

CHEMICAL HERITAGE FOUNDATION

EMIL L. SMITH

Transcript of an Interview
Conducted by

James J. Bohning

at

University of California, Los Angeles

on

19 June 1991 and 17 March 1994

(With Subsequent Additions and Corrections)

THE CHEMICAL HERITAGE FOUNDATION
Oral History Program

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Emil L. Smith
Emil L. Smith

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EMIL L. SMITH

1911 Born in New York City, New York, on July 5

Education

1931 B.S., biology, Columbia University
1937 Ph.D., zoology, Columbia University, (Mentor, S. Hecht)

Professional Experience

Columbia University
1931-1934 Teaching assistant, zoology department
1934-1936 Teaching assistant, biophysics
1936-1938 Instructor, biophysics

John Simon Guggenheim Memorial Fellow
1938-1939 Molteno Institute, Cambridge University (w/D. Keilin)
1939-1940 Yale University and the Connecticut Agricultural
Experiment Station (w/H. B. Vickery)

1940-1942 Fellow, Rockefeller Institute for Medical Research
(w/M. Bergmann)

1942-1946 Sr. Biochemist and Biophysicist, E.R. Squibb & Sons

University of Utah, College of Medicine
1946-1950 Associate Professor of Biochemistry
Associate Professor of Medicine
1950-1963 Professor of Biochemistry
Research Professor of Medicine
Head, Biochemical Section, Laboratory for the Study
of Hereditary and Metabolic Disorders
1958-1959 Acting Chairman, Department of Biochemistry

University of California, Los Angeles
1963-1979 Professor and Chairman, School of Medicine,
Department of Biological Chemistry
1979- Professor Emeritus

Honors

1961 Distinguished Service Alumni Award, Columbia University
1962 Member, National Academy of Sciences
1964 Utah Award, American Chemical Society
1965 Member, American Academy of Arts and Sciences

1973 Member, American Philosophical Society
1982 Foreign Member, Academy of Sciences, USSR
1985 Fellow, UCLA School of Medicine
1987 Stein-Moore Award, The Protein Society

ABSTRACT

Emil Smith begins this interview by discussing his family background and childhood in New York City. Smith learned to play the saxophone during high school and later earned money for college by playing concerts on weekends and holidays. Attending Columbia University, he studied biology under Selig Hecht. In 1938, he received a Guggenheim fellowship to Cambridge University, where he worked in David Keilin's laboratory. The outbreak of World War II in Europe forced Smith to return to the U.S., where he worked at Yale, the Rockefeller Institute, and later, E. R. Squibb & Sons. Smith accepted a position at the University of Utah and was a faculty member in both the department of biochemistry and medicine. He was later chairman of biological chemistry at the UCLA School of Medicine. Smith concludes the first interview by describing his activities after retirement activities.

In the second interview, Smith describes his research interests, which have included work with peptidases, immunoglobulins, cytochromes, subtilisin, histones, and glutamate dehydrogenases. He discusses his involvement with the International Union of Biochemists and the American Chemical Society. Smith concludes this interview with a recollection of his meeting with Chou En-lai concerning scientific exchange between the United States and China.

INTERVIEWER

James J. Bohning is Professor of Chemistry Emeritus at Wilkes University, where he was a faculty member from 1959 to 1990. He served there as chemistry department chair from 1970 to 1986 and environmental science department chair from 1987 to 1990. He was chair of the American Chemical Society's Division of the History of Chemistry in 1986, received the Division's outstanding paper award in 1989, and presented more than twenty-five papers before the Division at national meetings of the Society. He has been on the advisory committee of the Society's National Historic Chemical Landmarks committee since its inception in 1992. He developed the oral history program of the Chemical Heritage Foundation beginning in 1985, and was the Foundation's Director of Oral History from 1990 to 1995. He currently writes for the American Chemical Society News Service.

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INTERVIEWEE: Emil L. Smith
INTERVIEWER: James J. Bohning
LOCATION: University of California, Los Angeles
DATE: 19 June 1991

SMITH: Twenty-nine years ago, when I was moving to California, I threw out an enormous amount of material that I didn't feel I needed anymore. Since then, I have donated books, papers and correspondence piecemeal to the University of Utah Archives. I've been able to discard things I don't need any longer, including many volumes that the University of Utah can make good use of because of the inadequacy of their historical collections. I gave them something like two hundred bound volumes of reprints in the field of biochemistry. It is an invaluable set which I collected over many years. One of the main reasons that I had these bound was that I found that if I had loose reprints and I gave one to a student, it was never returned unless I yelled. But if I had them bound, my secretary could keep track of the bound volumes, and I always got them back. [laughter] These include papers of many of the great names in twentieth century biochemistry. I got most of these reprints because we were writing the Principles of Biochemistry. It was easier than going to the library and carrying home a big fat bound volume for the few papers I had to read.

BOHNING: Professor Smith, I know you were born on July 5, 1911 in New York. Could you tell me something about your parents and your family background?

SMITH: Their history is very simple. My father left what was then the Russian Ukraine sometime around the turn of the century because of the obvious reasons of oppression and lack of educational or economic opportunities. He lived in England for about a year and finally came to the United States because he couldn't stand the climate in England. My mother was born in White Russia (Belorussia), hundreds of miles from my father's area. She came to this country when she was quite young, sixteen or seventeen years of age. They met in New York City through mutual friends. I'm not sure of the exact circumstances. They were married in 1906 and my brother was born in 1907.

My father was trained as an apprentice ladies' tailor. There weren't that many professions open to people of Jewish ancestry. You couldn't live in the big cities, you couldn't own land, you couldn't do this, you couldn't do that. The educational opportunities were closed. He was apprenticed

through a relative, and learned how to become a skilled tailor, and he had that skill when he was drafted into the Czar's Army. At that time the custom was that you were paid practically nothing in the Army and you were given a ration of bread and salt and a few other things. But you were allowed, on your own time, to earn money, and he earned his money by making clothes for some of the officers who paid for them. They bought the materials and the supplies and he was allowed to use the machines to put together these things. It was because of his friendliness with one of the officers that he was tipped off to leave the country because word had gotten around that he was carrying on agitation against the Czar's government. He was quartered in Poland at that time, and the Poles were very anti-Russian, so that with a little money and a little bribery and the knowledge of an underground route, he was able to get out with a friend through Germany and then to England.

That's the early history. When he came to this country, he worked first as a skilled tailor for Saks Fifth Avenue, the famous department store. He found that it was very difficult because of the seasonal employment. You did well for some months and then you were laid off because things were slow during the summer. He decided to open his own little business, which he did and which prospered, I suppose, up to a point. He was able to earn a decent living and could afford a wife and a family. I grew up first on Manhattan Island.

BOHNING: Where in Manhattan?

SMITH: What is now Washington Heights around 160th Street between Broadway and Amsterdam Avenue. His tailor shop was near Riverside Drