and so forth are. That area is controlled by Washington commissions. It's really choice real estate. It will be a very good place. There's an Einstein statue on the grounds of the National Academy, which is visited by lots and lots of tourists. I've been there; it's practically never empty. People come and put their child on Einstein's lap and take a picture, and scientists come by and want to take a picture next to Einstein. So they thought it would be great to have a museum nearby which showed how science helps society, and it would be in a very prominent place. So we're working on it.

Community Service

Hughes: There is a family tradition of community service.

Koshland: My father was very active in all sorts of things, and I followed in that tradition, and so did my sisters.

When I lived in Bellport, which is near New York City, we were working for Brookhaven National Lab, and we had five children. They asked me to run for the school board. I was about thirty-five, which is a very important stage in any career. My science was going very well. I was asked to go to a lot of places to give speeches, and I had five kids, so there was enough pressure. So I told them I just couldn't do it; too many things going on in my life; I couldn't run for the school board at the same time.

I came home for dinner and was discussing what happened during the day. I said, "Oh, by the way, they asked me to run for the school board, and I told them of course no, I can't possibly do it." My wife says to me, "Oh, you did! Well, you have five kids in that school. You just go phone them right up and tell them you'll run." [Both chuckle.] That was an edict from my wife. So I phoned them up and said, "All right, I'll run." Nine years later, I got off the board by coming to California. It's a three-year term. Each time I said, "I'll serve my term and then Bunny will let me get off the board." There was always some crisis. I was fairly popular with a lot of people, so they really wanted me to run. In the third or fourth term, I was elected chairman of the board, and so that added work. But it was a very good experience. I enjoyed it.

Teaching a Freshman Course

Hughes: I read that last semester you taught a freshman seminar called, "Does Science Bring Happiness or Simply Technological Advances?" It isn't a usual thing for a full professor to do.

Koshland: Correct.

Hughes: Why did you decide to teach it?

Koshland: Number one, I really like to teach. I like to do research, so I don't want a really heavy teaching load. I consider it fun to teach, and I always did. I enjoyed pontificating to students and cracking jokes which they have to laugh at or they know they won't pass the course.

The university has--it wasn't my idea--a project to have senior professors give elementary courses, freshman courses, so a certain number of kids would have direct contact with a professor their first semester here. I think it was started by [Chancellor] Chiang-Lin Tien and then has been supported further by [Chancellor Robert] Berdahl. I felt it's a very worthwhile project. Somebody asked me would I teach a course, and I said, "Sure." The seminar is limited to twenty students because they figure that's about as many as you can get to know.

Hughes: Did you have them read?

Koshland: Oh, yes. They gave me no guidelines, and so I had to make them up. The first essay I gave them to read was a philosophy essay on happiness. The purpose was to get them to really think.

Hughes: Did the students seem to enjoy it as well?

Koshland: They seemed to. Remember, the course was totally voluntary. Well, they did get one unit of credit, but considering the amount of time they spent, was one credit worth it?

Awards and Prizes

Hughes: Which ones of your many prizes and awards are you most proud?

Koshland: Ah, that's difficult. I would say the first time is the best. [skimming awards listed in his curriculum vitae] The first award I got was the T. Duckett Jones Award of the Helen Hay Whitney Foundation [1977], which was early in my career. I was given that utterly out of the blue. I never even knew it existed before I got it.

Hughes: What was it for?

Koshland: It was for biochemical research. [reading CV] The Waterford Prize, the Scripps Institute [1984]. That was a fairly well-known prize. I enjoyed getting that. It was a nice one. After that I got the Rosenstiel Prize [Brandeis University] that year. Those are all good awards. They were the first.

I remember George Bernard Shaw's statement that love is a great exaggeration of the worth of one person over the worth of everybody else. I feel that a little bit about prizes. Most of these prizes could be given to any of a hundred people. It's sort of like winning the gold medal in the Olympics: you usually do it a tenth of a second faster than the person next to you. It's nice to have other people verify that what you're doing is important.

I am very pleased with my son, Douglas, who is a scientist, a professor at Johns Hopkins and at Carnegie Institution in Washington.[37] He went with me when I got the National Medal of Science [1990], which is given to you in the White House by the President of the United States. It is a very fancy ceremony and pretty prestigious. My wife was there. I didn't have my other children come because Douglas was living right nearby. I felt traveling a long distance just to watch Daddy get an award wasn't really good use of your time.

I always said to the kids that I wanted them to go into a profession--or a job; it didn't matter whether it was a profession or not--where they really enjoyed doing their work. I said that's the biggest reward in the world. I said it is crazy to work at something you don't enjoy because most of your waking hours are work. To work most of the time at something you really hate, in order to get enough money to enjoy your weekends, is a really bad distribution of time and effort. My daughter, Phyllis, once said, "You put the worst pressures on us. You say, 'You've got to pick a job you really enjoy.' Most parents say, 'You get a job; we're pleased with you.'"

Douglas said, when he walked out on the platform, "Dad, I understand why you said, 'Always do something you really enjoy.' You've gotten one of the most important prizes in the United States, and the ceremony took three-quarters of an hour." (It took much longer than that because you have to get security clearance to walk into the White House.) It was a very nice ceremony, and President [H.W.] Bush gave me the award. But it didn't occupy very much of my time, a few hours. So if you spend the rest of your life being happy that you've gotten an award, that's really not a very good way to fill up your time.

I've never worked for awards because it just seems so silly. But if you really enjoy solving problems, which is what I really enjoy doing, then the biggest thrill is solving the problem. I've enjoyed the fact that orbital steering and induced fit are now accepted by everybody. The other day we published an article on orbital steering and somebody said, "Oh, well, that's obvious, isn't it?"

Hughes: But it wasn't at the time.

Koshland: It wasn't at all at the time. Somebody said you don't deserve credit for being smart; you just get credit for living long enough to see that people accept the idea. Honors are a little bit the same way. I'm glad I got them, but it probably wouldn't have made that much difference.

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[37] In 2010, Douglas Koshland joined Berkeley's Department of Molecular and Cell Biology, his father's former department.

Hughes: You received the Lasker [Award for Achievement in Medical Research] last year. Did it come as a complete surprise?

Koshland: I didn't know I had been nominated, so that was a complete surprise. The person who nominated me was Robert Tjian, who was my student and is somebody I like a lot. He's here at Berkeley, and so he got my curriculum vitae from my secretary. He didn't consult me at all about nominating me. So I didn't know till they phoned me up. Then they phone the nominator and ask if he'd like to come to the award ceremony, which Tij did.

I received the Lasker for a number of things. One of them was the induced fit theory. I knew that it had been very successful because it's now in all the textbooks, and everybody refers to it all the time. Some of these awards come when something you did becomes very well known. So that's why it isn't totally a surprise I got an award for the induced fit theory. On the other hand, I had no idea that I was getting this award at this time.

Hughes: The Lasker has been called the American Nobel Prize. It is more than just community affirmation that you have achieved in science. It can lead to much greater things.

Koshland: Correct. It is community in the sense that it's a community of scientists. It's not a community of people in San Francisco. If you got elected mayor of San Francisco, that's an honor. So it is a community affirmation in a sense, and that really is very nice. It is true that in some of the big awards--of which the National Medal of Science would be one, and the Lasker, and certainly the Nobel is the ultimate one--the committees almost invariably pick people who have gotten other awards. A committee can't read all the papers of Dan Koshland and whoever else they're considering. Therefore the Nobel committee sits down and says, "Okay, we'll get a short list of Lasker award winners and people who have gotten the American Chemical Society Prize and this and that." Then they can concentrate on the smaller list to really find out who they want to give the award to.

So you're absolutely right. There's no question that it's very nice to get awards because then it develops other awards. In my life, I have not done things deliberately to get awards. Part of the reason is because I figure the probability is so low, I'm not willing to waste my time.

Hughes: [chuckling] Well, you've proved yourself wrong in that!

Koshland: My philosophy is pretty much I'm going to do what I want to do because it's fun. Then, if you get an award, it's icing on the cake. Robert Woodward at Harvard felt he deserved the Nobel Prize, which he did, and he eventually got it. But he just would go into a total depression every year around the Nobel Prize time when he didn't get it. That seemed to be totally ridiculous.

Member, Council of the National Academy of Sciences

Hughes: I think it's probably not productive to talk about all your memberships on editorial, educational, and governmental boards.[38] But I would like you to talk about the Council of the National Academy of Sciences. It is an honor to be elected.

Koshland: Correct.

Hughes: What are the responsibilities?

Koshland: The council is elected by the members of the National Academy who, as you know, are spread all over the United States, and there are foreign associates, so there are some members who are in foreign countries. The nominating committee screens proposals, so it's a little honor even to be nominated, and then it's more of an honor to get elected because almost all the people nominated are very prominent people. It's a pleasure to get elected or even get nominated for the reason that these are people who are largely looking at your scientific accomplishments. I guess they find out whether you're a nice person in addition, but it's very hard to judge that. Election is sort of a statement [about your scientific accomplishments.]

Hughes: Can any member nominate?

Koshland: Well, any group of members can circulate a petition and collect signatures. The nominating committee usually nominates at least two, maybe three, candidates for any one post. I think most of the time it's two. The council every two years has three new people. That means three people are elected every two years. The year I ran, I guess there must have been six people who were up for election, three of whom got elected. That's a nice honor. Those who elect us are scientists outside your immediate specialty.

The council determines the policy of the National Academy, and the National Academy is a very important group. So it's lot of fun. I enjoy being on it. This is my second term. The chairman of the nominating committee phoned me, and I kidded, "I'm never going to get elected. You might as well face it." He said, "Why?" I said, "Well, I was editor of *Science*, and we were turning down nine papers for every one we accepted, so I figured I made nine enemies for every friend I made. I was editor for ten years, so I don't think there's any scientist left in the United States who still likes me." [laughter]

Hughes: The editorship of *Science* must have made you more visible than practically any other scientist.

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[38] For a list of these memberships, see Koshland's curriculum vitae at the end of the interviews.

Koshland: Oh, yes. Of all the honors you get, I think being editor of *Science* makes you the most visible.

Koshland: The National Academy was formed by Abraham Lincoln. He was very foresighted and saw the rise of science and said the government has to be advised by an independent body. So he formed the National Academy with the mandate that it had to advise the government when the government requested.

[End Tape 24, Side A. Begin Tape 24, Side B.]

Hughes: Isn't the Academy supposed to be impartial?

Koshland: Yes. So if Congress wants to find out whether SST [supersonic transport] was really ruining the atmosphere, or was that just made up, then they'd have a committee of the academy find out. As you read recently, somebody said power lines are causing cancer; the Academy formed a panel to look into it. It gives advice to both the executive branch and the legislative branch.

[End of Interview]

Dan Koshland remembers Marian Elliott Koshland, Ph.D.[39]

Upbringing and Education

[Date of Interview: May 26, 1999]

[Berkeley, California]

[Begin Tape 25, Side A]

Hughes: Please tell me about your wife's upbringing.

Koshland: Marrying her was by far the most important thing I did in my life. It was a spectacular marriage. You're much too young when you get married to really realize all the things that go into it. But she was a most unusual person. I may be prejudiced, but there's pretty good objective evidence that she was.

Family

Koshland: Bunny grew up in a devoted family. The parents were devoted to each other but each was limited in different ways. Her father, Walter Elliott was a decent, honest man. He was a hardware salesman. He had grown up in the South in a family which he believed had been distinguished. I never could figure out how much. And he had southern prejudices. He would talk about his southern upbringing as though it was some glorious past.

His prejudices were important in Bunny's career. For example, when she was in high school, he said to her once, "Can't you bring anybody home whose name doesn't end in -sky or -vich?" He wanted good Anglo-Saxon names. And she did have some friends who were that, but she tended in high school to just like kids and didn’t care about their origin. Bunny never heard any overt anti-Semitism from her father, but when I came along, it became important because I was going to marry her. Her father never said anything to me, but I found out later that he had big reservations. He didn’t hate Jews, but he thought the marriage just wouldn't work. Whatever it was, she just overrode all of those obstacles. If you read that biography[40] of hers she just brought her Jewish friends to the house and did what she thought was right despite her father’s complaints. To be fair, he was always

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39 This interview first appeared in: Marian E. Koshland, “Retrospectives in a Life in Academic Science, Family, and Community Activities,” Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2003.

40 See appendix: Marian Elliott Koshland, "Sheer Luck Made Me An Immunologist," Annual Reviews of Immunology 196, 14:ix-xv.

polite and they never knew he had prejudices, but it was typical of her that she just serenely ignored them.

Bunny's mother Magrethe Schmidt Elliott was Danish and spoke Danish until the time she came to the United States. But she had learned English and came over to the States as an English-Danish teacher. She met Bunny's father, and they got married. She was, I would say, more intelligent and maybe more cultured than her husband but also knew very little about the world.

Bunny grew up in a family that was really poor. For example, she told me that at one time, when it was a nickel apiece to go to a movie, they had a family consultation whether they could afford (four of them) to go to a movie for twenty cents, or whether they really needed that money to buy bread. That's how poor they were. The construction business was not a good one during the Depression.

Education

Koshland: Bunny had a very good high school record, and her mother sent her to some dancing lessons with a very avant-garde woman who was highly intelligent and highly unconventional. Bunny did so well in high school that she wanted to go to college. It was quite clear her parents were not going to be able to help her, so she'd have to support herself. Bunny thought she'd better go to a public school. Public colleges in the East are not as good as they are on the West Coast, and this dance teacher, who took a great interest in Bunny, suggested to her that private schools provide much better scholarships. The tuition costs more, but if you get a scholarship, it covers tuition and room and board. She'd have an easier time than going to a public university, which has scholarships for tuition but not for room and board.

So Bunny went to Vassar. Her parents thought it was ridiculous when she applied. She did anyway and got scholarships for four years and lived in the co-op dorm, the dorm in which girls did everything themselves. So that cut down on expenses. She had a job as a secretary in the art department during all four years. She sewed all her own clothes. She was a very well organized and determined young lady who got excellent grades despite all the extra work.

When Bunny graduated, she wanted to go to medical school, and she applied to schools based on whether she could afford to get there. She discovered that if she went to the University of Chicago, she could sit up all night in a coach seat for some very small amount of money, and she therefore could afford to go to Chicago where she had gotten a scholarship. She decided she had to have a job to survive. So she got a job in a research lab, with a very nice professor, William Burrows. Her professor thought she was very good at research and encouraged her to go on. But he joked saying she would never go back to medical school. She said, "No, no," she was determined to finish medical school. He bet her that she'd never finish. He said she had the research bug. And he was right, she stayed in research. She met me sometime in that first year--I've forgotten exactly when. I was doing research, so she got more and more interested in research and decided that she probably would prefer to go to graduate school rather than finish medical school.

War Work

Koshland: She finished the first year of medical school, and then I went to Oak Ridge [1942-1946]. She needed a job, and so she went to the Colorado Airborne Diseases Project, a war project. [interruption]

Hughes: Do you know how that happened?

Koshland: Oh, yes. Because they were recruiting at the University of Chicago for people to do this project, some Chicago professors were in charge of the Colorado project. She was recommended, and so she decided that she better do that to get some money. I had gone to Oak Ridge. We weren't engaged at the time, but we were very interested in each other. We wrote letters maybe every other day. There was a big stack of letters. So we were clearly very interested in each other.

During that year Bunny visited me in Oak Ridge a couple of times, and we saw each other in Chicago a lot. And then we got engaged and married the following year 1945. And it was a <u>really</u> great marriage. She was a highly intelligent woman. She became a member of the National Academy, a member of the National Science Foundation Board, and so on with many honors. But she was also a great wife and a great mother. She was really a pioneer in the era when it was tough for women to get jobs. A lot of places discriminated but the determination of her childhood came through. She never complained, just persevered and succeeded.

Early Professional Career

Gender Discrimination

Koshland: When Bunny graduated from the University of Chicago [1949], they told her she'd had this spectacular record, but she should never count on working there because they didn't hire any women. Can you imagine? Now nobody would even admit to those sentences even if they did it. But at that time they were proud of it.

Hughes: Was that the only time she ran up against discrimination?

Koshland: Oh, no. For example, after we were married and had children, we went to Brookhaven National Lab. I went into the biology department, and we didn't want to be in the same department so we wouldn't have criticisms of nepotism. The head of the medical department, a Dr. Rogers, I think, said he wouldn't hire a woman. So that was eliminated. Fortunately, the head of the biology department, Dr. Curtis, not only didn't get perturbed by that but also didn't even worry about the fact that we were husband and wife, so he hired her. She did very well.

Immunologist, Brookhaven National Laboratory, 1952-1963

Hughes: What was that job?

Koshland: She was a staff member in immunology. She had her own lab, and she also helped publish the annual Brookhaven volume on biology.

Associate Research Virologist, Virus Laboratory, University of California, Berkeley, 1965-1969

Koshland: In 1964 I was invited to come to Berkeley as a professor, and by then I was pretty well known, and Bunny had published really very good work. My condition was that if she didn't have a job, I wasn't going to come. And so Berkeley offered both of us jobs. Her job was not a teaching job at the time because she said she couldn't do three things--teaching, research, and raising children; she could do two out of three but not three out of three. She would be interested in switching to a teaching job when her kids got old enough to go to college, and that's what happened; she later became a professor of immunology, but at the beginning she chose research and motherhood.

Hughes: Did her first appointment require a special arrangement?

Koshland: Not really. Wendell Stanley gave her a position in the molecular biology department. He gave her a lab and let her do research and gave her money. Then, when she got a start, she applied for her own money, and then paid him back the money he had sort of loaned her in the beginning, although he never said she had to pay it back. I was concerned because I thought at the beginning he would put his name on all her papers. He was a Nobel laureate, so that would raise a question of who had the ideas, but he never did. He was extremely nice to her. He liked her, and she liked him.

Professor of Immunology, Department of Microbiology and Immunology, 1970-1997[41]

Koshland: It turned out in 1970 that the immunology department had an opening, and they offered her a job on the faculty, and her last child was in high school and was about to go to college, so that's what she did. Bunny worked there a few years as a tenure-track person, and then they nominated her to get tenure, and she got tenure, and she was a full member of the faculty.

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[41] As a result of the reorganization of biology at Berkeley in the 1980s, the department in 1989 became the Division of Immunology, Department of Molecular and Cell Biology.

Chairman, 1982-1989

Koshland: Then she became chairman of the department, and it was really a good thing for U.C. The department had dwindled. Professor Weiss went to Israel, and one retired, and one formed a company. So the department was very depleted. Bunny was really crucial in building the department back up. She was instrumental in landing Jim Allison and others like Alex Glazer who wrote that up in the account read at her memorial service.[42] She had a really good eye for picking people. She was really a very dynamic influence in increasing the number of faculty in the department. She became chairman of the department for two terms, and they wanted her to do a third term but she said no.

Hughes: Yes, 1982 to 1989.

Koshland: Right, so that was seven years. That's longer than the usual chairman's term. That was a very happy period. She liked that department, was very pleased with it. She kidded me when I was busy with the reorganization of biology at Berkeley, that the LSB [Life Sciences Building] was a terrible building, and she said she'd never worked in an attractive building in her life, and remember all the things she'd done for me. I said, "You're going to have an attractive building before you retire." And she ended up in a very nice building, Life Sciences Addition, which she loved.

But the important thing about Bunny was that she was a very passionate woman-- passionate about life, passionate about her family, passionate about her science, passionate about teaching, passionate about citizenship, even passionate about her husband. It made her a wonderful yet sometimes difficult person to live with. For example, one of her passions was Christmas and sometimes when I was up at 3 a.m. wrapping packages, I would suggest maybe it wouldn't hurt the kids if all the packages weren't wrapped perfectly. But she would have none of it so we labored on. She took the same care with her students, her civil duties, and her gardening.

Family Life

Koshland: I was so spoiled because when I'd go home at night, I didn't care about having any other social life. I was just perfectly happy to be at home with her. I remember at the beginning of our marriage people would be sorry for me because I had a working wife. The tradition at that time was, the wives stayed home and took care of everything. So because Bunny worked part-time it ended up that I had occasionally to do chores for the family. She did almost everything regarding the family, but I had occasionally, for example, to pick a kid up at the dentist. [interruption] But the conventional people would imply that that was something the wife should do, but it meant in our life that we both worked at night because she

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[42] Marian Elliott Koshland, 1921-1997, Memorial Service, December 1, 1997, University Art Museum, University of California, Berkeley.

didn’t need the entertainment that a wife who’d “labored over a hot stove all day” felt was required at night.

Evening Routine

Koshland: We had a routine every night. We'd get home about quarter to six, and generally Bunny and I would have a drink before dinner and would start to hear what was happening at school.

Hughes: So the children were present?

Koshland: They were all there. Bunny would be cooking and the kids would start talking and telling what had happened at school that day. But we always all had dinner together. There was a rule that everybody in the community knew about: the Koshlands didn't go out in the middle of the week. Monday to Friday with both parents working, we'd always have dinner with the kids.

At the dining table Bunny was unbelievably relentless about going around the table and quizzing the children on their school day. The tales were usually random during the cocktail hour but dinner was really the time to tell all. She'd start with the first child: "How did it go today?" The child said, "Well, it was wonderful." She said, "What do you mean by 'wonderful'?" They still remember that. They mentioned that in the memorial ceremony. All remembered the grilling they got as we went around the table. A lot of people commented to me afterwards that they were going to start doing it with their children. Douglas, who was the youngest, complained bitterly because as the others left home he was the only one left at the dinner table, so he got the full weight of both parents for the whole dinner. She was really a wonderful mother.

Hughes: Did the children learn to tell in full about their day? Or was it always a struggle?

Koshland: They got so they learned how to do it. They knew that their account couldn't be superficial.

We frequently started dinner late because Bunny would come home and she'd cook really excellent meals for all of us. Remember, there were seven people at dinner every night. We'd sometimes be in houses where working women complained that they were worried about a big dinner party for five people. Bunny was cooking for seven people every night of the week, and they were really good meals. The kids just got used to that.

After dinner we parents would split up, and she'd read to a couple of them and I'd read to the others, based on age levels. We'd put them all down around nine o'clock, and then we usually both worked from nine to twelve. We'd read articles or write up notebooks. Not every night; sometimes we went out. It meant that instead of coming home to a wife who said, "I've been working at a hot stove all day; I want to go out," I had the luxury of being able to work at night because my wife wanted to work, too.

Sharing Scientific Interests

Hughes: Did you talk in detail about each other's science?

Koshland: Not really. It was really wonderful: she was in immunology, which has a lot of biochemistry in it, so I understood what she was doing, but I never became enough of an expert to do research in the field, and she understood my biochemistry but she never became that much of an expert at what I was doing. But we understood what each other was doing, and we frequently made comments. For example, I was doing molecular biology, and I was using so-and-so's procedure. She could say, "Oh, I used to use that procedure, but I discovered this new one that was published by so-and-so a few years ago." That was a great help to me. And I did the same for her scientific interests, but we were never expert in the other person's field, and that was fun.

Membership in the National Academy of Sciences, 1981-1997

Koshland: And then, of course, we knew a lot of the same people--science is really a small town. She did a lot of things on National Academy committees, and I was on National Academy committees, so we overlapped quite a bit in discussing things like that.

Hughes: Who was elected to the Academy first?

Koshland: I was elected first [1966]. I don't know how my ego would have been affected if Bunny had been elected first. Of course, she was always pleased that I got elected, and I was pleased she got elected. It was enough of a male world that I'm sure it would have affected me if she got elected first. But the way it was, we both got enough awards so that we got greater pleasure out of the other person getting the award than we did from our own.

Hughes: Her curriculum vitae doesn't give the date she was elected, but I'm surmising that there were not very many women in the National Academy at the time. [interruption to retrieve publication on Members of the National Academy of Sciences][43]

Koshland: I don't remember the date, but there were very few women in the Academy. I was driving one of my daughter's friends home, a very cute little kid. She looked up at me and said, "Dr. Koshland, how does it feel to be married to a woman who's

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[43] Dr. Koshland was elected to the National Academy of Sciences in 1981.

smarter than you are?" I laughed and said, "You know, it's one of the cleverest things I did. I can retire and depend on her anytime I want."

A Major Contribution to Immunology

Evidence for the Clonal Selection Theory

Hughes: Why did she choose immunology?

Koshland: That's described in her biography. She went to college sort of being interested in science, but not that devoted to any one area. Then she had a very excellent teacher in microbiology who got her going in microbiology and immunology. Microbiology departments were usually associated with immunology in those days. When she went to medical school, she got a job in the bacteriology department, though her graduate work was in immunology. So it was a gradual process. She went from general science to bacteriology to immunology.

Hughes: I read that one of her contributions was determining differences in amino acid composition of antibodies.

Koshland: That was a very big contribution. In my opinion, it probably was a Nobel Prize-winning discovery. She discovered the difference that decided between two theories of how antibodies are formed. One is the instructional and the other is the selection theory. She did a crucial experiment that really decided that it was the selection theory and not the instruction theory.

Hughes: Macfarlane Burnett's clonal selection theory?

Koshland: Correct, versus [Linus] Pauling's instruction theory. Bunny did the crucial experiment that could test the difference.

Facing Opposition

Koshland: She would present these results at meetings. She was a young, attractive, blond girl from Brookhaven, an institution that was not as well known as Harvard, Yale, and so on. There was a former Pauling student, David Pressman, who would occasionally get up after her speeches and say, "Well, I can't reproduce your work." I think if Bunny had been at a major institution, they would have just fluffed him off. But because she was a woman and sort of young and didn't have a big reputation, it took a while for her results to get accepted. I was just infuriated by this. I tried to coach her to just look at him very sweetly and say, 'Well, I don't know what's wrong, but I'd be glad to have you come to my lab and I could show you how to do it.'" But she didn't; she was just not going to be belligerent, and she didn't want to have a big fight, so she'd just let it go. But she won eventually; people gradually thought she did very good work. There were a number of people right from the beginning who thought she was right. But she didn't get the recognition she would have if she had been a man from a bigger institution.

Hughes: This was in the early sixties?

Koshland: Yes.

Hughes: People were still in debate about which theory was right.

Koshland: Yes.

Hughes: She was one of the people to swing opinion in favor of the clonal selection theory?

Koshland: Yes. Her experiment was really critical, and then people came along with other experiments, and it shifted for good.

Demonstrating That Different Antibodies Have Different Amino Acid Sequences

Hughes: Can you outline the critical experiments?

Koshland: Oh, the critical experiments are very easy to outline. She used an amino acid analyzer which was a very flighty and fragile instrument at that time. It was invented by [William H.] Stein and [Stanford] Moore, who got the Nobel Prize [1972] for it. Moore in particular was very fond of Bunny because she ran the instrument so well. [interruption]

A lot of people were sequencing multiple myeloma. In multiple myeloma, you make an excessive amount of one antibody, instead of making a moderate amount. It's sort of like a cancer; it just grows out of proportion. There were a lot of big labs all competing with each other in trying to get sequences of myelomas. But there was a real question regarding that work because myeloma is a disease, and so you could not tell whether those antibodies are really illustrative of natural antibodies.

So Bunny devised a system involving two different natural antibodies. She was able, using the amino acid analyzer, to show for the first time that the two antibodies had different amino acid compositions. That really completely excluded the instruction theory. The instruction theory was that all antibodies were exactly the same in sequence, but were molecules that fold around the antigen, which was the noxious element you want to protect against. So they all would have the same amino acid composition but just would be folded in different ways. What she showed is they were formed differently, and the reason they folded differently was because they had a different sequence. Once she determined that, it was unequivocal evidence for the selection theory.

Hughes: Was she the very first to show that?

Koshland: She was the first to show that, absolutely.

Hughes: What had Burnett shown up to that point?

Koshland: Burnett and [Niels] Jerne postulated theories. I don't think Burnett did any more than that. Jerne published a more detailed theory, and later [Cesar] Milstein came up with the monoclonal antibody, which I think was the first application of the selection theory, but was years after Bunny's demonstration. But that was appreciably later [1975].

[End tape 25, side A. Begin tape 25, side B.]

Hughes: Do you remember Dr. Koshland being excited by the Kohler-Milstein discovery?

Koshland: She was very excited by that, yes. It was more that it was an exciting discovery in immunology than that it was a practical application of the selection theory. By the time of Milstein's discovery the selection theory was believed by all.

Hughes: I read that she spent time in David Baltimore's lab, and that it was there that she learned recombinant DNA techniques.

Koshland: Yes, that's where she learned eukaryotic DNA techniques. She had a general knowledge of DNA techniques before, but with bacterial DNA not eukaryotic DNA. The whole idea that antibodies determine the three-dimensional structure was pretty much accepted in biochemistry, but it was not accepted in immunology, and so she had to fight some of the big honchos in immunology to convince them.

Hughes: How could immunologists not think biochemically?

Koshland: It was sort of ridiculous, in my opinion, but antibodies were bigger than enzymes and some (not all) immunologists thought they'd be different. The idea was that two antibodies had to get together--a dimerization phenomenon--and that's the way you influenced the formation of an antibody. The best antibodies were formed against big molecules, like the whole bacterial surface, and a small peptide generally was not a good antibody. The antigen had to be part of a protein to be very antigenic. The argument was that two antibodies had to come together to be active; it was called an association-dissociation model. Biochemists didn't like it as much as her idea, the idea that the three-dimensional structure was determined by the folding pattern. She then took two small peptides and that showed that the amino acid composition of antibodies against them was different, and that clearly was revolutionary. But the immunologists kept saying that the big molecule was needed to really get a very effective antigen.

Hughes: Did she take that more biochemical approach because she had access to an amino acid analyzer?

Koshland: Well, everybody had access to amino acid analyzers, because they were commercially available. I had postulated the induced fit theory, so she heard a lot about that because she was married to me.

Hughes: That theory seems to fit.

Koshland: Of course, that fit perfectly because, protein was a big molecule, and the antigen bound here [demonstrating] and then the antigenic part turned on something called the Fc region, which was the complement fixation region at the other end of the molecule, and that clearly suggested an induced conformational change, which she believed, too. The naysayers who were then reduced to a Henry Metzger at NIH didn't want to believe that. It was in his opinion not caused by the induced conformational change; it was the association of the molecules.

A Critical Experiment

Koshland: Bunny did what I consider to be an utterly brilliant experiment. She took a section of the active site of papain, which is a protein, and dinitrophenolated it. Dinitrophenol is known to be a good antigen-producing molecule. She dinitrophenolated it and she took the small peptide out. She found it was a much better antigen when it was part of the big protein than when it was just a little peptide. The reason that Metzger et al. gave for that was this association-dissociation reaction was made possible by the big molecule.

And then she made the protein to the dinitrophenol papain. Papain is an enzyme of about 25,000 molecular weight, whereas the peptide is 1200, let's say. And then she chopped the big protein down, down, down, down until she got back the small 1200 [molecular weight] peptide, where binding affinity was what decreased. But she could saturate the protein with the small peptide at high concentration and it was just as good as an antigen. So that was really good proof that what she was saying was correct and that the other people were wrong. This was work after her early work on the selection

Two Sabbatical Leaves in Boston

Learning DNA Technologies in David Baltimore's Lab

Koshland: Bunny was doing this rather biochemically and I wanted to go on a sabbatical, but Bunny didn't want to take a year off and just be a housewife. By then our kids had grown up, and so we tried to find a place where she could go to a scientific lab, too. So I went to the Harvard chemistry department, and she went to MIT, to David Baltimore's lab. She became really expert in DNA handling of mammalian systems; that was very advanced at the time. And I was doing DNA work with bacterial systems, which are a lot easier than mammals. Bunny became better at the DNA techniques in mammalian cells, than I was and I would get good advice from her.

Hughes: Why did she want to work with mammalian cells?

Koshland: Bacteria don't have immune systems. She was always telling me that fish, I think, are the lowest species that has an immune system. But she was working with rabbits and mice and humans, and eukaryotes and mammals.

Hughes: Was Baltimore one of the leaders in the molecular biology of mammalian cells?

Koshland: Yes, he was. He was just getting interested in antibodies. His main work before had been viruses, a very important virus, namely, polio virus, which of course was the basis for the Salk vaccine and a lot of vaccines, which was immunology. So he was pleased to have her in his lab. He taught her how to do molecular biology, and she taught him a lot of immunology, so he really liked having her. They got to be very good friends. Seven years later, I had a second sabbatical, and I went back to Harvard, and Bunny went back to MIT with David.

Hughes: Into Baltimore's lab?

Koshland: In Baltimore's lab. It was very hard to get into Baltimore's lab. It was very popular.

Hughes: What did she do the second time?

Koshland: She did the same thing. The second time, she broke her hip--fell down a staircase in an apartment we had rented. But she got her hip fixed, and she went to the lab on crutches and continued her experiments. The young students in Baltimore's labs were really impressed. The first time, she knew very little DNA cloning.

Hughes: When was the first sabbatical?

Koshland: I've forgotten when it was. [gets up to find his bibliography]

Hughes: Is that when you wrote the book on chemotaxis?

Koshland: I think the book on chemotaxis I wrote on my first sabbatical, and my second sabbatical was in the [Harvard] chemistry department. [skimming his bibliography to check publication date] Okay, 1980 was the chemotaxis. So I probably had my first sabbatical at least seven or eight years before that. But Bunny really got to be very good at working with mammalian cells. She used them a lot.

Hughes: Recombinant DNA?

Koshland: Recombinant DNA, all of that, yes. Working with human chromosomes is really a great deal more complicated than working with bacteria. My work started to go more in that direction. She was very helpful to me.

Hughes: Why is it more complicated?

Koshland: Because the gene is much bigger. And then there's splicing involved in mammalian genes--introns and exons. That's a much more complicated genetic system than it is in bacteria.

So anyway, Bunny was really one of the pioneers. You can ask Tij [Robert Tjian] about her. She did a lot in the [cell signals] transcription area, and she shared a lot of equipment with Astar Winoto in the department. They didn't publish together, but Winoto exchanged ideas with her a lot. She really liked him a lot, and they had adjacent labs, so their students would flow back and forth. She really liked that.

Contrasting Scientific Styles

Hughes: Please talk about her scientific style and compare it with yours.

Koshland: We kidded a lot about the differences in our scientific styles. I tended to be less cautious than she was. I would jump to conclusions with less data.

In World War II, I became a group leader at Oak Ridge, even though I only had a bachelor's degree. I had fourteen people working for me, seven of whom were Ph.D.s. Bunny was a pretty independent woman, and so she enlisted for a job in Oak Ridge, where they had the hiring center. She put her name down as Marian Elliott because she didn't want to trade on my reputation. They hired her, and they assigned her to a plutonium project run by a guy named Daniel Koshland.

Hughes: [chuckling]

Koshland: And remember, it was not easy to get jobs. She was not at all sure when she found out that she had been assigned to my group if she said no and left, she'd ever get another job. So she accepted it, and she had to work for me. That was a big strain. If you got a really good result, my theory was, you apply that result and go onto the next thing. If that blows up, you say, Well, maybe I made a mistake and go back and repeat. But the idea of running a duplicate result I always felt was silly because most of the time the result turns out to be right. So I say, think of a new experiment that confirms but goes on instead of just repeating what you did. Whereas the tradition in science is you always duplicate a result before you go on to the next thing. And so she really felt she should do that. I told her, "No, I'm the boss. Go on to the next experiment." So we had these terrible fights. I was kidded that she never would have stayed married if she had to continue to work for me. [laughter]

Hughes: Did she follow that rigorous approach throughout her career?

Koshland: Yes, I was upset with her and felt she didn't get as much credit as she deserved because frequently when she had a result and I thought it was 99 percent sure, she'd think it was only 75 percent sure, and she wanted to run one more experiment to really prove she was right. And then, in the modern, competitive world, somebody else would discover the same thing from a different direction, and she'd get scooped. And so I'd get impatient with her and tell her she just couldn't spend that amount of time on duplicating results. She had a small lab. She didn't ever have a big lab the way a lot of these competitors did, and so she really had to publish more rapidly. I would tend to publish a theory if I had just one result and my theory was based on a lot of detail recurring--and even that was risky but in fact my theories all turned out to be right. little questionable. So that was a different scientific style from her more careful approach.

Hughes: Did you ever get caught out?

Koshland: No, most of my theories were correct--induced fit and things like that. Well, I wouldn't say I published based on one result; that was probably an exaggeration. But if I had a theory, it was usually based on a fair amount of knowledge of the field. In addition, I had one or two supporting experiments, but they were perhaps not enough experiments for somebody who was cautious before you postulate some big new theory.

Hughes: Was that just her nature, or had she been mentored by a cautious person?

Koshland: No, I think that was her nature, but her Ph.D. advisor was very cautious, and probably a little bit due to being a woman and being less secure. She was a good scientist, and at the end she knew she was a good scientist.

Hughes: I would think that if she had had trouble with people disputing her results early in her career--

Koshland: That association you understandably jump to, but I don't think so. She knew then she was right and this other guy was wrong. And there she was looking at very small differences in amino acid sequence, but she was confident she had done the analysis so well, she knew they were real differences. But that was a big, big theory. Remember, the world was really watching, and she had a very exciting result. She did more experiments than I would have done, but even I would have been worried about those. I mean, she really stuck her neck out there.

A Woman in Science

Hughes: Do you think that if she hadn't been a woman and/or hadn't been at Brookhaven, that she would have gotten more attention?

Koshland: Yes. I think she certainly would have gotten more than she did, although at the end of her career everybody really respected her a lot. She was on lots of National Academy and NSF committees. But she would have certainly gotten the recognition earlier.

I was always infuriated because periodically she wasn't invited to big international scientific meetings, whereas people I thought were much less productive were invited. She was never that angry. She would get hurt because she'd see a program, and it was clear they were picking people that were less productive than she had been.

Hughes: Because they were men?

Koshland: Yes and part of it was that because she had a family, she didn't go to as many meetings as some of the men. People go to meetings, and are around when you plan the next meeting, the next convention. So the fact that she was home with the kids or had to go to a graduation meant she wasn’t there to be in on the assignments.

Hughes: She was invisible.

Koshland: Yes, sitting around a room, they didn't think of her automatically. So I think it was a combination of reasons. Certainly some discrimination against women was probably the biggest single factor.

Hughes: What effect did her experience have on you?

Koshland: I would say everything that she did was positive for me, but I became angry if she didn’t get her fair share of credit. I was chairman of the department of biochemistry for years. She became chairman of the Department of Immunology and Bacteriology.

Hughes: Did your terms overlap?

Koshland: Yes, we were chairmen at the same time [MEK:1982-1989; DEK:1973-1978[44]]. Once when we were having dinner, she announced to me that she had just gotten $26,000 from Sandy Elberg, the dean of the graduate school at the time. I said, "I am furious about this because Sandy Elberg just turned me down for $6,000, based on the fact that he had no money and couldn't do it." I wanted the $6000 for the department to have an Asilomar type of retreat. Clearly, that wasn't absolutely essential. And Bunny had asked for $26,000 because some professor needed to be bailed out in order to do very important research. I've forgotten what it was, but it was really needed.

So Elberg made an absolutely correct decision. But I can tell you, he never forgot that because I kept bringing it up. An attractive, blond, chairman of the department is going to get yes from Sandy Elberg while he's telling a poor old male professor in another department that the dean doesn't have any more money.

Hughes: That's all very interesting, but what I was really meaning by my question is: you were married to a woman who had had certain roadblocks in her career because she

[44] DEK was also chairman of the Chancellor’s Advisory Council on Biology from 1982-1993.

was a woman, and I'm speculating that maybe that opened your mind to the difficulties that women in science have.

Koshland: That is certainly true. I was always very supportive of women's rights. From the beginning, I was naturally that way anyway, but Bunny's experiences made me more so.

Bunny was great eyes and ears for me in the scientific community. When I was editor of *Science*, she religiously refused to meddle in any decisions about *Science* magazine. For example, she didn't read my editorials before I published them. On the other hand, she was in the midst of the scientific world. When *Science* had a special issue on immunology, she would suggest to me who might be a good author for it or what subjects to cover. We had ad hoc editors who dealt with a special issue. But she didn't let me solicit an article from her.

Hughes: I heard that she was somewhat jealous about the ease with which you wrote--

Koshland: Oh, yes, that's true.

Hughes: --that writing a scientific paper was much more laborious for her than for you.

Koshland: What she finally wrote was very good. She loved to be chairman of the department in terms of recruiting people, and she had <u>wonderful</u> rapport with the students, but she hated all the letter writing and committee reports. She was just great as a graduate advisor. The students thought she was their mother or even better than their mother, a sort of independent person who cared about them. She did care about them. She'd talk to them for fifteen minutes and learn all about their personal histories. I was always diffident to ask my students any personal questions. She had a great rapport with students.

I was helpful in terms of understanding women's problems. I was always active in getting barriers broken down for women. But Bunny really did much more than me with that. She'd go to meetings at the National Academy of Sciences and she'd interact with people, so she'd hear the latest gossip. And that was really very useful for me at *Science* magazine, even though she would not interfere with the magazine itself. I had management crises, and I would consult her about the situation. She wouldn't appear publicly in it, but she was certainly very helpful to me.

She was a really good chairman because she was imaginative. A lot of people think a chairman just bullies his way through it; you just say, "I'm going to have this." But if you're clever, you think of a way to solve the problem. Professor X needs this little room and Professor Y wants the room, too. You find if you can give Professor X a room down the hall which is bigger than the other room but a little out of his way, he will accept it. So she would come up with very imaginative solutions. But then she hated being chairman because a chairman has to write letters all the time. Her letters would come out excellent because she labored over them. I would write an editorial in an evening, and it just drove her nuts that I could write that quickly.

A 70th Birthday Gift

Hughes: [chuckling] I want to read something to you.

Koshland: I'm going to report you and say the trouble with Ms. Sally Hughes is she reads things about you.

Hughes: [chuckling] I'm reading from a mock issue of *Science* that your wife designed for you.[45]

Koshland: This was on my seventieth birthday. That was a wonderful birthday present. Bunny arranged for the children and colleagues of mine to write short articles and put them all together in the format of a *Science* magazine. They delivered this to me. I knew nothing about it. She got all the children, she got people here at Berkeley, she got people at *Science* all to contribute articles.

Hughes: Well, for the purpose of the tape, I'll say that it's an issue of *Science* in honor of Dan's seventieth birthday. It's modeled after *Science*, but tongue in cheek. All the articles are humorous. But I want to read an excerpt from one written by your daughter-in-law, Catherine Koshland, and edited by James M. Koshland, who identifies himself as "an attorney for Unaware and Filthyrich, and Catherine Koshland is a professor in "The Building Next Door, Blue and Gold University."

Koshland: [chuckling]

[End tape 25, side B. Begin tape 26, side A.]

Hughes: It relates to our discussion about scientific styles. [reading]:

> In a retrospective study to identify the antecedents of current behaviors, we learned that in the early days of his marriage, Professor Koshland was given the opportunity to work with his wife in the same lab. However, the behavior of each in the lab was the antithesis of the other. Professor M. Koshland was meticulous and precise, adding just the right 'spice;' Professor Koshland: throwing this or that in, and drawing sweeping conclusions. Needless to say, the chemistry of the lab wasn't right, and Dr. Dan Koshland concluded that it was time to retreat from the lab or 'kitchen,' a behavior that persists to this day. [chuckling]

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[45] A copy of the cover of the mock issue, featuring Daniel Koshland, is found in the appendix to the Marian Koshland oral history retrospective.

Koshland: Bunny liked to work in the lab, enjoyed doing it. I really liked theory, and I was really delighted to have my students carry out the lab experiments.

Hughes: She liked the experimental part?

Koshland: She liked to work with her hands.

More on Family Life

Gardener

Koshland: She liked gardening for the same reason. In addition to having a career and being a great mother, she not only liked gardens but really had great theoretical understanding; she knew when to grow plants and how to grow them.

Hughes: Was that intuitive?

Koshland: No, she just learned everything quickly. So she learned about plants and picked up quickly what would grow best. I didn't have trouble convincing her that California was a great place for a gardener. She would always have our garden in Lafayette in color. When the gardenias were dying or whatever it was, she'd rip them out and put in petunias or whatever it was--I don't even know what the names of these flowers are. But she knew that when they started to wilt a little bit--and they still looked perfectly good to me--they were on their way out and she had to get the petunias in. Then they would blossom in ten days or whatever it was, when the gardenias really collapsed, you see? So she always would be turning over the garden so that it was always colorful.

Paid Help

Hughes: Did you have help in the home?

Koshland: Oh, yes.

Hughes: Without help, I can't imagine how she'd have time for gardening.

Koshland: No, we always had help. When our children were growing up, we had a daytime maid in the house. That meant that we about broke even if you want to say, in terms of--because as a scientist she got paid more than a maid, but it meant that she came home and the house was clean and the laundry was done. The kids, of course, had gone off to school, so the person in the house could be on their own and do sweeping and things like that.

Both of my daughters-in-law were <u>very</u> fond of my wife--there were never any mother-in-law problems. They looked up to her a lot and really had a great rapport with her. One of them, Jimmy's wife, Catherine Koshland, who's now a professor here at Cal, imitated her right from the beginning. Mary Porter, Douglas's wife, sent the kids to daycare for a while. When you send kids to daycare, they take care of them during the day, but then when you come home, you have to do all the cleaning; you have to sweep the house. Bunny said to her, "There's a better way. If you get somebody who can do the cleaning up and watch the kids during the day, it doesn't cost much more than daycare." So Mary switched and just was delighted.

Hughes: Did that person live in?

Koshland: No. We never had live-in; we always had people who came in for the day. We liked the privacy of being alone at night.

Social Networks in Science

Hughes: One of the images that is associated with women in science is that they tend not to have a professional network in the same way that men do. Did your wife take advantage to some extent of the incredible network in science that you had created?

Koshland: I don't really know. That's hard to nail down. She was not as widely known as I am, but she was quite widely known and we certainly helped each other in that regard. I think that there's a symbiotic effect, which certainly worked for both of us in the sense of getting elected to the National Academy. Getting elected to the National Academy is mainly how good you are yourself in your own scientific discipline. You first have to be proposed by your own group, like the immunologists vote on the various immunologists proposed for membership. Then when you get beyond that stage, you have to be voted on by a bigger group, like all the biologists, and then you get to the next stage and are voted on by an even bigger group including chemists and astronomers. I would say there was no sense that I helped her in getting elected by the immunologists. They all knew her well. But once she got up to another level, the name Koshland probably was familiar to chemists and physicists that would not normally have known her and she helped me with biologists and medical people that probably didn't know me.

Later, if I as editor of *Science* magazine needed to call up an immunologist or needed something in the cancer field, then the fact that I was Marian Koshland's husband certainly helped. So I think we helped each other in name recognition. As far as doing my research, I would say that the network she had didn't help me very much, and I don't think mine helped her at all.

Team Sports in the Life of a Woman Scientist

Koshland: On the other hand, you put your finger on something very important. If you read that autobiography she wrote of herself, she claims that one of the things that women suffer from is not doing sports. She said sports are really a good network for learning how to work with people but also for learning how to be competitive.

She really felt the sports experience of learning at times how to subjugate yourself and pass the ball off to somebody else, but at other times be aggressive and take the ball to the end of the field yourself, was a kind of training that women needed to have if they were going to compete with the world of men. She ends her article very cutely by saying, "I didn't learn to play soccer, but my granddaughters do. Let’s see what happens."

Science and Motherhood

Hughes: When the twins came along and the number of children in the family was suddenly doubled, she considered quitting science entirely. Your advice was not only to continue to work part time, but also to choose projects that were a little far out. Why did you give her that advice?

Koshland: That was my instinct about research. I always liked sort of wild ideas. She really had very clever ideas. In her career, she had one really outstanding idea after another. So I didn't really need to point that out to her, but I did think it was worth emphasizing because all of a sudden she realized that with this big family she was not going to be able to work full time for a number of years. Whereas before she thought well, she'd soon be finished taking care of little kids--the children would be going to school and she could now work full time and have a regular lab.

Bunny was saying when the twins arrived that she wanted to quit, that she wanted to become a full-time mother. I knew that she would just be bored as hell. We had then two older girls, and the oldest of them was just starting kindergarten. It was only going to be a limited period until everyone was in school, and then she would really regret not having anything to do in science. So I felt she should do it just part-time until the kids were old enough. But then I said, If you're part-time, then you've really just got to emphasize the originality, quality instead of quantity. Bunny wrote that concept into that autobiographical article. What she didn't say is that everybody can't be original. It's the kind of advice which is good for people like her, but only a limited number of people can take that advice.

Hughes: That's interesting. I suspected that a routine approach would be safer; you could follow other people's lead and you wouldn't be sticking your neck out.

Koshland: That's true, and it's perfectly good to be safe with a routine career. But Bunny was ambitious enough that she wanted to compete with the top people. To do that, I said, you've just got to be very original.

Hughes: I remember Stan Cohen saying that he tried to choose projects that were in underpopulated fields where the competition wasn't as stiff.

Koshland: That's one variation. But there are a number of ways you can do that. If you're really original, you either pick a populated field but then go one step beyond, or you take an unpopulated field and discover something that everyone must learn.

Personal Qualities

Hughes: Tell me now about her as a personality. What was she like to meet on the street and what was she like to meet as a scientist?

Koshland: Bunny was a wonderful personality. She was lots of fun. She was not the stereotype of an ambitious woman. If you met her at a party you'd say she was a typical homebody. If you met her in the lab you'd say she was a typical scientist. She was very good at a party. She was unusual in the sense that she really was (a) interested in people and (b) remembered everything. I'm not bad at meeting people. I get along pretty well and easily, and a lot of people offhand might say, "Well, he's more gregarious and open to people than she is." But in fact, I'd go home and I'd sort of vaguely remember what somebody had said to me. Weeks later she'd say: "Well, the person that you introduced me to has a kid in the third grade in Connecticut," or something like that. By then, I had forgotten how many kids he had and most details of our conversation. So she really absorbed and remembered everything she heard.

I'd have a visitor to the department, and I'd invite him home for dinner. I'd say to Bunny, "Don't worry about it. He's a very nice guy, and we'll just have what we normally would have for dinner." She would say, "Oh, no, I can't because we're going to have ham and the last time he was here we had ham." I said, "Bunny, it was ten years ago. How can you remember what he had?" But she would! And she was right. So she said, "I'm not going to serve him ham again." I said, "He never would remember that he had ham here." So I went out and bought veal and he said at dinner, "The last time I was here we had ham and it was so good I still remember it."

Hughes: That is phenomenal.

Koshland: She was also a great typist. Every once in a while, in a crisis, she'd type something for me. If I had to get something off the next day I'd ask her. She was better than any secretary I had. She composed her own papers on the typewriter. She would sit there and just type them out. But she was very good at almost everything she did. She was very good at conversation. She was a very warm, easy person to get along with, but she was also tough.

Bunny was famous at faculty meetings and in the Academy for saying the equivalent of, "The emperor has no clothes." Everybody would be sitting around at these big scientific committee meetings, considering so-and-so for a job. People would be saying, "Oh, yes, Joe would be great; he just got this big award." Bunny would be the person to say, "Well, he's good at all those things, but he really isn't very good at giving a speech, and this is the kind of position where you have to give a lot of speeches." And then everybody would say, "Well, yes, Bunny is really right." One of those eulogies of her mentioned that she would tend to be very blunt.

And the grandchildren mentioned her high standards at the memorial service. They were very upset that she died because they said, "We don't have any standards to live up to anymore." And they have very good parents. (My kids are really very unusual parents; I'm very proud of them.) But the grandchildren knew Grandma loved them, but they had to live up to certain standards. If you didn't have your bib on straight or you didn't have good table manners, you knew Grandma would give you trouble. They knew that getting her approval was not automatic.

Hughes: Was that true of her own children as well?

Koshland: Oh, sure. We were both pretty old-fashioned parents in many ways. But I think we had very good rapport with our children. They were all really very good children, so we had very little trouble. But they knew that they had to toe the mark.

Childrearing

Hughes: Did the two of you agree about how to raise the children?

Koshland: Oh, the two of us instinctively agreed. I was a little bit more permissive about, say, whether they had to go up to bed immediately at nine o'clock. But I was a lot stricter about things like walking across streets safely. Bunny would be stricter about not eating before dinner, for example. They'd have to save their appetite for the meal. So they would periodically do things like coming to one of us to ask us about the thing they knew we were more permissive about. But we both had pretty good instincts about when we were being treated like that, so I'd think about what Bunny would say and Bunny would say what she thought I would say. The children would get very angry and say, “Why do you two always agree?”

But as far as anything serious about their lives was concerned--Bunny and I agreed almost completely. And it's a good thing because we were both very strong people, and we would have had one big awful fight if we hadn’t agreed. For example, my second daughter Phyllis, who was really a rebel but a very cute child, came home with a pomegranate from the grocery store. It wasn't a big thing, but it was more than she had money for at the time.

I said, "Well, how did you pay for it?" She mumbled and moved off. I deduced that my daughter had snitched it, and she confessed. The punishment I devised was, she had to go back and tell the grocer and pay the money and say she was very sorry and she'd never do it again. She was willing to pay the money, but she didn't want to have to go back. I said, "You walk right back and you tell him. You say this is what happened, and that you took it, and you shouldn't have done it and you’re sorry." Then I went out because I had to do something. Bunny came home, and I don't know what happened, but in the process my daughter confessed. But she didn't tell Bunny about my punishment, and Bunny gave her the exact same punishment. [chuckling] So we sort of instinctively brought up our kids the same way.

But we had various crises. I remember one famous episode. Our rules were that we agreed on a time when we thought they ought to be home, but we didn't care what the hour was, as long as we knew where they were at any time. So if they went out to a school play and then they all decided to go someplace and have pizzas, as long as they went to the phone and told us, "We're having pizzas and I won't be home till one o'clock instead of eleven thirty," we said that was fine. That was okay, and everybody in Bellport knew that when they went out with the Koshlands, they would have to go to the phone and report where they were. But one night Phyllis was very late and no phone call. (Later we found out she'd gone sailing and got becalmed.) She got home at 4 a.m. and found both parents sitting on the front steps waiting for her. She said that was the biggest shock of the evening.

We went to breakfast any old time because the kids were on double sessions. That meant some of them had to go very early in the morning, and some late. So we devised a strategy that the dinnertime was the time the whole family got together, whereas breakfast people could all eat on their own schedule. Everybody knew they had to be home for dinner. And they were. They claimed it was a terrible thing, but they really all liked it.

We had five just wonderful children. And they've been wonderful to me. When Bunny died, as you can guess, I was really in a depression, and my children just appeared. We knew she had cancer. She didn't want anybody to know, but we of course told the kids, and they all knew about it. So they would just arrive here. Ellen, my oldest daughter, just came and stayed at the house when Bunny was dying and I really needed her. And then the other kids came after. I'm sure they all conspired. All of them had jobs and were busy as hell. I felt guilty about it, but they would just announce, "Dad, I'm coming for the weekend." And I'd say, "You know, it's really inconvenient." "Well, too bad. I'm coming." And they really knew that I would make space for them, no matter what. And although it seemed inconvenient, it was good for me to be doing something with them.

At any rate, they were just good kids all their lives. I don't remember any real problems. Our first daughter, Ellen, was an ideal child from her start in the nursery. For the first year or so, Bunny and I acted superior as hell. We just thought all these people who were having trouble with their kids just weren't as smart parents as we were. Then our second daughter Phyllis came along. She was a rebel. She screamed in the nursery before she was even released from the hospital. She was a hellion. We really had a hard time getting her to sleep at night. She'd wake up all the time. Anyway, it was clearly genetic. The nurse told me, "Well, she's going to be a handful. But usually these types are very bright." And she was. But she was a big rebeller. So we sympathized with the other people who didn't have docile children.

For example, we complained about her spelling, and she wrote this letter, which I still have, when she first started camp. We had told her she had to write from camp. She couldn't spend two weeks at camp and not let us know what had happened. So we got this letter from her, "Dear Parents, I'm doing what you told me to do." She had misspelled many more words than normal. It was clearly just to get us furious! Anyway, that's the kind of rebelling she did. The other kids--well, you can read from that mock issue of *Science* the kind of irreverence they treated their parents with.

The family had a big tradition of kidding. That I didn't start. That was started with my parents. My father was a big kidder, and Bunny always said that one of the big things she had to learn in the family was how to take kidding. If you were the kind of person that got annoyed or weren't a very good sport, then they'd kid you about this, so you really had to learn how to take it. That was very good for the kids later on.

Hughes: So your mother and father had this same sort of relationship?

Koshland: Yes. Except my mother never went to college. It's something she always felt deprived about, because she was a very educated woman. She read a lot, and then she later enrolled in correspondence courses. She got married at eighteen. In that age, women did that, and they didn't go to college as was true of most of her peers.

Our attitude towards our kids was very similar to my parents' with me, and that is they really always gave me enormous security. I was expected to go out and do well, but it was never said, well, I had to be a big success. If I was conscientious and a good citizen, I’d be loved and anything more was up to me.

[End tape 26, side A. Begin tape 26, side B.]

Koshland: If I cheated, then I would get hell. But on the other hand, I wouldn't be thrown out of the house. If I was prejudiced and said nasty things about people because they were a different color, I knew the family would disapprove of that. Because we grew up in a household where we always had enough money, it was expected that we would be charitable and go out of our way to help underprivileged people. So we had to do those kind of things. On the other hand, it was never that we had to be first in the class or we had to make a lot of money in our careers. I think we conveyed the same thing to our children.

Cooks in the Family

Koshland: As I said, my wife was really so good at everything, it was hard for anybody to compete with that. On the other hand, the children learned that they were supposed to do things. My sisters didn't ever learn to cook very well, yet all my children, even the boys, learned to cook well. I never did. I was the disaster as far as that was concerned.

Hughes: Your sisters didn't learn because there was a cook in the house?

Koshland: Yes. They always had a cook, and they weren't that interested. They both now can run a household and they can cook, but they just never became good cooks, whereas Bunny was a superb cook.

Hughes: Did she deliberately teach her children how to cook?

Koshland: I don't think deliberately--they all just learned. We never had a cook. At the very end, when she was really quite ill and frail, she'd cook for me right up to the end. I tried to get her to have a cook, and she just wouldn't do it. Fortunately, she loved Chez Panisse, so I'd take her there. It was really sort of a struggle because it was hard for her to walk up the stairs there. She didn't want to have a cook; Bunny and I enjoyed the privacy, just being alone.

Social Life

Koshland: Both of us being so mutually sufficient affected our life in many ways. As long as I could have an evening with her, that was it. I always enjoyed talking to her more than I enjoyed talking to anybody else. We would come home from work, have dinner with the kids, and work, or just sit around if we were tired, and talk with each other. We had lots of friends, but they all really knew that we didn't like to go out a lot. That was just accepted.

Bellport was really a small world. It was sort of like having a big family. There were a whole bunch of couples who got along very well. We'd go to their houses, and our children would go there, too. I was president of the school board and was very much involved in the community. So was Bunny; Bunny was a force in the League of Women Voters; she led a big study with the zoning of the area which led directly to zoning law legislation for the area.

And then we moved to Berkeley. I was forty-five and she was forty-three. We decided we just weren't going to do the community bit. It would be enough to be interacting with people at the university, so that's all we did. We did make lots of friends among our colleagues, but we never made much effort in the community. We knew and liked all the people in the houses around us in Lafayette. But we made no effort to have them to dinner and go to their houses.

It was really busy. It's conventional for the wife of the chairman of the department to entertain his departmental affairs and for me to be there at all her department events. We just agreed we weren't going to do that. Everybody understood. Because of the number of professional things Bunny and I had to go to, if we each went to the other person’s events we never would have had time alone together at all. So I went to my things and she went to her things, and everybody sort of understood. If it was something very important, occasionally we would both go together.

Hughes: What do you most like to remember about her?

Koshland: Oh, she was just everything I wanted. We started out with this big physical and mental attraction when we were first met. We were attracted intellectually right away, and not just in science. She would challenge me intellectually, and make me confront reality. I tended to be kind of a rose-colored romanticist. I'd always come back from a first meeting saying so-and-so was great, and she would restrain me saying, "Why don't you get to know him a little better?" Which usually turned out to be excellent advice. I just enjoyed talking to her at every level. She was a very good dancer, so we used to go out and dance together a lot.

Her one failing that I remember is that she wasn't as good in sports, partly because she had terrible astigmatism, so she never learned hand-eye coordination. She was really very strong for a woman and for somebody her size--she was not very big. She could play tennis, but she was not really good at it, and it bothered her. She wanted to be good at everything.

Remembering an Early Incident

Koshland: I distinctly remember one thing. When I was taking her out, we went to a movie called "The Ox Bow Incident." It was a movie in which a bunch of people lynch a couple of kids that they think are horse thieves. In the West, that was standard. You got hanged for stealing a horse because that was stealing somebody's livelihood and so forth. There was a scene in which this mob of people comes in to a small town, and the two little sheriffs are clearly outnumbered. The sheriff stands there and says to the mob, "I'm going to shoot you if you come up these stairs." But they started advancing, and of course he doesn't shoot, and the mob takes the guys out and hang them.

I said, "The sheriff should have shot them." And Bunny said, "No, you can't shoot somebody if they haven't committed a crime yet. You could shoot them as they were committing the crime, but not if they were just threatening." I don't know what happened. This was just an intellectual argument. We were arguing on the front steps of her boarding house, where I was leaving her. Finally about two o'clock in the morning somebody said, "Will you guys please shut up?" We didn't have any idea how long we were talking. That was typical of the kind of discussions we had before we even got married, so by the time we got married, we knew each other very well.

Bunny was just a very warm person. She really cared about things. She remembered everything. I used to kid her all the time. She'd serve a dish and she said, "Well, was that better than last time?" And last time was about ten years ago, and I was supposed to remember! In the beginning, when I was inexperienced, I'd say, "God, I don't remember the last time." And that was worse than anything else! So I learned later to pretend to remember, "Oh, yes," I said, "you've done a little better this time." [both chuckle] But anyway, it was just a kick. I just enjoyed everything she did. She was a <u>great</u> mother for those kids, a great wife, a great gardener, a really talented architect, a real expert in art.

Hughes: Thank you, Dan

[End of interview]

Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

REORGANIZATION OF BIOLOGY
AT THE UNIVERSITY OF CALIFORNIA, BERKELEY, 1980s-1990s

An Interview with
Daniel E. Koshland, Jr.

Interviews Conducted by
Sally Smith Hughes
in 1999

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INTERVIEW HISTORY—by Sally Hughes

This oral history reflects the viewpoints of three significant participants in the reorganization of the biological sciences at UC Berkeley—a long and contentious process, which began in the early 1980s and continued for a decade. The result in organizational terms was the creation of two mega-departments, the Department of Molecular and Cell Biology and the Department of Integrative Biology, the reformulation of undergraduate and graduate curricula, the construction of three science buildings and an animal care facility, and the renovation of the Life Sciences Building. One goal was to realign the science faculty into research affinity groups perceived to have mutually enhancing research interests.

Daniel E. Koshland, Jr., in a chapter from his forthcoming oral history, reflects the views of the biochemically and molecularly-oriented biologists who saw Berkeley slipping in regard to sister institutions and biotechnology companies in adopting the new genetic technologies, such as recombinant DNA, gene sequencing, and monoclonal antibody technologies. His status on campus as a respected professor of biochemistry, editor of the journal *Science*, and member of the National Academy of Sciences ensured that his arguments for reorganization had weight with the faculty and the administration. He is frank in crediting Rod Park, the narrator of the second oral history, with "selling" the reorganization plan to the faculty, especially to the skeptical organismal scientists, who rightly feared that the molecular biologists had the upper hand. Louise Taylor, the narrator of the third oral history, was the woman in the trenches seeing that the myriad organizational details ran smoothly, attending virtually every meeting of the several committees involved in reorganization, and preserving key documents generated in the complex process.

All three oral histories record the occasional rancor of the process as long-standing departments were abolished and re-formed, office and laboratory space reassigned, and the Academic Senate marginalized—or so it seemed to some participants. The narrators also discuss contending with opposition from animal rights activists and campaigning in Sacramento for building funds.

This oral history volume represents a start on documenting an important episode in campus history. It leans heavily towards those favoring reorganization from the start. Left out are the voices of the opposition, vociferous at first and more subdued as the process unrolled. Also missing is the perspective of members of the Academic Senate. Although Beth Burnside was invited to record her viewpoint of the Senate's role, she declined in part because of her new appointment as Vice Chancellor for Research at the time the interviews were being conducted. Also of historical interest is the perspective of the animal rights contingent as well as the legislators in Sacramento involved in the campaign for construction funds. A second oral history volume seems called for in order to complete the historical record.

We are grateful to Louise Taylor for the donation of a binder of documents on the reorganization process, a valuable adjunct to the oral history and available for research in the Bancroft Library's History of Science and Technology Collection. We also thank her for careful annotation of her oral history, a reflection of her dedication to the university and outstanding organizational skills.

This oral history is an important step towards full documentation of the reorganization of biology at Berkeley. Many credit the effort with helping to raise faculty morale, improve faculty and graduate student recruitment and retention, and advance the university's stature as a research university. This oral history may also be of use in guiding other institutions contemplating the realignment of their own academic endeavors.

Sally Smith Hughes
Historian of Science and Interviewer

Regional Oral History Office
The Bancroft Library
July 2003

INTERVIEW WITH DANIEL E. KOSHLAND, Jr.

THE REORGANIZATION OF BIOLOGY AT UC BERKELEY

[Interview 12: April 6, 1999; Interview 13: May 7, 1999][1] ##[2]

Defining the Problems in Biology at Berkeley, 1980

Hughes: In spring 1980, the Chancellor's office appointed four committees to review academic programs in biology on campus.[3] The external review committee had not yet been appointed. They made some preliminary recommendations for a reorganization of biology at Berkeley. Do you know about those four committees?

Koshland: Yes. It really all started when my wife Bunny [Marian E. Koshland] and I were having cocktails at the Men's Faculty Club, at which point Roderic Park asked me what was the state of the biological sciences. Rod at that point was Dean of Biological Sciences in the College of Letters & Science [L& S]. Before I could say anything, my wife said, "Terrible." Rod was very upset and said, "We've been tops in graduate school evaluations in all these ratings."

My wife was in the department of immunology in the Life Science Building [LSB]. The people in immunology were just as smart as the people in biochemistry, but they were trying to recruit people into a building that was old and decrepit. My wife Bunny was a key leader in getting new, young people. But a lot of the people they wanted to recruit just wouldn't come when they saw the facilities.

Rod turned to me and said, "Dan, what do you think?" Being loyal to my wife (I didn't want to be too blunt) I said to him, "Well, she's really partly right. There are some

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[1]Interviews 12 and 13 were conducted as part of a long biographical oral history with Professor Koshland. Because there was some repetition, the two interviews have been combined, some duplication eliminated, and the chronology improved.

[2] ## This symbol indicates that a tape side or segment has begun or ended. A guide to the tapes follows the transcript.

[3]Vice Chancellor Roderic B. Park to Dean Robert Glaeser, March 6, 1981 (Office of Planning & Analysis, Vice Chancellor--Resource Planning & Budget, University Hall, University of California, Berkeley. Hereafter, University Hall documents.)

departments that are doing very well. (I wasn't thinking of just biochemistry.) But a lot of our departments are doing poorly, sometimes due to bad facilities, and sometimes because the current faculty aren't recruiting very good people, even in rather good facilities. There is a problem of program, and a problem of facilities."

A year or so thereafter, Rod became vice chancellor under Mike [Ira Michael] Heyman,[4] who was then chancellor. Rod remembered the conversation, which is rare for administrators and he decided that we should have an inventory of the life sciences. He appointed a committee made up of four principals. One person represented biochemistry (Alex Glazer), and one person represented cell biology (me), and one person physiology (Beth Burnside), and one person whole-animal (organismal) biology (David Wake). We called ourselves the Gang of Four because in China the Gang of Four took over the Cultural Revolution.

Our mandate from Rod was to make an inventory of biologists: how many people were there on the campus who called ourselves biologists? You might say it's pretty easy; you just look at the departments. But it isn't quite that easy. For example, the School of Public Health had a department which had a mixture of biologists and economists, and the College of Engineering had some people whom you would call bioengineers mixed with others who were largely engineers outside biology.

Our job was to find out who we were talking about, and we came up with a list. But as is inevitable, we poked our nose into other things, which is exactly what I think Rod expected us to do. We went well beyond our mandate and proceeded to say the things we thought were really not so good about biology at Berkeley and needed to be corrected, like facilities in LSB and departments that were being run very poorly. So we fulfilled our mandate in terms of getting a survey of biologists, but we in addition said what the campus needed to do to improve the biological sciences. We indicated to Rod that we thought biology needed a good deal of reorganization.

Our focus was on the very weak departments, of which genetics was a good example. There was also duplication, for example, a plant biology department in the College of Natural Resources and a plant department in Letters & Science, and we thought they should get together. And some departments had outmoded programs. For example, the zoology department was considered one of the best in the country. But, as it turned out, it was the only zoology department in the country because all the others had changed their names to integrated biology and were tackling more modern problems. In other words, the zoology department was not as modern as it should have been.

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[4]See the ROHO oral history in progress with Dr. Heyman.

Internal Biology Review Committee

Hughes: Dan is now looking at a document, "Report of Biology Review Committee," August 4, 1981.[5]

Koshland: So this was the internal biology review committee.[6]

Hughes: Which is different than the one that was assembling the inventory?

Koshland: I think so, yes.

[reading] "The Biology Review Committee was given the task of evaluating the programs in the biological sciences on the Berkeley campus and analyzing the space needs of these sciences." Okay, that's what I remember. There was a desperate need for space. "...there are certain organizational and programmatic changes which can be made immediately in the absence of added space...The combination of new space plus organizational and programmatic changes throughout the campus can make an extremely attractive intellectual community which could be in the forefront of the ferment now occurring in the biological sciences..." This was a pretty good report, but a little blander than probably it needed to be.

Hughes: Here is another document of this same period.[7]

Koshland: [skims document] I said in this letter that I felt that we shouldn't just go for a biology building; this was a chance to re-do the program, that the program was archaic as well as the building. The chancellor must have gotten news of what we were doing and complained, and I wrote that letter about it. Probably, I was going around the campus and talking about molecular biology, and the chancellor was very concerned. I don't know who Syme is.[8]

Hughes: [Leonard S.] Syme is a professor in the School of Public Health.

Koshland: Anyway, he was, I guess, concerned that I was going to push reorganization in the direction of molecular biology, and he was right, of course.

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[5] University Hall documents, folder: Biology Reorganization, Reports & Other Documents.

[6] The signatories of the report are: A. Glazer, D. Koshland, M. Schroth, and D. Wake.

[7] Koshland to Chancellor Ira M. Heyman, July 21, 1981 (D.E. Koshland, Jr. correspondence, The Bancroft Library, 84/33, carton 6, folder: 1-7/1980).

[8] According to Koshland's letter of July 21, 1980, Syme had written to the chancellor with concerns about the reorganization plan.

The Chancellor's Advisory Committee on Biology (CACB)

Bypassing the Deans

Koshland: At the beginning of the new Chancellor's Advisory Committee on Biology [CACB], we were at arm's length with the deans and were not going to invite them to join our meeting. But then we decided it was just too difficult to have all our meetings and then communicate with them after, because they would miss the flavor of our meetings. So we invited both the deans to come to our meetings, with the understanding that they were guests and that we could ask them to leave whenever we wanted to have a private discussion behind their backs. But, in fact, we never did. Both of them were very cooperative, and they added appreciably to the success of our meetings.

Hughes: For the record, it was the Dean of Letters & Science and the Dean of the College of Natural Resources?

Koshland: The Dean of Biology in Letters & Science. We started out with Bob [Robert M.] Glaeser, and he was later replaced by Beth Burnside. Beth Burnside was very able and was, originally, one of the Gang of Four. Everybody thought she did a very good job. When the time came to appoint a dean of Letters & Science, she was picked. She was a very good dean and good person in the reorganization.

I suggested a committee which would be called the Chancellor's Advisory Committee on Biology. I remember proposing this, and I remember the reason behind my logic. The logic was, we wanted an excuse to go directly to the chancellor because we had some very bad deans. It's difficult if you're a member of the faculty to go behind the dean's back, but if you went through the dean, he would say, "We've got to wait until we meet with the chancellor," and then the meeting would never come off. The idea behind the CACB was simply to make it possible for a group of ordinary professors to report directly to the chancellor, without violating all the formalities of proper channels. That was important because we really didn't have good deans at that time.

Part of the problem was, the deans were people who had gotten out of research and maybe were ossified, but they had a lot of power. The same thing was happening with the chairmen of departments; the deans tended to appoint people who were friends of theirs or who wouldn't cause them any trouble, and so everything was getting a little ossified. The CACB did address that problem. We wanted to address it structurally. We could have lobbied, I suppose, for getting the vice chancellor to kick out some chairmen of departments, but it would have been very temporary. We decided really to go for the whole enchilada, as they say. So we wanted the CACB to control new appointments and the new selection committees. That controls the area of science for new appointments and the quality of the new appointments.

The deans discovered that we were very useful to them; they actually could do their jobs a lot better by having the advisory council. And the advisory council for its part, as I said, didn't want to do the deans' work. So after we had this big discussion, we'd say to the dean, "This is the proposed membership for the search committee; you go out and actually appoint them." So as far as the appointee knew, the dean was phoning him up and asking him to be on the search committee. The dean had all his previous authority but was sort of told that he'd better take the advice of the advisory committee before he used that authority.

Hughes: The deans were "bad" in what sense?

Koshland: Well, nice people but behind the times. Many of the faculty in the sciences--certainly the biologists but I think also physicists--don't want to be deans. Deans tend to be the people whose research careers have sort of come to an end; then they go into administration. That's a little unfair because we need good administrators as well as good scientists. But when you're a young scientist and doing well, you look on your career as becoming a famous scientist, and you don't look on your career as becoming a dean. There was almost a selection for the less good members of the faculty to be deans because the faculty distrusted deans and denied them real power. The problem became bad because the deans were not up on the latest developments in the hot new areas of science and they had a role in selecting new faculty. I was also aware that most of the best scientists I knew didn't want to be bothered with administrative duties, and as a result administration fell by default to less able people.

It was a notorious fact in our department that every chairman that was selected didn't want to be chairman. I remember when I became chairman, a group of faculty came around and asked me to be chairman, and I said my career was in full flourish, and I didn't want to spend time being a chairman of a department. [tape interruption] I reluctantly agreed because Bruce Ames and a bunch of people came around and said, "Dan, it's time. You have to be chairman." So I became chairman, and then, when I finished my five years [1973-1978], the next logical person was Bruce Ames. I remember asking him, and he said he didn't want to do it; he was in the middle of his career. I reminded him that he had come to me, and I said, "It's your duty now," and he accepted.

We found that our chairmen were very conscientious once they accepted being chairman. If they took the job, they did a good job at it. But they never wanted to be chair. This was the lure of science. You could be chairman and still do science; you were still in your department, and you carried on your lab. Whereas as dean, in those days you had to move someplace else, and you could no longer do science.

The Chancellor's Charge to CACB

Hughes: The chancellor's charge to the CACB is dated July 14th, 1981.[9] Heyman's official charge is [reading]: "The charge to the Council is to provide advice and recommendations to the Deans

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[9]Chancellor Heyman to Professors John Gerhart, John Hearst, Daniel Koshland, Richard Malkin, Hiroshi Nikaido, Milton Schroth, and Gerald Westheimer (UCB University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

and the Provosts concerning the development of an integrated and coordinated program in Biology in order to achieve a leadership role appropriate for Berkeley. The Council will be concerned with: all aspects of Biology, including the organization and identification of new areas and potential faculty, resources and priorities for their allocation in order to maintain present areas and develop new ones, the continued review of the quality of teaching and research in the Biological Sciences, coordination and evaluation of teaching programs in the Biological Sciences [,] and reporting annually to the Chancellor on the status of Biological Sciences on the campus."

Koshland: Okay, that was really my idea. There were all sorts of nuances to that charge, which I can explain to you.

Appointing Members

Koshland: My memory is the following: We had a committee of nine--the Advisory Council on Biology--and the large committee didn't get very far in the reorganization.

Hughes: It was originally seven, but CACB was expanded to nine because there was criticism that the original committee was too molecularly oriented.

Koshland: Yes, correct. So it was nine, and the nine people solved the political problem of representation.

The criteria we had when we invited people to be members of the advisory council was: We appointed you because, for example, you're a biochemist, and we want somebody who knows the area of biochemistry. But the understanding is, you're not just representing your department or your discipline; you're responsible for the good of the university. If it means you have to cut back on the biochemistry department even though you're a biochemist, we expect you to do that. Or a zoologist and so forth.

It really was amazing what happened. People really behaved very well, and they really took membership on the committee on that condition. The job was to help the university, and they knew what was going on in their specialty, but their first loyalty was to the university, not the discipline.

Hughes: Who selected the members?

Koshland: They were all appointed by Rod Park, who was acting for the chancellor, but in fact Rod always asked me who we should appoint. That means he used my advice, but he also consulted others, and if he didn't like the person, he would tell me. But, in fact, he was by then doing a great many chores for the Chancellor, and I really knew a lot about the people involved , so it helped him if I made suggestions. But I think that was very typical of the relation I had with Rod. We exchanged information, so it really didn't matter. But the committee appointment was specifically the chancellor's appointment, for which the vice chancellor was the executive for the campus.

Hughes: What were your criteria for recommending a person?

Koshland: Well, the criterion was, number one, that they had to be an expert in their field, an outstanding scientist, because we wanted these people to select good new faculty. That was a very important part of the assignment. And B) that they were a responsible citizen; they would take membership on the council seriously. The condition for being a member was that you had to meet I'd say for a couple of hours maybe once a month, and then you'd go home and think about a problem. But it wasn't so demanding of time that you had to give up your research the way a dean had to. On the other hand, you had to be serious enough so you'd spend the time to go to the meetings and think about the problems.

Hughes: Did the CACB replace the Biology Council?

Koshland: It did, finally. But at the beginning it was appointed independently.

CACB's Advisory Status and Power to Appoint Faculty Search Committees

Koshland: I remember saying to Rod that I wanted the CACB to be only advisory. They were talking about giving us powers, and I only wanted one power: I wanted to appoint all the search committees looking for new faculty. And we had in the charter that once a year we met with the chancellor. That's all the power you really needed because then the deans knew we met with the chancellor.

The persons who had previously called up the search committee were the deans. The deans were very worried about this new power; it did threaten their power somewhat. But we were really altruistic and selfish in, one, sharing the power of appointment of search committees with them: they could call up the people and make the appointment, but they had to take the council's advice. And number two, we didn't want to do all the work. To be very honest, it was symbiotic. So we said we were an advisory group, and I felt it was a very good thing to be advisory because nobody is paying you; you have no power. So the minute your advice is no good, nobody's going to take it, either the vice chancellor or the deans.

The CACB Subcommittee on Reorganization

Koshland: The first person we put in charge of the reorganization subcommittee of the CACB was John Gearhart, who was a member of the original advisory council. He's a good friend of mine, member of the National Academy of Sciences, excellent scientist, a very nice person. But he just wasn't very forceful; not very much got done. The original committee [CACB] was nine people representing a whole bunch of biological disciplines.[10] But they didn't focus that much, and people didn't want to meet that often. I had been on the original Biology Council, which is automatic for a chair of biology, biochemistry, zoology, etc., and all of the people there were very nice. But each of us felt we were there to protect our own departments. So there was not the kind of give and take that resulted when we had a committee (the CACB) where the primary loyalty was to the university and the secondary loyalty was to the department.

My memory is that it was something like May or June, and I decided we needed to have a smaller committee, not the whole nine people, and really sit down and do a good job of reorganization. That smaller group, as I remember, was Beth Burnside, Jeremy Thorner, Alex Glazer, and I. It was a subset of the advisory council whose single purpose was to do the reorganization. We agreed to meet every other week, I think, for three hours all through the summer, with the goal to have the reorganization done by September that same year, and then we'd go back to the bigger committee, and if they approved it, then they would go ahead with the plan.

Deciding on a Radical Reorganization

Koshland: I wanted to have a really radical plan in which we would have a bunch of new buildings and a really reorganized program in the biological sciences. That was the bedrock. So we then discussed various alternatives, one of which was tearing down LSB. We came to the conclusion that we couldn't do it that way. We needed to have two new buildings because we had to put people into something while we were tearing things down. Eventually, we decided to have the two new buildings and then renovate LSB.

We started to think of who would be in what buildings and how we would organize them. And then it became very complicated, and I think someone in the middle of the summer said, "Oh, well, let's go back to a more modest plan." At that point, Jeremy Thorner made a famous statement that I still remember. He said, "No, this is the chance of a lifetime, and we shouldn't go backwards." And then everybody got their courage together, and we agreed on a really radical plan.

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[10]Chancellor Heyman to Professors John Gerhart, John Hearst, Daniel Koshland, Richard Malkin, Hiroshi Nikaido, Milton Schroth, and Gerald Westheimer (UCB University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

Presentations of the Reorganization Plan to the Campus

Hughes: The first reorganization plan that the CACB presented to the faculty was dated December 3, 1984.[11] It's fairly detailed. It told people where they might have to go and which departments would be amalgamated.

Koshland: The first one to the campus, you mean.

Hughes: The first one to the campus.

Koshland: But we sent a report to the faculty before this.

Hughes: This December 3 plan was presented at the Men's Faculty Club meeting that Rod Park presided over.

Koshland: Correct. But we had sent one a good deal earlier--it had to be well before '84--where we talked about abolishing departments. That's the one that caused the tremendous fuss.

Hughes: I think it's this one, the report of the internal review committee.[12]

Koshland: I think this may be it. We decided we were not going to send it just to the chairs because we knew a bunch of chairs were deadly opposed to it, so we determined to send it to everybody on the biology faculty.

External Biology Review Committee: The 1981 and 1986 Reports

Koshland: Then we got together an external committee.

Hughes: Who made those appointments?

Koshland: I gave a list of names to Rod, who invited the people. So I gave Rod some names of good molecular biologists and biochemists and so forth, and David Wake came up with some names of people who were organismal biologists, and then we got some names from the College of Natural Resources. Botany people came up with some names. And so we had a

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[11] Chancellor's Advisory Council on Biology to Chancellor Michael Heyman and Vice Chancellor Roderic Park, December 3, 1984 (University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

[12] A. Glazer, D. Koshland, M. Schroth, and D. Wake, "Report of Biology Review Committee," August 4, 1981 (UCB University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

very distinguished list, a big range of expertise. William Barker from Cornell became the chairman of the committee, and he was very good. That committee was great.[1]

My approach is, you don't say to an external committee, "What's wrong with the campus?" and expect them to learn everything in a weekend and come up with sensible solutions. What you can do with an external committee is present them with a plan and have them criticize it, from their own point of view, their extensive expertise and experience. When they first came in, we gave them what we had as a rough plan and asked them to make their comments. Basically, what they said is that they concurred with it in general.

When the external committee came back the second time [February 1986], we came up with a much more detailed plan.[2] But the first time, they basically said we were right that the administration desperately needed to reorganize the program and build new buildings, which are the key things we wanted from the external committee. At that point, Rod and the chancellor supported the general conclusion that we really had to do a reorganization.

Hughes: That was the turning point?

Koshland: There were a number of turning points. That's what's important in a campaign like this. If we had lost our energy at that point, the whole thing would have gone down the tubes. But it was certainly a very crucial point because the chancellor and vice chancellor stood on the side of the people who wanted to do a major reorganization. That's what it really meant: a major reorganization.

Hughes: The external review committee met with some faculty members and administrators on their first trip.

Koshland: Well, of course they did. They interviewed a lot of people.

Hughes: Among others, they met with a group of seven younger faculty, who presumably were particularly interested in renovating the science.[3]

Koshland: Yes, they were good measures of the problems we had to correct. The people who were pushing it, to name a few, were I and Alex Glazer and Beth Burnside, who were older. But the young assistant professors did help because they saw the elements of decay in various departments. So they supported the reorganization plan.

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[1]The first report is: "The Biological Sciences; University of California, Berkeley, April 1981." Report of the External Review Committee. It lists the committee members. (University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

[2] "Biology at U.C. Berkeley," Report of the External Review Committee, February 26-28, 1986 (University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

[3] The 1981 report of the external review committee lists the groups with which it met, including "seven younger faculty members selected by the Internal Review Committee..."

Hughes: I didn't mean that they were leading the charge, but I imagine that they represented a vested interest in the new biology.

Koshland: Yes. I'm just adding that the supporters were not all young people. Some people become ossified at an early age and many older people welcome change. The genetics department was hiring very poor choices. What you're saying is right. I'm just saying it isn't exclusively young people who are innovative.

Hughes: Getting back to the external review committee, one point that the committee made was that it was urgent to change the administrative structure of biology. They saw the existing structure as far too complicated--the line of command was too lengthy--so that scientists couldn't easily get to where the power was.

Koshland: Exactly.

Recognizing the Commercial and Scientific Possibilities of Molecular Biology

Hughes: I'll read one more section of the external review report, which is dated April 1981. What is beginning to happen in the external world is the emergence of the biotech industry. Note how the committee recognized that: "The industrial applications of biology will lead to new sources of support for research and bring new students to the field. Both will be foci of administrative and academic concern." [tape interruption]

Continuing the quote: "It will be necessary to construct mechanisms for the conduct of industrially related research. Industrial applications will present new opportunities and responsibilities in teaching. As with advances in chemistry and physics that led to new areas in engineering, new specializations in biotechnology will emerge from recent biological discoveries. To meet these emerging demands will require new lines of communication and collaboration between biology, chemistry and engineering and completely new programs of instruction will have to be developed."[16] It's interesting to see the commercial applications for biology spelled out so clearly.

Koshland: Right. We picked a very good group.

Hughes: This is 1981, just the beginning of the biotech industry!

Koshland: Oh, sure, but remember, recombinant DNA was already out.

Hughes: Oh, it was out, but the industry was just beginning.

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[16]"The Biological Sciences," University of California, Berkeley, Report of the External Review Committee, April 1981 (UCB University of Hall documents).

Koshland: I would argue at that time that we needed a lot more molecular biology. Then the old-fashioned botanists were saying that I was just trying to convert everybody to a biochemist--because most of the people who did the early molecular biology were biochemists. My argument was that molecular biology was a tool, the way a computer is a tool, and your definition of whether you call yourself a botanist or a biochemist or geneticist is what problem you want to solve, not the tools you're using to solve it.

In migration of populations, the way the old-fashioned zoologists were doing it was by what color a squirrel was, and you could trace his origin from the color. Some of the early zoologists were already beginning to trace the migration of squirrels by their DNA. So today DNA turns out to be a very powerful tool for the zoologists, and most of our faculty at that time were missing it completely (a few were not).

Hughes: And that was happening already in 1981?

Koshland: Not right then, but that was the kind of thing that those of us who thought molecular biology was an exciting tool foresaw was going to happen, and that's why we wanted to start to get it into every department. And this outside committee saw it also.

Hughes: Yes, it did. The external committee stated that the molecular approach, the new biology, will eventually affect absolutely every branch of biology.

Koshland: Yes. And those of us who wanted change made that presentation to them when they came.

CACB Appoints Faculty Search Committees

Hughes: You said the genetics department was hiring "poor choices." In what sense?

Koshland: They were really way below the standards that we would expect at Berkeley.

Hughes: It wasn't merely the fact that they were doing classical genetics?

Koshland: Some of it was. They were doing old-fashioned genetics. We'd go to National Academy meetings, to biology meetings, and we'd meet people from other universities who we knew were very good. And they'd say to me, "Berkeley's genetics is really in terrible shape. You hired so-and-so, and we interviewed that guy. He's really terrible. Why did you ever hire him?" So it's that kind of gossip you hear. And then you look up the records, and this guy is not getting grants, so you realize the genetics department is not doing well.

We realized we had these old-fashioned departments. The logic was, if you have a terrible department, you could announce that they were not allowed to hire any more people, and a very good department, you allowed them to hire their own people. But then there were some departments that were halfway in between. And so we decided that the tactful way-- [tape interruption]

--was that we would appoint all the search committees. We had decided in the reorganization we weren't going to fire anybody. That's just too complicated in a university. But we were going to make good new appointments. We had to have some device for making good appointments. If the department has a faculty opening, the standard procedure is to appoint a search committee, because the whole department can't do the detailed work of recruitment.

This was devised as the crucial way to improve the place. The CACB would pick the people for the search committee, usually a couple of people in the department and a couple of people from outside. If it was a very good department, most of the members would come from the department, and at least one person from outside. If it was a poor department, almost all the people would come from outside the department.

Hughes: Didn't you receive complaints from the department in the latter case?

Koshland: We got a few but fewer than we expected. If you want my honest opinion--honest but arrogant--this new approach to faculty recruitment was one of the more important things I did in the whole reorganization. I get credit for getting appropriations for campus buildings from the legislature and all sorts of things, but the most important contributions were the CACB and the recruiting idea. The method we chose treaded a fine line between faculty prerogatives and the need for making a change, between giving too little power to good departments and too much power to poor departments.

Hughes: You said, when I read the charge from the chancellor, that there were implications.

Koshland: [reading a portion of the charge]: "The Council will be concerned with: all aspects of Biology, including the organization and identification of new areas and potential faculty, resources and priorities for their allocation," etc. So that is the wording I had discussed with Rod, which I'm sure he had discussed with the chancellor.

There were certain areas of research that were really very old-fashioned. People were studying ferns in botany--did this fern fit into Category A?--when people in other universities were doing molecular biology on plants and genetically engineering new plants and things like that. And we didn't have anybody doing that. So instead of arguing that we could have a botany department that did genetic engineering, it became genetic engineering exclusively in biochemistry. And people argued that doing genetic engineering was converting the botany department into a biochemistry department. So there was that kind of resistance to change.

Secondly, there was a general kind of resistance, which was caused by old-fashioned people. When somebody retired, the conservative people would say, "We've got to replace good old Joe. We've got to teach his course." My attitude was that anybody in the profession who was very good could teach an undergraduate course. A graduate course, you've got to be up on recent advances in a specific field. But anybody who's good should be able to teach an undergraduate course. Therefore, you want to pick the people in the forefront of research, and then you tell them, "Okay, you're going to have to teach this course as part of your teaching load." You don't hire people just to replace an old-fashioned course,

My standard illustration used the abacus. In the modern era, you don't want to hire one person in computers and five people in abacuses because we always taught courses in the abacus. We were hiring many too many abacus professors and not enough computer professors. But that's the essence of the change that caused the fuss. We also changed departments and organization, but it was the philosophy that was the biggest change.

Hughes: You suspect that Dr. Park wrote the charge?

Koshland: Those were the changes that Rod and I wanted. The chancellor, Mike Heyman, had to depend on his vice chancellor, Rod Park, for advice. And I'm sure Rod explained it to him enough so that he knew what he was getting into. If you're a good vice chancellor, you say, "There's going to be some opposition to this." But he also said, "We've got to do it."

Hughes: Trow says that it was your August '81 internal review committee report that he believes provided the justification for reorganization that was needed in order to present the problem to UC Systemwide administration and to Sacramento.[17] I would have thought it was this whole body of work, including the external review committee report and what the CACB was doing.

Koshland: Trow was correct. The internal review committee report was a key document,[18] but the external committee's support of the internal committee was important in getting the chancellor (a lawyer) and legislators on board. Is it the one we sent to everybody?

Hughes: That's the one that <u>you</u> think was probably sent to everybody.

More on the Chancellor's Advisory Committee on Biology

Koshland: The advisory council, which we proposed in here, is the most important single thing I advocated. In my opinion, it was clever in terms of organization. You see, the great advantage when you have a professor who is advanced in research, he's on all sorts of committees in Washington and in the country. So not only is he himself very involved in the forefront of new developments, but he also goes to committees and he meets all the other people who are in the forefront of science. So he really picks up what's advanced in the world and who's doing the advancing. That's the kind of person you want

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[17]Martin Trow, "Leadership and Organization: The Case of Biology at Berkeley," *Higher Education Organization*, Stockholm: Almqvist & Wiksell International, 1984, p. 158.

[18] A. Glazer et al., "Report of Biology Review Committee," April 4, 1981.

constantly thinking about the future of the university. That's exactly the kind of person who won't take the job unless you convince him that his time will be well spent.

So this advisory council was a device, first of all, to get those top people who had big research labs to be willing to spend a few hours a month on the future of the university. Even then it takes a little arm twisting, but at least they're willing to do that, as compared to being chairman or dean. Their specific role is slimmed down mainly to get out the areas that should be covered in the new faculty positions where departments are going to hire new people and to make recommendations of names as to the people who should be hired.

A device which I'm really proud of was that the committee would meet once a year with the chancellor. Why did we say that? The answer is that I wanted to have some device whereby the committee could talk to the chancellor face to face, without going through department chairmen or deans. Because if you say to the dean, "I want a private meeting with the chancellor," the chancellor's not likely to arrange it outside the formal administrative structure if he's a non-scientist and you're a group that's protesting. He doesn't know whom you represent. You might be another crackpot group of professors.

If you are law-abiding and send your report to the chancellor up through the dean, then it's never going to make it to the chancellor. So this device was a way whereby the advisory council legitimately can once a year communicate directly with the chancellor. And don't worry, the deans caught the significance of the arrangement right away. That meant that any dean who then ignored this committee would have to face the probability that the committee would say to the chancellor, "Dean X is really old-fashioned, and we've given him this idea and that idea, and he rejected them all."

As I mentioned, the charge also said, this committee is totally advisory. So implementing everything we did decide on the advisory council had to be handled by the deans. Then it finally dawned on the deans that if the CACB was a good committee, the dean was going to get credit for doing a lot of good things. That's why I said specifically I didn't want the advisory council to have any administrative duties. So on one hand you could say, "The advisory council doesn't want any direct-line function. They're not grabbing power." And we didn't want administrative duties because we were recruiting people who didn't want to have a lot of duties; they wanted to give advice and let somebody else do it. When it dawned on the deans it was totally symbiotic, they said, "Oh, boy! This group is going to be advising, and we're the ones who are going to call up the chairman of a department and say, 'You can recruit in this new area.'" It became obvious to everybody that the advisory council would be good. But at the beginning, the reaction was, you're going to change things; it might be terrible. So lots of people were resistant.

The Academic Senate

Bypassing the Senate

Koshland: I knew, mainly because Rod told me, that the Academic Senate would block everything we did. But I didn't know how to get around it. Rod was smart enough to say what we would do is constantly notify the senate but that we would never consult them. We did do the standard thing of putting your hat on a pole and seeing who shoots at it [chuckling], without risking yourself. At the beginning we had a trial balloon: we did consult the Academic Senate Policy Committee about one of our early provisions. Just as we expected, it took them three months to report back. They were against almost everything. It was a big waste of time.

Rod and I discussed it, and we even sent a report to a second Academic Senate committee, Privileges and Tenure. Same thing happened. By then we knew it was going to be ridiculous to consult any committee of the senate. So from then on, we always notified the Academic Senate what we were doing, but we never asked them for any advice.

Carol D'Onofrio was not the chairman of the Academic Senate at the beginning, but she became it. She was smarter at discovering bypasses than the others. She said to me at some luncheon we were at, "You're being very clever." I said, "Gee, we're telling you what we're up to. What more do you want?" You know, innocence all over my face. She said, "Yes, but you're always notifying us; you're never asking us." Then I just sort of waffled and went on.

Hughes: Rod Park yesterday confirmed what you're saying. He said it was a deliberate strategy to bypass the Academic Senate.

Koshland: It was his idea basically, which was very smart. By sending all these notices and telling them, the Academic Senate couldn't say they didn't know what we were doing, you see. But they would have to overrule a vice chancellor to stop it. [tape interruption]

I will guarantee if we had gone through the Academic Senate there would have been no reorganization. At one point I had eighty faculty members working for me on various committees. I got very good people, like Gerry Rubin, who's very reluctant to get on committees of this sort. And part of the reason they accepted membership was we were really getting things done. Important, active scientists didn't want to be in the Academic Senate because it really doesn't do anything--it comes up with a report, and it's almost always ignored. People are willing to do a lot for the university if they really feel it's going to be implemented. So my promise to people I recruited was that we were really going to make a difference. [tape interruption]

To achieve real reform in the world--this is a pontifical statement by D. E. Koshland--you need a good committee, and you need them to maintain interest. There are a lot of people in this world who become very interested in a subject--all the way from the U.S. Congress to the University of California to the PTA of your local school. And they will stay interested if they see their ideas are being used. Rarely, even if you have a brilliant idea, does it get implemented. To do so, you have to build up allies. If people who are not good administrators then fail to follow up, the people with good ideas lose interest and go back to their individual efforts.

So anyway, I heard some gossip late in the game when we were ready to implement the reorganization that the Academic Senate was going to turn down our plan--not really turn it down--but delay it by not letting us announce it in the catalog. I fortunately knew somebody named Professor Sandy Muir, who's a very prominent political science faculty member, not a scientist. We were friends. We had been on committees together. He was on an Academic Senate steering committee and told me about this. Anyway, Sandy headed it off, and our reorganization plan went through.

That event was an indication that Rod Park had bypassed the Academic Senate. Carol D'Onofrio was head of the Academic Senate. She apparently felt that these maverick people had gone off on their own.

Hughes: I found a letter from D'Onofrio.[19]

Koshland: Which says?

Hughes: She's writing concerning "consequences of Senate non-involvement in discussions to date about the reorganization of biology." And then she goes on: "...the Berkeley division has not formally been asked to review specific proposals for the reorganization of biology...[M]any view the course of events to date as a profound break with Berkeley's strong position of shared governance. Indeed, it is widely perceived that the changes taking place in biology represent a 'coup' engineered by the Administration and certain faculty members of the biological sciences. This group has been referred to as an oligarchy and an 'outlaw government'."

Koshland: [laughing] That's right.

She is not quite correct. She said she wasn't informed, but we consulted them [the Academic Senate Policy Committee]. The policy committee came back after a couple of months--a long period of time. If we had waited--but in fact we just kept going with the reorganization.

It was clearly evident that if we had to go step by step through the Academic Senate, reorganization would never have gotten done. As I said earlier, Rod said, "We got their attention"--reorganization really was important. Everybody thought reorganization was an exciting event that was going on. The Academic Senate committee was not on a realistic time schedule. Rod and I were very worried--at least we discussed it--that maybe

[19] Carol N. D'Onofrio to Roderic B. Park, September 29, 1987 (University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

the Academic Senate would appoint a committee to look into the reorganization plan. That would have stopped everything dead in its tracks.

Hughes: But they didn't do that.

Koshland: They didn't do it.

The next thing was, the Academic Senate has to approve the courses, changes in the catalog, so that keeping good relations was a very important move.

Hughes: There's D'Onofrio's letter to you, and here in my other hand I have your response.[20]

Koshland: Because reorganization would move professors around in departments, they could argue, Privileges and Tenure really had to take it up because now you were hired by one department and you were going to be judged for tenure by another. So it could have taken years for senate approval.

Hughes: She says in this letter that there's a procedure for creating and dismembering departments.

Koshland: Correct.

Hughes: Which you hadn't followed.

Koshland: Yes, we had had all these meetings with faculty about the reorganization plan. She couldn't really say we didn't tell the faculty. But the procedures of the Academic Senate dealt with getting rid of or creating a new department. We were saving seventeen departments and creating new ones with no simple one-to-one basis. That would have taken decades by Academic Senate procedures. And second, I think Rod said to me privately that the senate will never turn down something that 80 percent of the relevant faculty is in favor of. And we were pretty sure that it was more than 80 percent.

However, this plan for reorganization--I've forgotten the exact events--had to go to the Regents [of the University of California] at some point. Establishing departments, I think, has to be approved by the Regents. I remember being worried at the time, but Rod wasn't that worried. Rod said to me when we broke ground for one of the new buildings that we were making facts on the ground and the senate would have to go along.

[20][Daniel E. Koshland, Jr.] to Carol D'Onofrio, February 9, 1988 (UCB University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

Scientists' Opinion of the Senate

Hughes: My understanding is that the Academic Senate on this campus has a reputation for being a very strong organization.

Koshland: Yes, a very powerful force.

Hughes: So this took some doing.

Koshland: It took some doing. But, on the other hand, the Academic Senate is not considered as powerful an organization to the scientists as it is to the humanists.

Hughes: Why is that?

Koshland: It's because your interests in the sciences are elsewhere--making your reputation in the world. To be appointed to an Academic Senate committee in the humanities is a big thing. In our department, very few people will even accept a committee appointment.

Hughes: It is a diversion from their science.

Koshland: A real diversion from science, right. At other universities, the reputation of the University of California Academic Senate is of a very powerful force that the chancellor must bow to. So it really was something.

More on the External Biology Review Committee

Koshland: It was important in this case that the internal committee prepared the groundwork and followed up with adjustments to the plan. But then we knew that when we had the final plans, we had to have some outside group come in, mainly to give the chancellor a good argument based on outside peers to present to the rest of the faculty. The outside committee was such a good committee, they had our respect as well as that of everybody else's. They had the respect of people based on their personal credentials and the positions they occupied; they were very distinguished people. They were chairmen of departments, so they could say, "This is the kind of thing that works, and this is the kind of thing that doesn't."

We had them come back for a final report after we had had all these faculty meetings,[21] and we had taken account of the critiques of our plan. Remember, that was a big change to ask the chancellor to go along with, the abolition of many departments, and then we asked for two new buildings and the renovation of a third.

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[21]"Biology at U.C. Berkeley," Report of the External Review Committee, February 26, 27, 28, 1986 (University Hall documents, folder: Biology Reorganization, Reports & Other Documents).

Of the few people who still complained at the end, almost nobody wanted to go back to what it was before. They might have argued a little about the details of the reorganization, but if we had had to ask for a vote at the end, "Do we want to go through with the reorganization or go back to what we had before," I don't think anybody would have voted to go back. So we really had the support of the faculty by that time.

Hughes: Yet this really was an end run, was it not?

Koshland: Oh, yes.

Reorganizing the Academic Program in Biology

The First Reorganization Plan, December 3, 1984

Koshland: And then the question was how do we do it? The advice I got from a number of people was the way you should do this revision of the academic program is you go around to the senior people in the university and explain your plan to them, and then, when you've got a fair amount of support, you break it to other people. This was going to be a big, big shock--which it was.

I wish I could say I was brilliant and saw this was not the way to do it, but I didn't. I was doing my research; I was publishing a lot of articles, and I didn't want to spend a lot of time talking it over with everybody. So I said we'll just write up our plan, send it to all the affected faculty, and we'll write in large letters on the first page that this is a draft of a possible reorganization plan for Berkeley, and we welcome faculty criticisms. We had heard of cases where the department chairmen who didn't like a proposal didn't even send it around to the members of their department. So we decided to avoid that problem, and we'd just send it to every faculty member directly. So we sent the whole original plan to every biology faculty member of the Academic Senate. You can imagine what happened.

I don't think many people knew that we [CABC] were in existence. They sort of knew that Rod had appointed this committee to think about reorganization. Nothing was kept secret, but people are busy and never really hear about things. And so, as a faculty member, you get on your breakfast table an outline in which your department has been abolished, and you've been assigned someplace else.

Hughes: Dan, is this it? I have a thirty-seven-page document dated December of 1984.[22]

[22]Chancellor's Advisory Council on Biology to Chancellor Michael Heyman & Vice Chancellor Roderic Park, December 3, 1984 (University Hall documents, Reports & Other Documents).

Koshland: Yes, this is probably it. This was from the Chancellor's Advisory Committee, the big committee that approved the final plan from its subcommittee.

Hughes: You see that the plan is very, very detailed. There are general statements, and then there are plans for the reorganization of specific departments.

Koshland: We really made it detailed.

There were three or four of us who really did the reorganization. We amalgamated a number of departments, eliminated some departments. We put the botany department, which had department offices and labs in the Life Sciences Building, together with the botanists in the College of Natural Resources. And they, at the beginning, really largely hated each other's guts. The College of Natural Resources people were out in the field, and they felt the academic botanists were totally impractical dreamers, ivory tower types that weren't any help to the farmers. And the botany people in the College of Letters & Science, who were much more the well-known botanists, thought the College of Natural Resources was just farmer types and not at all academic or prestigious.

Today, they're getting along fine in the College of Natural Resources. But at that time, the idea of amalgamating would have sounded terrible to those involved. Our plan put them together. That was pretty radical at the time. We eliminated the Department of Zoology, picking all the people who were interested in whole animals and putting them together and calling it the Department of Integrative Biology. We eliminated the department of biophysics. I won't go through the details, but we made a lot of radical changes. And then the small group brought all these ideas back to the advisory council, which then made some further suggestions.

Approach to Improving Departments

Koshland: One of the early ideas was to create some really strong departments by taking all the good people and assigning the people who are not so good to some "garbage department." One decision at the beginning was that nobody was going to get fired. Departments would gradually get better by getting new good people after losing people by attrition. Secondly, we decided it really was wrong to put less good people in a "garbage department," even if we could define them. The departments always had a certain number of "stars" and a certain number of "dogs," and it was unfair to give good departments all the "stars" and poor departments all the "dogs." The "dogs" had to be distributed somewhat fairly, and the "stars" had to be distributed the same way. We were trying to make every department as good as it could be.

Starting with a Written Plan

Hughes: The subcommittee made most of these decisions?

Koshland: Yes, initially. But we referred the final plan to the full committee, which polished it further. We then sent this first reorganization plan to the entire biology faculty, not just chairmen or special people. And it caused an enormous reaction. People denounced me. I was walking in the middle of the campus, and my friend Gunther Stent was near the Campanile--a small figure in the distance. He started running down, waving his arms, shouting, "Dan, you are doing a terrible thing. It won't get anywhere." Gunther eventually supported the reorganization and was very helpful. But at the beginning he didn't like it.

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Koshland: I said to Rod at one point, "Maybe we shouldn't have done it this way, but I was just too busy to do it any other way." As I told you, he said, "Well, Dan, you certainly got their attention." That was a great understatement. A university is very busy, and everybody is going about their own business. In something like this, it was worthwhile getting everybody's attention at once instead of one pocket of faculty learning about it in January; another pocket gets around to it in April, etcetera. By giving everyone the same document at the same time, everybody was talking about it at once. It was big excitement.

Hughes: Talk about your idea of starting with a written document, instead of negotiating with the faculty first.

Koshland: We really started with a written document, this 1984 plan, partly because Berkeley is so big. To try to explain the contents of that document to individuals one by one would have taken ages, even for a small group. To think of explaining it to a large fraction of the faculty was even more daunting. The other problem that occurred to me was, whom do I select? If I select a very small group of highly influential people, then a lot of people don't know about it. And if I select a larger group and anybody is left out, they're going to be very hurt and say, "Am I not important?" So it really was just a lot easier to write it all down and send it to everybody. As I said, the idea of doing it wasn't sheer brilliance. It was sort of a compromise between the amount of time I was willing to spend and some good arguments that it was more democratic.

Opposition

Hughes: One downside of this approach that I picked up by looking at the documents was that some people apparently accused the CACB of not just thinking about reorganization but having <u>done</u> reorganization.

Koshland: That's right. I've forgotten exactly what we said in the cover document, but we said something like, "We invite your comments, and we'll change the plan based on your suggestions." People said to me at that time, "Dan, we're not fooled. Anybody who turns out a thirty-seven-page, single-spaced document--it's all decided. That's the way the university does things, and it's just token democracy that you're pretending to consult us."

I think the first thing that I would like to mention is, it really was good of the vice chancellor, Rod Park, to support the reorganization plan. I think the whole thing could have been aborted right then because of the amount of furor that it caused--it really did cause a big furor. If we had had a conservative administrator, the plan would have died right then. Most people would say, "We just can't do this [reorganization]. There are just too many people opposed." A third of the faculty in biology were opposed. Remember, there were three hundred to four hundred biologists when we did the census. That's a big fraction of the Berkeley campus, with a thousand professors. A lot of them were very angry, and a lot of them had been colleagues of Rod Park in the botany department and I knew had a first-rate "in." They could call up Rod at any point, and some of them were among the angrier ones.

We countered this as much as we could. We said, "Write in your criticism, what you want changed, and we'll consider it." We got a certain amount of flak from people who said, "You're not going to change this plan. It's all written out, and you're not going to make any changes." A lot of people did complain, and--I should be fair--there were a lot of faculty that thought the plan was wonderful. I remember one person, Fred Wilt, who was a voice that I loved because he said, "Dan, this is the most exciting thing. Since I've been at Berkeley, nobody has proposed anything as big and exciting and new as this." So there were a number of people who really liked it.

My department, which was in a new building and on top of the world, was sort of resentful of the reorganization plan because it leveled its lofty status. My wife's department [immunology], which was in the rickety old Life Science Building and having a hard time recruiting, liked the idea because there was going to be a big change.

Meeting with the Biology Faculty

Koshland: We decided one of the first things we'd do would be to get all the biology faculty together in a big room and talk about the plan. They could comment on anything they wanted. My experience was influenced by the fact that I had been president of the school board in Long Island. It shows how experiences coming from all sorts of directions help. I discovered that having a general school meeting and letting everybody speak usually ends up in chaos. But everyone learns of all the other opinions and realizes the school board has to come to a decision that won't please everyone.

I figured that would be much the same thing here. And so we had a meeting, and I remember specifically telling Rod that he didn't have to come. I figured he needed to be sort of like a supreme court: when all the fights were over, somebody had to decide. So I wanted to preserve his unbesmirched reputation. Rod really wanted to be there. He was wonderful. He answered questions directly and took a lot of the heat. It was very good he came, because even though he got accused of letting us go ahead, he left the clear opinion that the reorganization was going forward and the faculty should cooperate or their opinions would get lost.

Hughes: This was the first faculty meeting to discuss reorganization?

Koshland: This was the first meeting. What we had announced was a meeting on the reorganization--anybody on the biology faculty could come. Remember, we weren't a department then; we were biologists in many departments and four different colleges. It was a free-for-all. Everybody spoke up.

As a result of that meeting, we appointed a second subcommittee to make corrections in the first draft. I remember Bob Zucker was on one of the committees, and we called it the "second iteration." They were really a subcommittee of the original committee to reform the original plan. It came up with a second report, and after that was circulated to all the faculty, we had another meeting and another subcommittee, which we called the "third iteration." The people who were infuriated by the first iteration got some of their way in the second iteration. But then a lot of the people who had been enthusiastic in the beginning didn't like the second version. So there was still a lot of fuss.

Affinity Groups

Hughes: Was the disagreement mainly in terms of the affinity groups?

Koshland: No, differences ranged all over the map. There was a little difference between Rod and me about choice of affinity groups. Rod said we should let people vote themselves into their own preferred affinity group. I was more for assigning the people on programmatic grounds and letting them argue if they felt we were wrong. There were affinity groups in the sense that we put the zoologists together and the biochemists together and the geneticists together. There are people who just obviously fit in those categories. But there are other people right on the borderline; you don't know whether he's a geneticist or a biochemist. So you had to adjust the arrangements. So it became a mixture of what Rod and I had suggested.

Hughes: Affinity group meant affinity by discipline, right?

Koshland: Right. And use of equipment.

Hughes: You modified the concept of an affinity group because of practicalities?

Koshland: The affinity group, as I said, was never that dominant a theme in the sense that we never defined affinity group precisely. It was something Rod pushed and something in the back of all of our minds. But I think Rod's idea was that people would just say whom they wanted to be with. That was a little too vague, so we had to assemble people by discipline. But we did have many exceptions and we did take people's wishes into account.

The disagreement was mainly from people who didn't want to be in the group to which they were assigned, or they felt their group was too big, or they wanted a different mix of disciplines. The net result was that the affinity group concept was modified. Then some people who liked the original plan didn't like the modification, and so I think we finally went through three iterations.

Hughes: Four.

Koshland: Four?

Hughes: At least there were four meetings to which the faculty was invited.

Koshland: Okay, well, whatever--it was three or four. I think there were three written plans.

Hughes: Louise Taylor told me that faculty attendance at the meetings on reorganization gradually declined.

Koshland: Declined, yes. People were getting happier with the procedures after each iteration, so there was less vocal opposition. Our subcommittee was very good and really modified the reorganization plan to improve it. The fact that we did change in response to the criticism also mitigated the charge that we had no intention of changing.

The third iteration brought it back closer to the original plan than the first iteration. In other words, our original ideas were really pretty good. It was quite clear when the second iteration people made some changes that were more radical than was wanted. Then other people saw they weren't so good and changed them back closer to the original. But there were real changes that improved the plan.

Merging Biochemistry and Molecular Biology into a Mega-department

Hughes: You mean you took Professor A out of Group B and put him or her somewhere else?

Koshland: For example, I remember in the beginning, we did keep molecular biology and biochemistry separate. Then it became very logical to merge them. Those were two of our better departments. We had decided it wasn't logical to put two of our best together. But then in the final plan we decided to merge them. This was a big decision for the following reason: biochemistry and molecular biology were two of the bigger departments, and they already filled up buildings. We had no building to put both of them in. We finally decided, educationally and structurally and organizationally, it was better to have them in one department. They would be in two buildings, but they'd be one department. That meant we had to think of ways of running departments even if they were in separate buildings.

Another change was that we had people up in Stanley Hall doing animal experiments, and we were told by the animal care committee that we couldn't possibly have everybody in every department using animals. The new rules required animals to have very special care, and they had to have them in central buildings. So we had to change the plan from that point of view and put all the animal facilities at the other end of the campus. So there were really substantive changes from the initial plan. [tape interruption]

Hughes: Why put molecular biology and biochemistry together?

Koshland: Well, we said they went so logically together in terms of interest and common equipment. We were concerned that it was too big a department, and then we decided that wasn't true; it was better to have a big department. And then people argued, well, the genetics department wanted to be in the molecular biology and biochemistry department because it's very similar, and genetics needed the association with stronger departments. So then the department became even bigger. I remember one of the criticisms of the plan: people called it the mega-department, which is the department we now have, which is a hundred people. That is the biggest department on the campus. The argument was, "it was ungovernable; it was too big."

Hughes: Isn't molecular and cell biology an affinity group?

Koshland: That is an affinity group. I think the idea was that it included all the people using ultracentrifuges and molecules and that kind of equipment versus the people using cages and whole animals. If you define affinity group by concepts, it's one way; and if you define it by equipment, it's another way. In fact it was good to have people together who thought along similar lines because they read the same literature and they had more reason to talk to each other. But in fact, there were people using cages who were all the way off in biochemistry, and there were people using ultracentrifuges all the way in genetics. So even though you had general concepts, you finally had to decide that Professor X, who was a geneticist, belongs in the biochemistry group, rather than in the population genetics group.

At the beginning, I thought we would keep the old department names the way they were and lump the departments into a division. Our feedback from the faculty was they didn't like that. They wanted to call the overall thing the department and then call for divisions within the department. Some explained it to me in the following way: I want to be in the department with Professor X, who is very well known; being in the same division isn't the same thing. The outside world uses "department" as the smaller unit, like biochemistry, and "division" as the amalgamation of departments, like Letters & Science. So people wanted to be in the same department as the stars.

Several Iterations of the Academic Reorganization Plan

Koshland: We had the third iteration, and we got a pile of letters back. We always invited letters. Each person on the CACB got a packet, so each member of the council could read these letters. At a meeting after the third iteration, the members of our committee were all a little depressed at the number of people who wrote in criticizing. I came in late, hadn't heard the conversation, and dropped my packet on the table and said, "Well, there's nothing important in that stack." And everybody burst out laughing, because they had all been depressed. What I meant was not that it wasn't important to answer each person, but the criticism was all by that point about petty things that we'd expect from many individuals. These were a myriad of little problems that had to be fixed up, but it was quite clear that the general principle of reorganization was now pretty well accepted as there were no criticisms of the general structure.

At one other subsequent meeting I said, "Well, I think 90 percent of the faculty is now behind the reorganization." And I think Beth Burnside corrected me and said, "Dan, you're wrong; it's 95 percent." So it was pretty clear to everybody that we were on our way in the final lap. The adjustments we made in the iterations were very important to people, so they were real improvements. The mergers and movement were not just cosmetic changes; they were substantive changes.

Support from the Chancellor and Vice Chancellor

Hughes: There's an oral history in progress with Dr. Heyman in which he says that he bought the idea of reorganizing the biological sciences. Why was he supportive?

Koshland: I think we made a good case. I think biology is easier to sell in the modern era than, let's say, physics. Physics was easy to sell after the atomic bomb. You had to have physicists around to keep ahead; otherwise, other nations would get ahead. The Russians were now getting the bomb, and they weren't very friendly. The same need is true nowadays for biology. It was pretty obvious that health and disease were becoming very big factors in the life of everybody, and therefore biology was a pretty good sell. It's even more in the headlines now.

Heyman is a smart person, so A) he felt that it was a very important subject, B) a good fraction of his campus, I think 30 percent or something, were biology professors, so it was an area that he knew was important, and C) I think we did a pretty good job of selling him that we really were archaic in certain programs and needed them improved. And then we had some physical plant inadequacies. The age of LSB was the same as San Quentin. San Quentin was so dilapidated, you couldn't ask prisoners to go there. We were asking students to go in a building that was equally old. So anyway, we exploited the negative that the buildings were old and the positive that our new program was good.

The mood changed from a majority in opposition to a majority in favor about the time of the second iteration. It became pretty obvious that reorganization was going to be achieved. Part of the reason was that the vice chancellor was just very good. He didn't meddle individually, but he made it clear in private discussions that reorganization wasn't some crazy idea of a couple of nuts, that it was something the chancellor was really behind.

Hughes: Did he do that by relying on his own network of science colleagues?

Koshland: No, I don't think there was any one network. Rod was very supportive, right from the beginning. I urged him to be less supportive because I thought he'd damage his credibility, that he'd be considered too much on our side. He was much more willing to be there early than even I thought was a good idea. But in retrospect, he was right and I was wrong. But what I did say to Rod was that anybody who complained should be allowed to go to him. Rod was a little concerned that I would worry if people were encouraged to go behind my back. I said, "Absolutely not, Rod. I want everybody to be able to complain to you. This is a free speech area. We're not going to fiddle around with that." He suggested letting everybody come to him, but that he would always inform me of the criticism and preserve the anonymity of the complainer. We used that system.

For example, if somebody said, "Well, Koshland is doing everything just to help the biochemistry department." Rod would sometimes answer just from what he knew, but sometimes, if he didn't know, he would call me and say, "I heard this gossip." But he'd never say which professor had said it, and I didn't want to know. I just gave my answer and let him handle it from there.

Hughes: And then what did <u>you</u> do?

Koshland: I had plenty to do. I didn't have time to go around answering all gossip, so I just depended on Rod. Sometimes it worked in reverse. If I heard various people were criticizing him, I'd give him what I called my early warning system. I'd call up and say, "They're saying this and this about you. I thought you'd like to know."

Hughes: And then he would take steps to--

Koshland: --counter that.

<u>Importance of the Koshland-Park Relationship</u>

Koshland: The informal relationship that I had with Rod was very important to the success of the project. His willingness to stand up to criticism and the fact that he was honest with me, and that we both could take criticism without reacting, "I want that guy fired," really helped. That's the kind of informal factor that doesn't appear in Trow's report.[23] I think in many of these things, the personal relationship between the principals becomes very important. Rod had to handle the reorganization from the governing structure, the Academic Senate point of view, and I had to handle it from the faculty's. It's just better if a faculty member communicates with other faculty members, and it's better for an administrator to go around with other administrators.

Hughes: Had you known and worked with Roderic Park before this?

Koshland: No, not at all. It worked out wonderfully, and we've become very close friends. One might say, reorganization would have worked with anybody as vice chancellor, but I know it wouldn't have. The people who followed Rod were one named Kui and a second named [John] Heilbron.

If either [Ken] Kui or Heilbron had been vice chancellor instead of Rod at the time we started, it never would have worked. And--I'll be honest--I don't think it would have worked without me. You needed a faculty member who was willing to spend time on the reorganization. The faculty member has to be pretty prominent. In other words, I had to have credibility as a scientist, and the fact that I was a member of the National Academy and things like that was a big help. I had, in addition, to be willing to go around and talk to people.

Hughes: What about having a well-placed spouse?

Koshland: That was very important. But I got feedback from a lot of people of whom she was the most important.

Hughes: She was another pair of ears.

Koshland: Yes, she was, and a very honest and perceptive pair of ears. I'd come home and I'd tell her what happened during the day, and she'd tell me, "You should do that over again," or "You made a mistake here." She was very wise and very helpful.

The Construction Phase

The Building Plan

Koshland: We then had to go to the legislature, and we got approval for the building funds.

Hughes: Who is "we?"

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[23]Trow, pp. 148-178.

Koshland: We ought to go back one minute: Mike Heyman entered into it very importantly on the overall scheme. Of course, Rod was the person I dealt with day-to-day. Our committee finally decided that we needed two new buildings and to renovate LSB. The ideal plan was to tear down LSB and build two new buildings. I've forgotten how expensive it was, but it was plenty, over $200 million. And then there was a middle plan, which was the one in which we would build two new buildings and refurbish LSB. And then a minimal plan, where we took people out of LSB and sort of refurbished it.

What we said to Heyman was if we did the minimum plan, we were going to lose faculty and would not get very many good new ones. That would really be a disaster for Berkeley if it still wanted to be number one in the country in biology. And the ideal plan, we were pretty sure, was going to be too expensive. So we recommended the middle plan, and that's what Heyman went along with.

The committee came up with a building plan and a program plan, and the two were inextricably related because we knew we'd never go to the legislature and get the money just to fix up the buildings. You had to have an exciting new program. The legislature always says, "Berkeley has got plenty of money; we don't need to give them any more." [tape interruption]

One third of the money was to renovate LSB, the idea being that you would build the two new buildings and move a bunch of scientists into those buildings, and then move the people out of LSB into temporary quarters, refurbish LSB, and then move the people back in. And that's what was done.

I remember I was called by the president's office--Bill Baker, I think, who told me the people on the governor's budget committee in Sacramento would give us two-thirds of the money if we'd raise one-third. I was then called into the chancellor's office, and I presented that proposal to him, thinking this is the end of it. He's going to say there's no way Berkeley is going to raise $50 million or something like that. A public university had never raised anything close to that amount. I remember Heyman jumped up from the table and he says, "All right, let's get it."

Hughes: Really!

Koshland: Just like that. I mean, it was just wonderful. I reported this to people all over the campus.

Rod also did something else clever near the end when some faculty were still dragging their feet. He put up a chain-link fence around the construction site and tore down some trees. It sort of indicated it was a fait accompli; you can't stop it now. By then, the biology faculty was pretty much in favor of the reorganization plan, and so we were really over the hurdles.

A Shift in UC Fundraising Policy

Koshland: The chancellor not only said, "Let's go," but he really started putting fundraising on a professional basis. I think that is a blessing of the biology reorganization, that it really started a major public institution depending more and more on private support. But that was the dramatic shift.

Hughes: Was it?

Koshland: Oh, yes! Berkeley had always had little alumni groups asking for support, but this was a major undertaking.

Hughes: Before that, the state was the main source of UC funding?

Koshland: Yes, but in the 1980s state support was constantly dwindling. This was the first time anybody really got enormous commitment to raise a major part of the money from outside the campus.

Hughes: Did you go to Sacramento and lobby?

Koshland: I've forgotten whether I went once or twice. I remember a guy in Oakland offered to fly me up in his private jet. I refused, and it turned out he was a very big developer who was trying to influence Willie Brown, who was the speaker in the legislature. He wanted to get something out of Willie Brown. I turned him down because it was easy to drive. It's only about an hour away. I just felt I wanted to have a car and be able to get out on my own time table. But it would have been very bad if I had gone up in a plane with him.

Dealing with the California Legislature

Koshland: Heyman, who was chancellor of the UC Berkeley campus, was the main person dealing with the legislature, and Heyman's relation with the legislature was excellent.

Hughes: Why was that?

Koshland: He was a good liberal Democrat. He spoke their language. He's a very personable person. David Saxon, who was a physicist, was president of the UC system at the time, and he had terrible relations--

Hughes: With the legislature?

Koshland: Terrible relations. A lot of the legislators would call up and get advice from Heyman on things in relation to the university when they should have called Saxon. The legislators didn't like the chancellors of each individual campus coming up to them and lobbying, so they made a rule that it was only the president of the whole university that could talk to the legislature. But you couldn't stop an individual legislator from phoning Mr. Heyman and saying, "What's going on here?"

I really wasn't involved in that, so I don't know for sure. But I talked to enough legislators and people at the governor's office, and they all said that Heyman got along very well with the legislators. This was money in the bank of cordial relations for the approval of the final project. Those relationships held us in very good stead.

Hughes: How hard was the proposal to sell to the legislature?

Koshland: Oh, it was very hard. At the time, Jerry Brown was governor, and he was not very friendly to the UC campus. That was well known. When Brown started out, there was a state deficit. Certainly it didn't look very good. But there was one big advantage I didn't realize. What we were proposing was a construction program that would have taken up the whole university allotment for buildings and capital campaigns. What had happened was Berkeley in the previous ten years had asked for very little money from the legislature.

Hughes: Trow made the point that one of the reasons that biology had slipped at Berkeley was that the UC system as a whole was putting its attention on building up the new campuses.

Koshland: That's correct. Berkeley had built very little in the previous ten years. As a result, when we came along with this project, it was considered by the other campuses as only fair; now it's Berkeley's turn. Remember, you had to do two things: You had to convince the president of the UC system to back this thing, and then the president of UC and the local campus had to get it in the governor's budget and go to the legislature and argue for it.

Hughes: How were Heyman's relations with Saxon?

Koshland: I think they were good enough. Near the end, it switched to [President David] Gardner. I'm not sure Heyman's relations were always great with Gardner. At least I heard rumors. But good enough.

Hughes: Getting Gardner's support wasn't a problem?

Koshland: That wasn't a problem. Gardner certainly felt this was a good project, and he was completely behind it. I think the person who presented it and who had a key influence in Sacramento was Heyman. That was very lucky for all of us.

The other person who was key in the legislature was Bill Baker, who was in the [UC] president's office. He was the one that gave me all the advice about dealing with Sacramento. Heyman really did it in the final persuasive presentation. I never dealt with any of those people, although they came down here and asked us questions. But the rules were, I didn't go up there independently, only chancellors and presidents dealt with the legislature. But we had to provide him with background.

Hughes: Did the CACB provide the background data?

Koshland: Yes, and we had to have new special data with new committees once the campus approved the project. Then, when we started to meet with architects, the CACB couldn't be at every meeting. So Rod would delegate it to me, and I in time got Alex Glazer to head the faculty committee on construction. With information I gave him, Rod appointed Louise Taylor to be the administrative liaison for the whole project.

It went sort of fast. They announced a legislative committee was going to come down in two months, and we had to have a presentation--how much the buildings were going to cost, what professors were going to go into this building. Those things all sound very easily done, but it's not so easy. [tape interruption]

A Dinner with the Governor

Koshland: I hosted a dinner in San Francisco with Governor Brown and Willie Brown and Julius Krevans. Krevans was chancellor at the time of UCSF. The person who arranged it for me was Bill Coblentz.

Hughes: And who was Coblentz?

Koshland: Bill Coblentz was a regent and a very prominent lawyer in San Francisco, who was also very prominent in Democratic circles. He was very, very helpful. He's a friend of mine and a distant cousin. I wouldn't even know how to go about getting the governor and Willie Brown to attend a dinner with a bunch of professors, but Bill arranged it. Governor Brown came in late. He had met Sargent Shriver that day, and he proceeded to describe how Shriver had said there was a new development in--remember, this is 1980--computers such that kids--for example, in Africa--wouldn't need to learn to read and write; they would just learn computers, so that in this modern age, we wouldn't be teaching kids in Africa the same way we were teaching kids in the United States. Everybody was very skeptical of it. He was going on and on.

It was quite clear that the tone was kind of condescending about the kids in Africa. I could see on my left that Willie Brown was getting madder and madder about the whole thing. It went through my head that I had to stop the governor but here's a little professor at Berkeley, and it wasn't my role to interrupt the governor. On the other hand, nothing was going to get through the legislature if Willie Brown didn't want to do it.

This dinner wasn't to propose the plan; it was to get people together and talk about the background a little bit. I could see the plan was going to hell in a basket. At this point, Julie Krevans spoke up right across the table and said, "Dan, I want to tell you about a great program we're doing here at UC San Francisco." And he talked for about ten minutes about some cardiac clinic. But I knew exactly what he was doing. He was just so smart. He figured out there was no way that I could interrupt the governor because I had a program which needed his support. He had no immediate program. He could afford to have them furious at him for a brief period if he appeared like a bore who wanted to talk about his thing. And he talked just long enough so everybody forgot what they had been saying. We eventually resumed talking about something totally different. I said to him after the meeting, "Julie Krevans, anytime you want to ask anything of me in the future, I'll do it for you. That was such a wonderful thing to do."

Hughes: Did Krevans admit that he had wanted to interrupt the governor?

Koshland: Sure, he knew exactly why he did it. It was just wonderful. I knew Willie Brown was about to get up from the table and walk out. It was really funny how well Krevans did it.

Hughes: So Dr. Krevans saved the day.

Koshland: Dr. Krevans saved the day.

Finding Support from the Legislature

Hughes: You said you went to Sacramento once, but I gather Heyman and Rod Park were handling the legislature.

Koshland: Yes, I don't think they went that many times, either. The main person who did the Sacramento thing was Bill Baker.

Hughes: Who is he?

Koshland: Bill Baker was in the president's office in University Hall in Berkeley. They've now moved to Oakland. He was legislative aide to the president of the university, and he was very, very helpful.

Baker really knew all the ins and outs. In spite of the fact that [Governor] Brown was sort of lugubrious: he didn't have the money, and he clearly didn't want to help the university. But Baker would come back and tell me that he knew people on the staff of Governor Brown who were Berkeley grads, real afficionados of the university. Brown is a person of low attention span, so that he wouldn't even know the details of the budget till almost a week before. The governor would have to present the budget to the legislature. The staff, with many UC loyalists, would include this big construction project for the University of California at a stage when it was very difficult to turn down.

Baker knew how to maneuver. The state had committees, and the people in the governor's office came down and visited us. Essentially we got the plan almost done, including the money and what the buildings were going to be, without the governor ever even seeing the plan. It wasn't concealed from him; it was just routinely done, and they just didn't discuss it very much.

What happened was--and this was Baker's cleverness--it finally came to the governor a very short period of time before the legislature for the whole statewide appropriations met, of which, you can imagine, this was a large amount of money to us but quite small to the whole state budget. So Jerry Brown was not going to hold up the whole budget just for this little item for the University of California. His advisors all said yes, it's the right thing. I don't know whether he opposed it or not, but whatever happened, he went along with the process.

Hughes: What is there to say about the construction?

Koshland: Well, the actual construction was also something I thought Rod handled very well. Everything, except the animal facility, was more or less routine. Rod had the area where the construction was going to be down by Oxford [Circle] fenced off well ahead of time. With no announcement, all of a sudden there were bulldozers and they were doing it. So it was a fait accompli very quickly. As a result, there weren't any sit-ins.

Diffusion of the Molecular Approach

Hughes: We've talked a lot about the internal pushes for this reorganization, but what about the external ones? Namely, the flowering of the biomolecular sciences and the growing need for interdisciplinarity.

Koshland: That's very important, and I'm glad you brought it up. Molecular biology, the recombinant DNA revolution, was one of the things that I felt we had to introduce into some of the departments. Particularly botany, integrative biology, and zoology were way behind the times. Since molecular biology really started in biochemistry departments, the organismal (whole animal) people identified this field as biochemistry. When I said I wanted people doing molecular biology, they thought I was trying to impose biochemistry on everyone in the biological sciences. A lot of the older people thought Dan Koshland is just trying to convert all of us into biochemists.

I responded by using computers as an analogy. "What you're saying to me is, we've had the abacus for years, and we want to continue to use the abacus. I'm asking to replace those old standard things we've had for years with a new fad called computers. What I'm saying to you is this new molecular biology is just like computers. It isn't a science by itself; it's a way of doing science. It's a new, powerful tool that will be useful across the entire range of biological science. You're going to be studying things like populations and lineages using molecular biology, not the way the way I'm using it. But you're going to find DNA and those things very useful to your goals. You've got to start getting people in that area in your department or Berkeley is going to be left way behind."

Hughes: How receptive were they to that argument?

Koshland: At the beginning, there were some people who were dead-set against it, but there were others who were for it. One of the people on our advisory council [CACB] was James Patton, who was a professor of zoology. He was all for doing molecular biology. In fact, that department held out longer than almost any other department, but now they're doing molecular biology all the time. Some of the foresighted ones saw that they had to start doing it. But I wasn't trying to impose biochemistry on them. I just wanted them to be more modern.

More on Faculty Recruitment Policy

Recruiting in New Fields

Hughes: Louise Taylor said that one of the premises of this reorganization was that because Professor X had left or was retiring, didn't mean that you necessarily appointed a new person in that very field.

Koshland: That's correct. So now we come back to the advisory council and appointments. What we used as conditions were, we, the CACB, would name the members of the search committee. If we proposed radical people, the dean could always say no. Moreover, the department was making the final decision on the appointment. They could say no to a proposed member of the search committee. But they would have to give a reason, and the dean could overrule them. In fact, it never arose; I mean the department never used a veto against a search committee.

Moreover, what we asked is that the search committee report back to us. You generally have a list of candidates, and you decide to offer the job to number one, and if he doesn't take it, you offer it to number two. So if the department made a preference list of A, B, C being one, two, three, and the search committee made a list of A, B, C being one, three, two, we didn't worry. If the search committee was totally out of sync with the department, the advisory council would look it over and say the department is not doing very well. But mostly what happened was that the department and search committee agreed.

The advisory council never imposed anybody on a department. We always said the department has veto power. However, if the department chose somebody we didn't want, we felt free to recommend that the faculty position we preferred be given elsewhere. So the department would lose the appointment. They couldn't argue we were imposing somebody on them that they didn't want, but if they weren't willing to be modern, they wouldn't get a new appointment.

But the main conflict was about going into new scientific areas. Let's say we didn't have anybody on the campus in developmental biology. We said, "Okay, we'll give the botany department a chance to recruit in developmental biology." And if botany said they didn't want to, we just said, okay, the zoology department will be developmental biology. So then the botany department would lose the chance of going into it, and they'd lose the FTE [Full Time Equivalent position]. There was no obligation to replace Professor X with someone in the same field. The rules on this campus are if somebody doesn't get tenure in department X, then the FTE automatically goes back to the same department. But when somebody retires or leaves the campus, then the FTE goes wherever the chancellor assigns it. And then the chancellor can assign it to a new department. Most of the time, he assigns it to the department that lost somebody, but he doesn't have to.

Hughes: Who advises the chancellor?

Koshland: Oh, all sorts of people--chairmen, deans, and everybody. The department can write a letter saying, "We want the FTE back." But if somebody retires in English, the chancellor can give a new FTE to physics.

Hughes: Does the CACB enter into discussions of that nature?

Koshland: Of course. For example, one of the first things that really pleased me--one of the key events right after the reorganization was approved--molecular biology put in a request--that was one of the better departments; it had a lot of prestige--to replace Robley Williams, who was an electron microscopist, with another electron microscopist because they had all this equipment left over, and they really wanted it to be used.

At that time, we felt that developmental biology had no representative on the campus and was an area we all felt was going to be big. So we said, "No, we won't give you the FTE to hire somebody just because there's a lot of equipment lying around. It will be difficult for other departments that don't have the prestige of molecular biology to get somebody in this new area, whereas molecular biology would be perfect. If you want to recruit for a developmental biologist, we will say 'go.' If not, we'll give the FTE someplace else." They said, "Sure, we'd like to do it." In fact, there was a fair amount of pressure from the advisory council, but it was all very polite. It helped our credibility, since I was identified with molecular biology and biochemistry, that we were willing to tell molecular biology to change and that we did not just give in to them. So that was very helpful.

Gerald M. Rubin

Koshland: We were lucky that one of the first recruitments after the reorganization was Gerry Rubin. We had figured out that he was a very logical candidate. He was young but already famous in molecular biology and in *Drosophila*, fruit flies. Thus, he had interaction with entomology, biochemistry, and genetics. Many departments were very, very excited about having him. They knew about his work. We said when we recruited him that he could go to any department he wanted on the campus. All the various departments made overtures to him. It helped a lot as people realized that we were recruiting for the good of the university. No matter what department Rubin ended up in, the entomology department would be pleased he was here, the genetics department would be pleased he was here, the biochemists were interested. He was a very important appointment because he was the first after reorganization and a very prominent young man at the time.

The Howard Hughes Professorships

Hughes: Now, he's a Howard Hughes professor.

Koshland: Correct. He wasn't a Howard Hughes when we recruited him.

Hughes: That wasn't a plum?

Koshland: No. In fact, the Chancellor, Heyman, had given me a MacArthur chair to bestow. He called me up and said, "You can use this for recruiting." It was very important to me that the first major appointment after the reorganization would be a plum appointment. I wanted it not only to be excellent so various people would say it's very good, but I wanted it to be seen across all of biology as a very important appointment. He was absolutely ideal.

Hughes: Did the Howard Hughes professorships come as a result of reorganization?

Koshland: I would say yes and no. The yes was, the caliber of the people we were recruiting made it more probable to get a Hughes professor. Tij [Robert Tjian] was here during the reorganization. We had hired him before. Gerry Rubin was one of the people we hired after the reorganization. And they were the two first Hughes professors at Berkeley. That was very, very important because they had never given Hughes professors to any nonmedical school before. That required a great deal of maneuvering, which I did. And I was helped by the fact that I was editor of *Science* at the time.

The Project Planning Guide for Construction

Koshland: The architects were supposed to draw up a plan to present to the legislature for the new building and answer to the state legislature's code and other things. They basically didn't do it.

Hughes: They didn't do it at all?

Koshland: They didn't do it at all; they didn't even start on it. Somebody in the chancellor's office paid them their final bill before they had done this. As a result, Alex Glazer and Louise Taylor--I've forgotten who else--spent a weekend preparing the whole document. It's called a PPG.

Hughes: Project Planning Guide.

Koshland: Okay, the Project Planning Guide. That had to be submitted, and that had a lot of detail in it: the size of the building, how it was going to be taken care of. For example, the legislature would only allow us to increase the amount of space per professor by a certain amount. We were already going over the code they had established statewide. We said this was the last building, and if we were going to compete with Harvard, we had to give our professors more space.

So then this overall plan had to show we didn't exceed those standards by more than agreed upon for the average space given to professors. Space for teaching classes or for the library or things like that didn't count against research space. But it meant you had to look over the whole space and what each professor was getting. This group from the legislature was coming down Tuesday, and on Thursday we found out this other group, the architects, hadn't done it. Alex and Louise and somebody else spent the whole weekend writing a PPG, which is unbelievable.

Hughes: Yes, you had some good people.

Koshland: Well, we had good people, but I said we're never going to do that again!

Appointing a Judicial Council

Hughes: I read in Trow's article of a judicial council that was appointed to deal with complaints.

Koshland: Correct.

Hughes: What was that about?

Koshland: I've forgotten--some of it is pretty vague--but Rod and I agreed right at the beginning. We said sooner or later we're going to be assigning people to buildings, and the biology faculty as a whole is going to vote on whether or not we do the plan. But then if you do the plan, you're going to eventually say Professor X has to go to Building Y and he won't like it.

We wanted to have some device to adjudicate, since Rod was very closely identified with reorganization and so was I--we wanted a supreme court of people who were not involved in this, to make a decision on whether or not this guy who, let's say, was an outspoken critic of the plan, got a fair judgment.

If you had to have the judicial committee made up of somebody, say, in the law department because everybody else had a big axe to grind, they might not understand the problems. But fortunately, at the end of the thing, there were some people who were not directly involved. So Rod appointed a committee to take up complaints. My memory is, the complaints were almost zero. We had maybe two or three cases at most.

Hughes: Over time, you had a lot of complaints.

Koshland: Oh, we had a lot of complaints about the plan, particularly at the beginning, but, in the final plan that went through, I think we had only one or two professors that really objected to where they were being asked to go.

Failure to Create a College of Biology

Hughes: Why was the idea of forming a College of Biology rejected?

Koshland: The College of Biology was really a good idea, and the main reason was because you could form some cohesiveness to all the biological programs. We were getting cohesiveness by informal cooperation anyway, so it wasn't quite that crucial for the programs. What it was really good for was raising money. The College of Engineering and the College of Chemistry were the two best groups on campus for raising money. I don't know about the law school. They have their own colleges, and they can hire their own development officers. It's something we still feel.

The opposition came from two groups: The College of Natural Resources--a lot of the chairmen were against it because they were still representative of a more old-fashioned group, and they didn't want to be overwhelmed by the College of Letters & Science, which they felt had more prestige and would be likely to outvote them. The second opposition came from the College of Letters & Science. The provost, Ken Kui, an astronomy professor, and many other people were opposed. The biologists represented a big, major intellectual and financially powerful group. They didn't want them to leave the college. They felt it would create a big vacuum. So we had opposition from the College of Natural Resources people, who didn't want to be engulfed in the college, and from Letters & Science which didn't want the biologists to leave. I think it could have been done. It's just we couldn't do everything all at once, and so nobody got in charge of it.

Hughes: Is forming a College of Biology still a discussion point?

Koshland: I think it's still discussed. They haven't found any good leader to do it.

Reorganization and the Teaching Enterprise

Hughes: We haven't talked specifically about how reorganization affected teaching.

Koshland: No. The outside group complained to me that we had organized this [reorganization plan] pretty much around research and that we hadn't organized it around teaching. In fact, they called me in to a special session. I basically said to them, "You're absolutely right. We have not focused on teaching for a couple of reasons."

First of all, the feedback in general was Berkeley's teaching was very good. When the kids from here went to graduate schools or medical schools, in general we got no complaints. They were really well trained compared to others. In fact, many of the students complained that they were hearing the same things over again in medical school as they had heard as undergraduates.

So A) we didn't have a major problem. And B) I had exhausted all the people who were willing to work on committees. I had so many faculty on so many committees that I felt there was no way I could organize a whole separate group of committees. We'd just run out of people to do it. I felt that by getting good professors, they'd teach well. We did have to consider teaching and do something about it, but it wasn't urgent. It was not as urgent as getting people in the right areas, because you can't teach if you don't have the right people. And so I just threw myself on the mercy of the court and said, "We just can't do it all at once." So that's the way it ended up.

Hughes: When you actually began to move people--first out of LSB and then back in--was teaching disrupted?

Koshland: Well, sure. One of the great things was that Beth Weil, as biology librarian, kept the whole library going. It was in quonset huts and special facilities. She did a great job. You always have to cope when you're building a new building and people are moved. But in general we moved pretty fast. There was a certain amount of money set aside to make the faculty have an easier time moving than they might have otherwise.

Some of that money got used up in overruns on the building. But even so, we had a fair amount. I didn't want people, in addition to being forced to move, that they were also forced to pay for their own move. Most of the money was provided as part of the reorganization.

Animal Rights Activism

Opposition on Campus

Hughes: How did the animal rights issue work out?

Koshland: The animal rights issue ended up as a big plus in a very peculiar way. Because it was biology, animal rights were always important. There were a couple of scandalous things that had occurred--scandalous from the newspapers' point of view but not really important. We had broken a rule because the walls in the rat quarter weren't washed down once a week.

Most of the professors were very conscientious about their care of their animals. But there was a case where somebody had some cats and rats, and they were taken care of by a student who was doing the research, and the student left on a vacation and delegated it to one of his friends, who forgot about it and then didn't feed them. The rats were starving and ran out of water and things like that. This got in the newspapers and added fuel to the fire. As a response to these problems, we decided to build the Northwest Animal Facility. We needed more animal facilities anyway. So that became part of the reorganization. It wasn't in the original plan.

Episode in the California Legislature

Koshland: Elliot Katz, a lawyer and an outspoken opponent of the university, was always denouncing the university on every occasion. The reorganization plan had gone through legislative committees and been approved by the governor. Then the whole appropriation had to go through a final joint Senate-Assembly committee for approval, which was chaired by Senator [David] Roberti, who was a big animal rights advocate. He was supported by a whole bunch of movie stars, who complained about fur coats and all sorts of animal agenda items. The fundamental plan was 95 percent with a 5 percent animal facility tied into it. We were very apprehensive about it.

The animal rights people were mainly interested, of course, in the facility for the animals. But it was a facility which would be a Waldorf-Astoria for animals. It [chuckling] would have animals living under more palatial conditions than any animal had ever lived before.

Hughes: Including the faculty [chuckling].

Koshland: Correct. But even so, we knew the animal rights people were going to oppose it one way or the other. Heyman was to give the final speech for the plan, because he was the chancellor. It was decided I wasn't needed, and I'm not sure whether Rod went with him or not.

It made us very apprehensive because Heyman was a lawyer and couldn't know many of the details. We filled him in as much as we could. We had been a year or so into the actual construction, and so he had a fair amount of knowledge. But he, himself, was a little nervous if these guys started to sharpshoot at him.

When Heyman came back, I asked him what happened. He said, "Dan, you're not going to believe it. This committee called me up, but before I got up, Roberti called on this guy Katz to make a statement. He gave a statement which I thought was going to be the end of the world, saying how terrible the university was and that this whole animal facility was for torturing animals, and it was a sadistic chancellor and sadistic professors and sadistic students, and this wasn't a reform at all. And he went on and on like this. It was so beyond logic that you could see after a little while, everybody was saying this was stupid, even Roberti. By the time I got on, Roberti was apologizing to me about Katz. He was saying, 'Chancellor, I want you to understand that we all think the university is a great place' and things like that."

Heyman has great political instincts, so he said, "I realized I almost didn't have to say anything. The less I said, the better. So I said something like, 'You have been through this plan. It's something that's very important to the university. We want to be in the forefront of teaching our students the best subjects, and we really have to do this reorganization to teach them good biology, and there's no point in my going into details.'" He made it extremely short. Almost all the preparation that we had given him, he didn't need. His instincts were absolutely right because it just went through.

Hughes: An amazing story.

High-Tech and Low-Tech Science Buildings

Hughes: I read of some tension over the fact that the two new buildings--Koshland and Life Sciences Annex--had been described as "high tech."[24] I thought it might bring out an undercurrent of tension between the molecularly oriented scientists and the organismal scientists.

Koshland: No. We used "high tech" mainly for the legislature. It was not a matter of condescension; it was to characterize for the legislature in a word, which is what you have to do with legislatures, that LSB was a low-tech building and we couldn't do certain things in it. Old LSB was really a hazard to everybody. Therefore, we would put research that was high tech, like viruses, in these new buildings. We had rooms where you have everything sealed--no cracks in the walls. That means you can get in there with a hose and wash the whole room down. If scientists in LSB had to do high-tech experiments, they could do them in the other building.

Incomplete Reorganization of the College of Natural Resources

Hughes: In the end, only one new department was formed out of the College of Natural Resources. Was not the original plan to fully incorporate the entire College of Natural Resources in the reorganization plan?

Koshland: Correct. What happened is the following: at the beginning, when we wrote these letters to the Academic Senate, I also wrote a couple of letters to Doris Calloway, who was the provost for the colleges, including the College of Natural Resources, to ask some routine questions about cooperation. I was leaning over backwards to be cordial and helpful. Apparently, she had heard enough about me or my intentions that she never answered. I'd see her occasionally on the campus. She was pretty curt, so I could see she was not very happy about any reorganization.

[24]Trow, p. 161.

The dean of the College of Natural Resources was named [David] Schlegel and he was followed by a guy named [Albert R.] Weinhold, both of whom were very helpful. They were a little apprehensive in the beginning because they had had some bad relations with Letters & Science. I had not been involved with them at all. They really liked the idea of merging the botany groups--the plant group in Letters & Science and the plant group in the College of Natural Resources. They cooperated with us, and so that was the biggest single department that was involved. There were other departments, like nutrition, that should have been involved. Later on, public health did become involved. But Calloway was so negative and we had so many big problems, we eventually decided we were just going to forget about anything other than the plant scientists. We'd go back to the others later if we got a chance. But as a result, we didn't really do a good job on reorganizing the College of Natural Resources.

There's an ironic final touch because later on, when the Chancellor's Council on Biology was working, Wilford Gardner became the dean of the College of Natural Resources and asked, did he really need to complete the reorganization of the college. We said, "Yes. Please do it." He was an interesting guy. He said, "Dan, I think you did it all wrong. What you should have done is consult the Academic Senate and do the reorganization of the college with their advice." He was a relatively new dean at the time. I told him why we hadn't done it. I said, "You can reorganize the college with the Academic Senate if you want, but my prediction is it will be a disaster." Well, he tried it, and it was a disaster. He didn't get anywhere. So at least we believe Rod's end-running the Academic Senate was a good move.

Hughes: Dr. Park said that one of the stumbling blocks was that many of the people in the College of Natural Resources were paid on an eleven-month schedule.

Koshland: Right.

Hughes: And they were also apprehensive about being included with the Letters & Science scientists because their track record in terms of grant-getting wasn't as good. They were afraid of being left in the dust.

Koshland: Yes. There was tremendous hostility in the two groups. The summary that I can give you is that the College of Natural Resources people were very practical. They could advise a farmer, and they looked down on the botany people as being ivory-tower people who weren't doing anything of any use to anybody. The botany people, on their part, were members of the National Academy and had all kinds of academic honors, and they looked down on the College of Natural Resources people as sort of dirt farmers who weren't intellectually worth anything. So that was a really big thing when we merged the two departments. I think they're really pretty happy now to be together.

Hughes: Are they?

Koshland: Well, you'll have to find that out. But they're in a building together, there are joint appointments--so it worked.

Louise Taylor's Role in Reorganization

Hughes: You said last time that you wanted to say a word about Louise Taylor.

Koshland: Oh, yes. It is true that I was the sparking force behind the academic plan, but we also really needed the buildings. The buildings was a carrot to offer the faculty, to be willing to go through this reorganization. On the other hand, we needed the reorganization because we needed to go to the legislature and say we had a new program. If we just went and said Berkeley deserves the buildings because they're a bunch of good guys, that would not be a very salable proposition. By saying we were revolutionizing biology--and we were--it was a much better selling program. So I was focused on the academic plan.

Rod was smart enough to say, "Dan, this is going to be a big, big program, and you're going to need somebody in the administration who helps keep an eye on it." So he said, "Would you identify somebody to do this?" I didn't know anyone in those echelons. I was a good professor, working at my lab, and so I didn't want to bother with anybody up there.

I had lunch with Horace Barker, a very distinguished professor in our department who had been chairman for a while, and was discussing this problem. He said he had been on a committee with Louise Taylor, and he thought she was very good and I ought to try to get her. So knowing nothing more, I suggested Louise Taylor. She had heard about me through a relative. She had gone to a swimming pool of a relative of mine. But that was the only connection I had with her.

Anyway, Louise was put in charge of the administrative part of the reorganization, and that was <u>wonderful</u> because she was just <u>excellent</u>. She wasn't a Ph.D., but she caught the atmosphere, she understood the academics, and she could deal with the administrative people, so she kept charge of the program. It became, as you know, a big, big program. It was big construction, changes of academic personnel, everything. So it was extremely lucky we had her.

More on the Role of Personality and Personal Characteristics

Hughes: Rod Park was a botanist, so he could presumably immediately appreciate the importance of what you were trying to do to reorganize biology.

Koshland: I think it saved both of us a lot of time. In the long run, I'm not absolutely sure it's an advantage to be working with a scientist. If I'm dealing with somebody who is out of my area and they think I'm sensible, they may defer more because they just don't know anything about science. But if the two scientists like each other and can complement each other's ideas, which is what we did, it works out very well.

That Rod was open to the idea of change, number one, and was willing to stand up there and take the heat, number two, were the two personal characteristics that were most important. I think both of us knowing about biology was a help but not as important.

Hughes: Less so. But there must have been an ease in your day-to-day communication.

Koshland: That's absolutely true.

Hughes: Do you think that without Rod Park you could have kept reorganization out of the Academic Senate?

Koshland: Each of us contributed. I think I contributed things that were important, and I think Rod did. Rod was really very good about a large number of things. He was the kind of person who could take criticism. If there are many people complaining, many administrators would have just said, "That's [reorganization] not worth doing. The campus is running pretty well."

One of the worst and most important apothegms of the English language is: "The rich get richer and the poor get poorer." It's true. By "rich" I mean the people who are advantaged. The thing is if you have certain advantages and you know things and it goes well, you learn to call people who also are successful, you are secure enough to take criticism so the program goes quickly. If you're deprived of those resources, it's much harder for you. That's partly what happens in something like this.

The more Rod and I trusted each other, the easier it was to do everything subsequently. I'd call up and say, "Rod, what do you think of this?" And he'd say to me, "Dan, I don't think that's going to be much of a problem. Go right ahead." You may think that's trivial, but a lot of things have to occur quickly.

Hughes: What you seem to be saying is that attitude and personality played an enormous role.

Koshland: Absolutely. I think so much depends on mutual trust. I think personality is an enormous factor. There are certainly procedural things that really involve good organization and good management, and I think you make life very hard for yourself if those are done badly, and impossible if they're done very badly. But I think you could do everything mechanically perfectly, and if the personalities don't mesh, you really don't have much chance in a big controversial plan like reorganization. If you're an efficient department chairman and you're very fair but you have no rapport with anybody, then I think you probably can carry department administration off well by just being mechanically correct. But in a big deal like reorganization, my reaction is there is no way you can do it if the leaders are not compatible personalities.

The personality factors involve all sorts of combinations. I will give you a couple. First of all, egotistically, to start out with myself. I think that it was important that I be pretty well liked by a number of the faculty. There were a number of the faculty that were going to hate my guts without knowing me personally at all because I was advocating something that would be threatening to them. So you have to have a certain number of people who will loyally support you.

I would get a certain number of people who would support me anyway, because they agreed with what I was advocating. But a friend is willing to do a little extra. He's willing to write a letter to the chancellor. Some people who may be just academically on your side but emotionally they may not be willing to do that. I think that interaction I had with a fairly large number of the faculty was important. The second personality factor that was incredibly important was my relation with Rod. And I really didn't know Rod almost at all before this started. But we just got along very well. I liked him, and I think he liked me. We just were very informal with each other.

Rod did something which I think was partly because he liked me but partly just smart machinery. In the beginning he was very loyal and was going to say, "I'm not going to listen to any complaints." I really felt that was wrong. He devised the following system He said he would let anybody come to him, but he would always tell me what the complaints were, so that I would always be able to answer the complaints. He wouldn't say who made them, so the person would have confidentiality. But if they said, "Koshland has put his daughter on the payroll" or something like that, he [chuckling] wouldn't let that become a big gossip thing without my having a chance to put the record straight.

That was done right from the beginning. I consider that a very smart move. So we never really had any big problem because if somebody said, "Koshland is trying to impose molecular biology on us plant morphologists," and Rod would come to me and say, "Dan, is this true?" I'd say, "Yes, that's exactly what I'm trying to do, but it's for their benefit."

We each served as an early-warning system to the other. If we heard some rumor, we would warn the other that it was something he was going to have to face. It worked very well. And then, of course, we got together on the strategies in regard to the Academic Senate. I think that was very important. And Rod's relation with Heyman and my relation with Heyman were important. We both got along well with him. The great thing was that Rod and Mike really listened to all the criticism, but they didn't get deterred, so we went on.

Colleagues would ask, "How are you so sure that Rod's behind you on this?" I said, "I'd know the minute Rod is not on my side." They'd say, "How do you know that?" I said, "The minute Rod is not on my side, he'll just say, 'Dan, we'd better refer this to the Academic Senate.'" I said, "Then I know he wants to kill it." And that was my standard explanation. And since he never said that to me, I knew he was for going ahead with the reorganization.

Transcribed by: Mim Eisenberg/WordCraft
Final Typed by: Julie Allen & Kathy Zvanovec-Higbee

APPENDIX

Robert Tjian, PhD interview on Daniel E. Koshland, January 7, 1999

D.E. Koshland, Jr., Bibliography

The Nine Lives of Daniel E. Koshland, Jr. (1920-2007) obituary by Randy Schekman

Daniel E. Koshland, Jr., memorial service program

Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Robert Tjian

Supplementary interview

Interviews conducted by
Sally Smith Hughes
in 2000

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of Northern California, the West, and the nation. Oral History is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is bound with photographs and illustrative materials and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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It is recommended that this oral history be cited as follows: Robert Tjian conducted by Sally Smith Hughes in 2000, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2011.

<u>Robert Tjian, PhD, Interview on Daniel E. Koshland, Jr.</u>

Robert Tjian was first an undergraduate student in Daniel Koshland's upper division biochemistry course and a student research assistant in the Koshland laboratory. Much later, after obtaining a Harvard Ph.D., he became Koshland's colleague at Berkeley in the Department of Molecular and Cell Biology. At the time of this interview, Dr. Tjian was Professor of Molecular and Cell Biology, Howard Hughes Investigator, and co-founder of Tularik, a biotechnology company based on transcription factors, the subject of his basic academic research. As of 2011, Dr. Tjian is head of the Howard Hughes Medical Institute, director of the Berkeley Stem Cell Center, and remains a professor at Berkeley. In 2003, Amgen bought Tularik. Dr. Tjian kindly agreed to the following interview as part of the interviewer's preparation for the oral history with Dr. Koshland. It is an apt summary of some of Dr. Koshland's scientific contributions and for the view it provides of Koshland as teacher.

[Interview 1: January 7, 1999]

[Begin Tape 1, Side A]

Tjian: Dan arrived in Berkeley around '65, I think.

Hughes: It was '65.

Tjian: The early work on induced fit had already been formulated. He continued to do various other things to do with allosteric changes in proteins and positive and negative cooperativity and all that.

Hughes: Yes, I want to ask you about that work. I understand that the model that preceded Dan's work on induced fit was the Fischer model.

Tjian: Yes, the lock-and-key model.

Hughes: Right. Why did he begin to think that that model might not be right?

Tjian: I don't know the history in detail, since I wasn't around, but as I understand it from reading various things that Dan has written, the initial idea was really quite simple. If the idea is that the catalytic site of an enzyme has to be perfectly shaped to fit the substrate, then why shouldn't a substrate that was smaller than the actual substrate not be able to fit into it and make it work? Because all you had is a size problem. That's what I think got Dan onto this whole idea that, hey, it can't just be a perfect fit. There has to be some kind of give and take. That's really what led him to this whole idea of an induced fit, that the actual structure of the enzyme's catalytic site may *not* be perfectly cut out to the shape and size of the substrate but rather to some structure that's intermediate--we now call it the transition state--and that there's pliability, there's flexibility to the enzyme. I think that's a really important concept.

Hughes: Can you think of the transition state as three states? The enzyme sitting out here [demonstrating], unassociated with anything--

Tjian: Non-ligated, yes.

Hughes: And then moving in conformation?

Tjian: Yes. There are many different ways of thinking about it. But you have a catalytic site that's got to be about right. You're obviously not going to have a tiny catalytic site and this huge structure come in. They have to be somewhat compatible, but it's not going to be a perfect fit. The substrate comes in and induces the protein into the right shape. The protein's three-dimensional structure is constrained so that it assumes only a certain state when it undergoes the conformational induced fit, which then really is most similar in structure to the, quote, "transition state," because what you want is to force the substrates-- Often there are two substrates that are coming in that have to be aligned properly and so forth. You want the structure to most closely mimic the transition state so that you're going from the substrate into the products of structure. I think this whole idea of having flexibility gives you the pathway to get there.

Hughes: People didn't like that idea at first, did they?

Tjian: No, because people really didn't have a good idea of what an enzyme structure was going to be. You start thinking about the fact that people were getting crystals of proteins. A crystal is a very rigid kind of thing. You don't think of a crystal as something that's going to be floppy, and yet that's what it is. Proteins within the crystal lattice can undergo conformational differences. So I think, yes, induced fit wasn't received with a great deal of immediate acceptance at all, as is the case with the vast majority of paradigm-breaking ideas. It takes many, many years of accumulated evidence to prove some new theory. It's not something easy to prove, right?

Hughes: It particularly wasn't easy to prove because some of the techniques, such as X-ray crystallography and NMR [nuclear magnetic resonance] weren't available.

Tjian: Exactly.

Hughes: So how *did* Dan do it?

Tjian: He did it by biochemical and kinetic experiments. He did everything possible. There's a whole list of papers. They are all small increments because it was very, very difficult to nail this down. I would say ultimately it was the structural biologists doing NMR and crystallography, showing that when you do a crystal structure of the unligated protein, it would be one shape; and then you do the protein structure of the ligated crystal, and it would have a slightly different shape. That's still going on; we're not at the end of the story. Not every protein does that, and most proteins do undergo some kind of conformational shift.

From my perspective, since I'm not really into enzymology that much anymore, what I find really important about the induced fit mechanism is that, although it was primarily developed through the study of enzymes and catalytic sites--and that's what Dan was really interested in--the impact on many other kinds of proteins that don't have catalytic sites is, in my opinion, even greater. Transcription factors, which I *do* work on, when they bind DNA, they undergo a conformational change. In fact, there's a bit of a two-way street. Not only does the protein have to undergo a conformational change to fit the DNA, often the DNA undergoes conformational change to reciprocally fit with the protein. Here's a perfect example [pointing to molecular model], where the DNA is bent way out of whack by this protein.

Hughes: The concept, then, of flexible molecules, you would attribute to Dan?

Tjian: Absolutely. This is classical induced fit. It's when two macromolecules--whether it's two proteins, a protein and a ligand, or a protein and a nucleic acid--when these two sets of molecules come together, their interface flexes to fit each other. It's a perfect example of what he called the hand in the glove. It's really the best analogy, because a glove already has a certain constraint, but it's a little floppy, and when you stick your hand in it, then you can make that glove fit. But if your hand is too big, it won't fit into the glove. Or if it's too small, it can fit in it, but you'd be kind of swimming around in it, right? So I think it's the perfect analogy, which is the one Dan usually used, the hand in glove.

Hughes: I believe that some of the problem in establishing the theory was the minuteness of these changes.

Tjian: Yes.

Hughes: I'm assuming that some people said, how do you know that they're not just an artifact?

Tjian: Well, it was very difficult because you're talking about fairly subtle changes. You're not talking about some arm of a helix moving over twenty angstroms. These are really small adjustments. Dan's hypothesis about orbital steering is that small changes in angle, the way you align things, can really affect catalytic activity of an enzyme. And that one is still debated and controversial in some sense. Again, it's very difficult to prove precisely for a given enzyme-substrate interaction that orbital steering is a major player.

Hughes: What is orbital steering?

Tjian: Orbital steering is the electron configuration, the position of the atom--it's down to that level. If you believe that you have to position the substrate perfectly so that the angles of all the atoms are adjusted right before you get a high rate of catalytic conversion, then all of these small-scale conformational changes become extremely important. If you shift the angle by three degrees, that's enough to throw you off.

Hughes: Did Dan arrive at that hypothesis on a theoretical level, or was there some experiential evidence?

Tjian: Both. Dan is one of the few people I know of who is driven a lot by theoretical calculations. So he often will base some theory partly on that, but then he gets his students to do the experiments to test it. It usually takes years to nail down. Usually, when you make a hypothesis, you're not going to be correct in every detail when you first start. There's just no way. If you're primarily correct about it, then that's already a major, major step.

I think the most important thing is to get people thinking about the fact that--wait a minute--a protein isn't rigid. It's not like a lock, where if the key doesn't fit, it doesn't fit. No, it's not that way. It's much more like a hand in a glove. No one debates that anymore. Proteins are very much flexible.

Hughes: Was the controversy with the [Jacques] Monod group at Pasteur too far in the past for you to be in on?

Tjian: Yes, it is pretty far in the past. And that controversy wasn't so much to do with the induced fit as to do with the allosteric mechanisms.

Hughes: Tell me how these concepts fit together. What exactly does allostery mean in terms of induced fit?

Tjian: They're clearly related since allostery involves protein-protein interactions within a multi-subunit enzyme, whether it's hemoglobin or whatever, where you have multiple subunits that are talking to each other. And you have positive cooperativity or negative cooperativity, where once the conformation of one protein changes, it induces the other ones to change. So they're definitely related problems or processes, but they are also distinct issues because you can have induced fit with a single subunit; you don't have to have multiple subunits to see induced fit. Whereas allostery, you're really talking about proteins talking to each other.

Hughes: Those two concepts arose more or less at the same time?

Tjian: Yes, because they both have to do with the plasticity, if you like, or the ability of protein structure to undergo change.

Hughes: How much of this was technology driven? Or any of it?

Tjian: I don't think it was at that time. We're talking back in the sixties.

Hughes: I was trying to think when [Eugene] Sanger was working on hemoglobin. Was that the fifties?

Tjian: You mean Max Perutz?

Hughes: Yes.

Tjian: You must be thinking of Max Perutz and the structure of globin. That was in the late fifties, early sixties, yes. In fact, my first project as an undergrad in Dan's lab was to build a model of the contact points between the alpha and beta subunits of globin. The structure was already available, so you could get coordinates, and I actually did a hand model. I built a scale model of just the contact residues between the alpha and beta subunits. So clearly Dan was very much thinking of using structural information either to prove or disprove his hypothesis.

Hughes: Crystallography was providing new and more precise information. On the other hand, it was working with crystals.

Tjian: Oh, yes. You're looking at a snapshot of a protein frozen in a particular conformation. You have to do a lot of work to get at the issue that the protein is actually changing conformation. And there's another problem intrinsic to crystallography, which is always true, and that is when you do solve a structure of a protein in a crystal, you don't know how much of that structure has been, quote, "distorted" by the formation of the crystal. The formation of the crystal lattice itself can impose certain limitations on which conformations a protein can assume.

For example, maybe a protein normally can assume fifteen different conformations, but it only crystallizes in one. And so that's the only one you see, and then you're going to miss the others. So that's why I think NMR is a very important tool here. With NMR, you're looking at the structure in solution, and when you solve structures in NMR, you don't solve one structure, you solve whole families of structures. So you can see what range of flexibility there is, and people have done that. I'm not that up on that literature, since that's not my area.

Hughes: Is NMR more a tool of the seventies?

Tjian: Well, both NMR and crystallography have been advancing in the last two, three decades. NMR is very difficult. There had to be major advances in the machinery--the size of the magnets and what kind of resolution you can get--that didn't really happen until the late seventies, maybe really eighties, when we started getting bigger magnets. It allowed you to do what's known as three-dimensional NMR, as opposed to straight, two-dimensional NMR.

Hughes: And that kind of work supported the induced fit theory?

Tjian: Yes. There may be a few Flat Earth Society people, but other than that, most people are pretty much assuming that proteins are quite flexible.

Hughes: When you pick up a textbook nowadays, does it present Dan's view?

Tjian: Oh, yes.

Hughes: Monod and his supporters had the upper hand for a while. Was some of that due to their reputation?

Tjian: Very much so. Here you had guys [Jacques Monod, Francois Jacob] who were Nobel laureates and who had a lot of power in those days. Like in anything, people took sides on it. I think Dan stuck to his guns through some fairly difficult periods, but in the end I think the fundamental mechanisms of induced fit and negative cooperativity were proven. There's no question about that.

Hughes: He had an opponent right on this campus in the person of Howard Schachman.

Tjian: Yes, Howard was very much opposed because of the ATCase story.

Hughes: What is that?

Tjian: I think Howard felt that his multi-subunit complex of the aspartate-transcarb-amylase enzyme really fit the Monod model better than the Koshland model. I'm not sure that's true anymore. You'll have to ask Dan about the details, or Howard. I think there's evidence from Howard's own lab in the last few years that suggests Dan may be more correct than he thought.

Hughes: Even in regard to Schachman's enzyme?

Tjian: Even in regard to his case, which is one of the best cases for the Monod model.

Hughes: I don't know what stage of his career Schachman was in when he was in the Pasteur group.

Tjian: Well, see, I don't think you'd want to conclude that the Monod model is incorrect. I just think it's incomplete. And I think Dan's model probably is more encompassing of the many mechanisms that are being used by proteins. I learned in biology that anything you can think of probably is being done. Mother Nature is not boring. She is very flexible.

Hughes: Are you saying that the Monod model would work with certain enzymes?

Tjian: Absolutely. I don't think there's any doubt about that.

Hughes: My understanding of the Monod model is that it's a two-state proposition.

Tjian: Exactly. It doesn't have as many variables, as many steps and transitions. Dan is not intimidated by complexity, so he doesn't try to force models into very simple binary systems. In many ways, I think intuitively biological systems are never that simple. We'd like them to be because practicing biologists have to be in some ways reductionists. If we weren't, we'd just be overwhelmed with parameters we can't control. But the truth of the matter is if you look at any system in detail, you're going to find that there are a lot more states of flexibility than you would have guessed.

Hughes: Apparently the mathematical complexity of Dan's model was off-putting.

Tjian: Oh, sure. You couldn't pigeonhole it very easily. You couldn't write a simple reaction. I believe that one of the things about biology that drives some scientists crazy is you can't quantitize everything. There's a lot of slop is basically what it comes down to.

Hughes: Dan's background is chemistry.

Tjian: He has a chemistry background, but Dan has always been a maverick. He is a classically trained organic chemist, but he's not at all constrained intellectually by the ground rules. I think he kind of revels in that. I think he likes to break convention.

Hughes: Plus, the way he tells it, is that he majored in chemistry here not because he ever intended to make that strictly his career, but he had the idea--he probably got it from his mentors--that a strong basis in the physical sciences was the way to go into biology.

Tjian: Absolutely. I think he always is more fascinated by complicated problems. That's why he went into chemotaxis. It's not exactly your simple problem. Going from enzyme mechanisms into chemotaxis is a big jump.

Hughes: What should I ask him about chemotaxis?

Tjian: His studies on chemotaxis were really nice because he really did bring a quantitative analysis to bacterial chemotaxis. He developed assays which allowed him to measure quantitatively whether a bug was traveling in this direction or that direction or how frequently it turned around. He had two postdocs in his lab who were brilliant. One was named Rick? Dahlquist, who is a professor up in Oregon, and the other one was Peter Lovely, who was a physicist, instrumentation guy. They developed an assay using an instrument--I can't remember the details because I never worked on this--which allowed them to measure movement of bacteria either towards attractants or away from repellents. They did it quantitatively.

The old way people had developed was you had a petri dish, and you put a drop of some nasty material or some good stuff in the middle, and the bacteria will either swarm towards it or swarm away from it. But it wasn't a quantitative thing. You'd look at the plate, and you'd look at the size of the swarm. It's not very quantitative, and it didn't measure kinetically how fast they were going or what their movement actually was.

Dan developed an assay which allowed him to figure out the way bacteria decide whether they're going to move towards something or move away from it by how often they tumble.

Hughes: Literally, spinning over?

Tjian: Yes, exactly. Remember, they're in three-dimensional space, right? They're in some kind of solution. And bacteria have a whole series of flagellae, which are like little propellers, if you like, all over their body. Apparently, when they get into a gradient of good stuff--sugar, something they want to eat--they want to swim towards the source. They shut down their tumbling mechanism more frequently than otherwise, and they tend to travel in straight lines for longer periods of time. So on average, when they're in an environment where there is good stuff to be had, the receptors detect these sugar molecules or amino acids, and they move more linearly. [Interruption]

Tjian: Dan's assay allowed him to come up with a whole mechanistic and biochemical description of why bacteria are able to determine how they get from point A to point B and know that they're going in the right direction. [moving to blackboard and drawing] Here's a bacterium, the flagellae. The old idea was that somehow bacteria were able to sense there was more sugar over here than over here, over the length of the body of the bacteria. The bacteria are only two microns long. Dan thought, This can't be right. What they've got to be doing is integrating the information over time, which is a very different concept, and that turned out to be the case. So bacteria are randomly zipping around, but if they run into an environment where there are goodies, they stop tumbling as frequently, and they move in straight lines longer.

Hughes: How do they detect--

Tjian: They have receptors. They have a little receptor out here [drawing] that's detecting some sugar molecule that they like, and that receptor is hooked up in some way by a signaling pathway to the motor at the bottom of the flagella, so it's either turning on the flagella or turning it off.

Hughes: Isn't that wild!

Tjian: It's an actually fairly sophisticated system.

Hughes: Dan also speaks about bacterial memory.

Tjian: He does. That has to do with a modification mechanism where the receptor has a certain amount of time where it's bound to the ligand. It knows to bind to the ligand because then there's a chemical modification, a methylation event, which Dan discovered, on these receptors. The receptor has to be demethylated. So there's kind of a time lag.

Hughes: The system works only for bacteria or is it generalizable?

Tjian: The methylation part so far, I think, is for bacteria, but many of the principles that he came out with, in terms of how molecules respond to their environment, I think can be extended. Let's face it, the memory that you see in bacteria isn't going to be an accurate reflection of memory in the human brain, but it's going to be some skeletal aspect of that. Again, I think it's best to talk to him about how he made those connections because I wasn't in the lab at all at the time.

Hughes: Do you know any other broad areas of his research?

Tjian: He went from bacterial chemotaxis and understanding the importance of receptors to looking at receptors in neuronal cells, in animals. So he did make that jump and start to work on tissue culture cells, neuronal cells, PC-12s and so forth. I would say, the last phase of his research career was really going into that. Dan changed what he did about every ten years. He went from being a classical chemist to an enzymologist to a bacterial geneticist. He used a lot of genetics when he did the work with chemotaxis and *E. coli*, and salmonella.

Hughes: He had a background in bacterial genetics?

Tjian: Not at all. I think he benefited from having Bruce Ames and Giovanna Ames around to help him do the bacterial genetics. That's the advantage of being in a place like Berkeley. If you want to learn something, there's always somebody around who's an expert at it. So he had in his own department one of the world's experts in bacterial genetics. Dan could have gone directly into animal cells, but then he never would have had any of the genetics to help him out, so he went into bacteria first. Once he figured out what was going on there, then he moved to animal cells.

Hughes: Do you think that was his thought process?

Tjian: I'm pretty sure it was. Dan is pretty deliberate about how he does these things. Part is also who he happens to attract to the lab. That's how any of us operates. It's very hard for us to single-handedly go and learn a new science;

it's a lot easier if we attract a good graduate student or postdoc who's going to learn it. The idea was Dan's to do chemotaxis, but the actual execution was done by these postdocs and graduate students who came in and learned about receptors. I think some of what happens in the lab is dictated by whom he happens to attract to come to the lab and whom he then can convince to work on these problems.

Hughes: Yes, it seems a very interactive sort of thing.

Tjian: It has to be because he's always trying to do new things; he's not stagnant.

Hughes: Speak from your experience of what it was like to be in the Koshland lab.

Tjian: Well, I was there as an undergraduate for a fairly short period of time, two years. For me, it was like heaven. There I was, a student. I was given a great deal of freedom, lots of responsibility, interacting with some of the smartest guys in the world. He had an absolutely superb lab at the time, with extraordinary graduate students and extraordinary postdocs. I just ate it up. It was the thing that absolutely turned me on to doing science, and I knew what kind of science I wanted, having experienced it.

Hughes: You weren't so clear before you came into his lab?

Tjian: I knew I wanted to do science, but I didn't know what kind. I had started off as a mathematician, then went into chemistry, and then sort of gravitated towards biology. I think Dan took a huge risk, taking somebody like me. My grades weren't all that spectacular when I was a freshman or sophomore. I mean, my grades were fine, but I wasn't a straight-A student. He put a lot of effort into mentoring me.

Hughes: So you really saw him?

Tjian: I saw him, but more importantly he must have told his graduate students and postdocs to treat me well. Otherwise, why would they? So somewhere along the line, information came down, or maybe they recognized that I was really interested in what they were doing. I worked forty, fifty hours a week.

[End Tape 1, Side A. Begin Tape 1, Side B.]

Tjian: It was certainly common in those days. I think students have a lot more choice these days. In those days, if you got into a lab, it was such a privilege that you made sure you didn't waste your time. These days, I don't know. Maybe there's more choice.

Hughes: Why did you end up in Koshland's lab?

Tjian: Dan was probably one of the most accomplished scientists at the time, who also gave fabulous lectures, and was just a really nice person. Demanding, but very interactive.

Hughes: You had had a course from him?

Tjian: Yes, I was taking courses from him. Some of it was probably chance. I probably talked to a number of people--I can't remember.

Hughes: Say something about him as a teacher.

Tjian: Well, he's a superb teacher. He had been for years teaching Biochemistry 100, which is the upper-division biochemistry course. He's hilarious.

Hughes: I can imagine.

Tjian: He's a stand-up comic half the time, but he's very serious about his material. You can tell that he really loves the material.

Hughes: Did that confuse some students? Did they tend to dismiss the science because he was funny?

Tjian: No, you couldn't do that. Dan was funny, but he wasn't funny all the time. He just kept us awake with a few good jokes here and there. But the bottom line was he gave you a tremendous amount of information, and you also knew his exams were going to be very difficult. He didn't give rote exams, memorization exams. They were all very much based on thought process. He was a tough teacher, definitely not an easy teacher. I really liked his style of teaching. Compared to some of the other lecturers, who were much more traditional and boring, Dan was a breath of fresh air.

Hughes: Was the class interactive?

Tjian: Oh, yes. And he got it. When I was here [as an undergraduate], it was in the late sixties and the students were very aggressive. This was the Free Speech Movement era, the Cambodian invasion era, and you felt like you were there to challenge the faculty. That was our job. We didn't take anything for granted. Teachers like Dan really shone because they loved interactions. They loved being challenged by students and getting asked tough questions, not being able to gloss over things. We just didn't let them.

Hughes: What information would you like to find in these interviews?

Tjian: What's the purpose?

Hughes: It's an oral history which is intended to document as fully as possible not only Dan's scientific career but his life in general; it's a biographical effort.

Tjian: Well, I think Dan is one of *the* most remarkable and unique individuals in science that I know. He's not only intuitively a very good scientist, but he clearly has a great talent for science policy and management and understanding. I think the most important thing is, he recognizes quality. He somehow is able to figure out who is really good and who isn't, and how to reward those people and get them to be in a situation where they have impact. That's made all the difference in the world. Over and over again, I get asked to be on a lot of review boards in other universities, and they always say, "What we wish we had is a Dan Koshland." That's what they say because they know it doesn't matter how big or how well established a university is, you need some kind of leadership. It has got to be forceful leadership--risk-taking, forceful leadership. That's what Dan is. Everybody in the field, anybody who has ever interacted with him knows that that's what he is.

I think Dan's science is superb, but I think his ability to build programs-- I think he had an immeasurable impact on Berkeley science in the last two decades. First, because of his own quality of science, which then attracts more and better students. But he transcended that. Many of us can do that. We can do our good science and attract good students. But he went way beyond that. He completely revamped what biology looks like on the Berkeley campus. Very few people can do that or have the intuition to be able to do it, even if they wanted to.

First of all, there are very few people who would want to, right? It's an amazing amount of effort, and, second, to be good at it. There are lots of people out there who might want to do it for the power, and they're no good at it. Dan, I don't think, ever did it for the power. He never took on a deanship or became this provost or that. He just did it because he wanted to ensure Berkeley had good science. I think he's a great model for us, for our next generation. I think every generation better have a couple of people like him or we're going to be in trouble. I think that's what some of us hope, that one or two will rise to the occasion as Dan did.

I think Dan has really done two things in his scientific career. One is to do great science, to be very creative and to make major discoveries. And the second is really to build an institution, one that he loves. He clearly loves Berkeley. There's something about his deep family commitment to this institution, and its unwavering in every aspect that he has ever done, to this day.

He is now building a big program again. In the northeast quadrant of campus, he's trying to build molecular engineering, something that to me is the essence of Dan. Dan has always loved physical chemistry, but he likes biological problems, so his whole thing has been how you get the physicists and the chemists to talk to the biologists and the engineers to talk to biologists. And that's what he's doing. He's trying to build a building over there where you could put his chemists, engineers, and biologists all in one building. I think that's absolutely the right thing to do for the next century. I think it will change education on campus. There won't be quite so many classical barriers between these disciplines, if Dan can succeed in putting together the right people that will have the desire to be interactive. We've always had the opportunity. Nobody prevented you from talking to others; it's the question of having the desire.

Hughes: Has interdisciplinarity been a theme of his?

Tjian: Absolutely. More so as time went on, as his own science drove him to be a geneticist or a crystallographer. I think as his own science went in that direction, he also realized the whole institution really needed to go in that direction. I think he derived that from his own experience.

Hughes: Thank you. [End of Interview]

D.E. Koshland, Jr.
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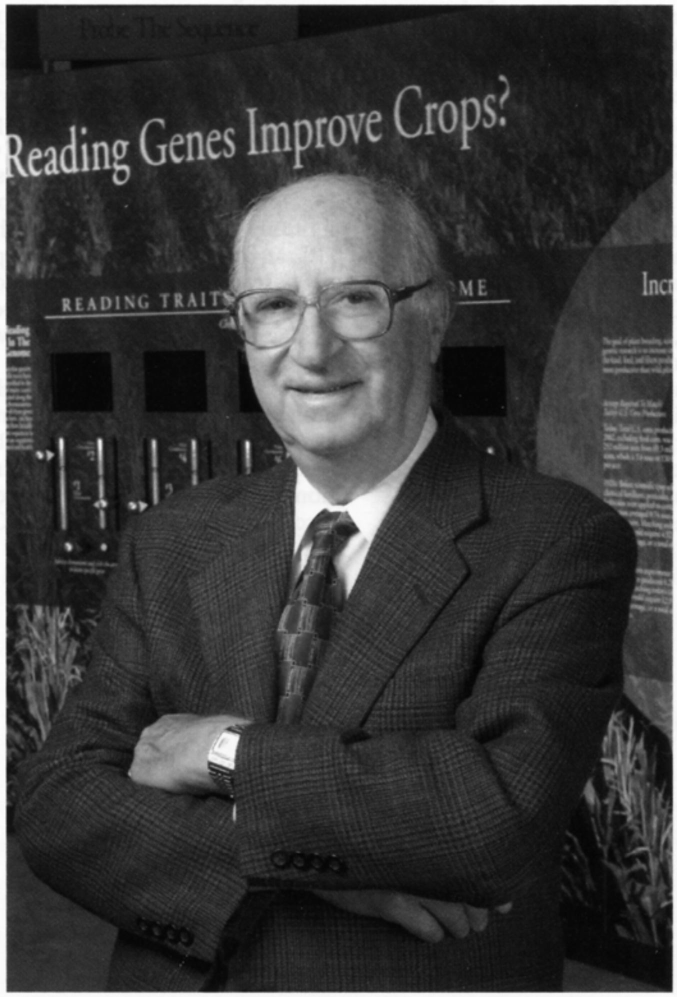
The nine lives of Daniel E. Koshland, Jr. (1920–2007)

The scientific world lost a friend and pioneer with the passing of Dan Koshland on July 23rd of this year. Dan's singular contributions have left an indelible mark on those who had the pleasure of his company. In rough chronological order, he started as an inorganic chemist, then became an organic chemist, a biochemist, a professor, a department chair, the Editor-in-Chief of PNAS and then of *Science*, the czar of life sciences at the University of California, Berkeley, and in the last 10 years of his life, a benefactor and elder statesman. His model of science and service has inspired generations of young scholars.

Dan trained in inorganic chemistry as an undergraduate with Wendell Latimer at U.C. Berkeley and spent the war years in Chicago working on plutonium enrichment under the guidance of Glenn Seaborg for the Manhattan Project. A nascent interest in biology and Ph.D. studies with an inspiring young organic chemist, Frank Westheimer, tempted Dan away from inorganic and nuclear chemistry and into a lifelong passion for enzyme reaction mechanisms. Further training at Harvard University (Cambridge, MA) and a brief stint in Fritz Lipmann's laboratory led to Dan's first independent position at Brookhaven National Laboratory (Long Island, NY). During his work on the stereochemical specificity of enzyme reactions, Dan developed a deeper understanding of how an enzyme may adapt to a substrate, which led to his brilliant formulation of the induced-fit model of protein–ligand interaction.



Daniel E. Koshland, Jr.

In 1966, Dan and his wife, Marian (Bunny), a distinguished immunologist, and their five children returned to Berkeley, the scene of Dan's scientific awakening, where he took a faculty position in the Biochemistry Department. Dan continued his passion for enzymes in a department that focused on classical enzymology, with such luminaries as Horace Barker and Esmond Snell. Perhaps because of his move west or the mood of change in Berkeley, Dan grew interested in bacterial chemotaxis, a field that had been introduced into modern bacterial genetics through the pioneering efforts of Julius Adler at the University of Wisconsin (Madison, WI). This work carried Dan's effort into genetics, bacterial physiology, and, of course, biochemistry, for the next 20 years. Perhaps his crowning achievement was the construction of a machine to track bacterial movement in three dimensions. With this device, he, Rick Dahlquist, and Bob McNab showed that chemotactic bacteria sense gradients in time, not in space, through a series of biased swimming motions consisting of "swims" and "twiddles."

But Dan, the man, was more than just his science. The scion of a prominent San Francisco family with deep roots in the community and the University of California, Dan was imprinted with the responsibility gene. For Dan, this commitment included his children, his colleagues, his university, and his nation. He served as president of the school board when his children were in the public school system in Long Island, NY. Upon returning to Berkeley, he became chair of the Berkeley Biochemistry Department, and in 1975, he took pity on me, a green refugee from Stanford University, and took me in (but never failed to remind me of the profound disadvantage of my Ph.D. training at Stanford). Two years later, he welcomed back his star undergraduate, Robert Tjian (Tij), who accepted a faculty position at Berkeley. Dan took Tij and me under his wing and guided us along the path from independent scientists to responsible academic colleagues.

As an editor, Dan brought his good humor to a task that requires diplomacy and thick skin. At PNAS (Editor-in-Chief, 1980–1984), Dan was one of the first editors to impose external standards on the publication of Academy members' contributed papers. Few aside from Dan would have dared face down Linus Pauling and some of his questionable views on the efficacy of megadoses of vitamin C. In 1985, at age 65, Dan took the position of Editor-in-Chief of *Science* (from 1985 to 1995), a job that had previously been considered full-time but which Dan handled part-time along with his research and a leadership role in the reorganization of life science departments at Berkeley. Before Dan, *Science* had a respectable but conservative portfolio and was not considered the most appealing venue for top-flight original research reports. With his broad network of colleagues in the physical and life sciences and his keen insights about people, Dan rebuilt *Science* with an independent staff of in-house editors and expert external board members. During his 10-year term, the impact factor of *Science* more than doubled, bringing it on par with *Nature* and *Cell*.

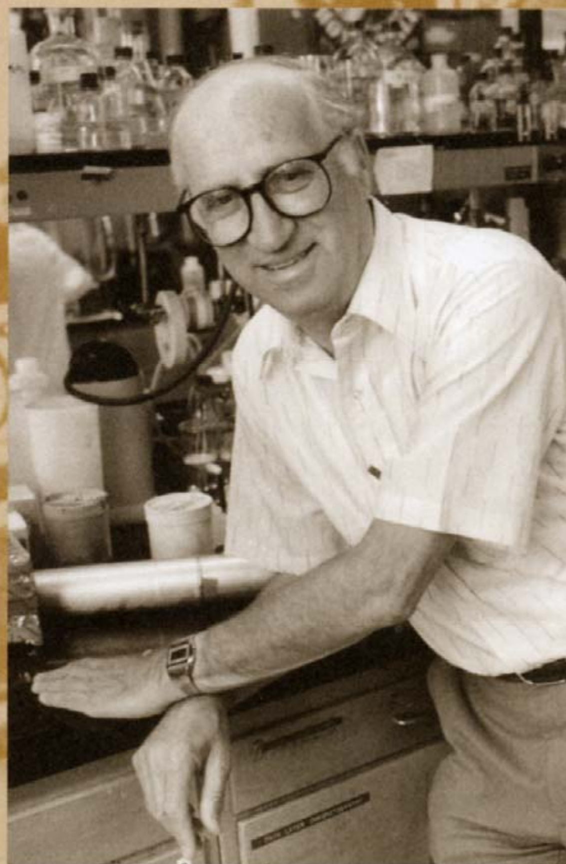
For those of us who had the gift of knowing Dan Koshland as a colleague, these were heady years with a mandate for change on the Berkeley campus. A supportive Chancellor, Mike Heyman, and Provost, Rod Park, afforded Dan the opportunity to shake things up with a reorganization of the life sciences. Using his considerable political skills and wide network of influence, Dan assembled an expert external advisory panel, prompted them to issue a dramatic call for a new vision of life science, and stood back to catch and rearrange the pieces that fell when the Chancellor distributed the advisory report to the Berkeley life science community. Over a period of two years through several iterations, Dan forged a new alignment of disciplines, dispensing with 16 different life science departments crafted into three large units in two different colleges: Molecular and Cell Biology (MCB), Integrative Biology (IB), and Plant and Microbial Biology (PMB). The arrangement may seem obvious in hindsight, but the opposition, spearheaded by the chairs of the 16 departments that were disbanded, was visceral. Fortunately, Dan had the escape of a monthly trip to *Science* in Washington, DC. It was no accident that copies of his periodic reorganization reports were distributed to the faculty mailboxes on Friday afternoons just as Dan was jetting east.

The legacy of just this contribution alone would satisfy most, but in the past 10 years, Dan's generosity has blossomed with major gifts to the institutions he loved. He and Bunny endowed a science center at Haverford College, the alma mater of his sons and a future daughter-in-law; he established the Marian Koshland Science Museum of the National Academy of Sciences in Washington, DC, in honor of his wife; he generously donated to the Weizmann Institute; and, in many ways large and small, he built a Koshland legacy on the Berkeley campus that rivals the great founders and benefactors of this institution in the 19th and 20th centuries.

After Bunny's death in 1997, Dan renewed an acquaintance with a woman he had briefly dated as an undergraduate at U.C. Berkeley. He and Yvonne were then married in a small ceremony at their home in Lafayette, CA. Remarking on the brevity of their vows, Yvonne said she and Dan had agreed to skip the part about obeying each other. That quip made it clear why she and Dan, and Dan and Bunny before, were such good matches.

It feels somehow empty to return to the building, Barker Hall, where Dan spent most of his 40-plus-year career at Berkeley. But the talented Koshland family and Dan's legacy live on in our hearts and in this the great institution of American science.

Randy Schekman, *Editor-in-Chief*



Daniel E. Koshland Jr.
1920 – 2007

"I am still amazed that I was actually paid to do something I loved — and others could describe as work."

Daniel E. Kos

Professor Emeritus Daniel E. Koshland, Jr.

An eminent scientist and influential editor, Professor Koshland was born in New York in 1920 and grew up in San Francisco. After receiving his B.S. in chemistry from UC Berkeley in 1941, he joined the Manhattan Project, working with Glenn Seaborg in Chicago and Oak Ridge, Tennessee. Professor Koshland went on to earn his Ph.D. at the University of Chicago, where he met his first wife, Marian E. Koshland, who passed away in 1997. He met his second wife, Yvonne C. Koshland, when they were both undergraduates.

He returned to Berkeley in 1965 as a member of the faculty. A preeminent researcher, his scientific contributions include his fundamental discovery known as "induced fit" theory, which led to new understandings of enzyme action and protein chemistry. He served as editor of *Science* from 1985–95, leading the prestigious magazine to new heights. An insightful scientist, Professor Koshland was also known for his wit in his column for the magazine, which featured his alter ego, "Dr. Noitall."

His luminous legacy to the University is enormous and enduring. In addition to his work in the classroom and the laboratory, he reorganized the biological sciences at Berkeley in the 1980s. Since the 1990s, he served as one of the principal architects and a major intellectual force behind the campus's Health Sciences Initiative. As a result of his leadership and vision, Stanley Hall, a new laboratory facility for bioscience teaching and research, opened this fall at Berkeley.

Professor Koshland was the recipient of many awards, including the 1990 National Medal of Science, the 1998 Albert Lasker Award for Special Achievement in Medical Science, and the Welch Award in Chemistry in 2006. He was a member of the National Academy of Sciences and the American Academy of Arts and Sciences. The California Alumni Association named him Alumnus of the Year in 1991.

A Builder of Berkeley, Professor Koshland was generous in his many gifts to the University, which included funding for the Marian Koshland Professorship in the Humanities, and construction of the Marian Koshland Bioscience and Natural Resources Library in the renovated Valley Life Sciences Building. His legacy will have a positive impact on faculty and students for decades to come.

hland Jr.
Campus Memorial Service

September 16, 2007
Zellerbach Auditorium
University of California, Berkeley

Welcome

Robert J. Birgeneau
Chancellor

Poem

"Birth Is a Beginning"
by Rabbi Alvin Fine
read by
Catherine Koshland
Mary Porter
James McCaughey
Children-in-law

Remembrances

Bruce Alberts
Professor of Biochemistry and Biophysics, UCSF
Former president, National Academy of Sciences

Raymond Dwek
Professor, Glycobiology
Glycobiology Institute, University of Oxford

Donald Kennedy
President Emeritus, Stanford University

Musical Interlude

"Sons of California"
The UC Berkeley Men's Octet

Remembrances

Ann Stock
Professor, Department of Biochemistry
Howard Hughes Investigator
University of Medicine & Dentistry of New Jersey-
Robert Wood Johnson Medical School

Joseph Goldstein, M.D.
Regental Professor, Molecular Genetics and
Internal Medicine
University of Texas, Southwestern Medical School

Randy Schekman
Howard Hughes Investigator
Professor of Cell & Developmental Biology
University of California, Berkeley

Robert Tjian
Howard Hughes Investigator
Professor, Biochemistry &
Molecular Biology
University of California, Berkeley

Dr. Noitall Tribute

Family Tributes

Stepchildren
Philip Keene
Elodie Keene

Brother-in-law
Ted Geballe

Grandchildren
Hannah McCaughey
Sarah Koshland James
Margrethe Koshland
Jessica McCaughey
Eliza Koshland
Sophia Koshland
Jacob Koshland
Benjamin Koshland
Nadine Wachtel

Children
Ellen Koshland
Phlyp Koshland
Jim Koshland

Musical Interlude

"Hail to California"
The Golden Overtones

The University of California
Marching Band

Reception

Lobby of Zellerbach Auditorium

Birth Is a Beginning

Rabbi Alvin I. Fine

(1916-1999)

Birth is a beginning
And death a destination.
And life is a journey:
From childhood to maturity
And youth to age;
From innocence to knowing;
From foolishness to discretion
  And then, perhaps, to wisdom;
From weakness to strength
Or strength to weakness —
  And, often, back again;
From health to sickness
  And back, we pray, to health again;
From offense to forgiveness,
From loneliness to love,
From joy to gratitude,
From pain to compassion,
And grief to understanding —
  From fear to faith;
From defeat to defeat to defeat —
Until, looking backward or ahead,
We see that victory lies
Not at some high place along the way,
But in having made the journey, stage by stage,
  A sacred pilgrimage.
Birth is a beginning
And death a destination.
And life is a journey,
A sacred pilgrimage —
  To life everlasting.

Donations in Professor Koshland's memory can be made to the
Marian Koshland Science Museum
500 Fifth Street, NW, Washington, DC, 20001

or to the UC Berkeley Foundation to support bioscience and energy teaching and research.
Write to the:
UC Berkeley Foundation
Attention: Vice Chancellor-University Relations
2080 Addison Street, #4200
Berkeley, CA 94720-4200

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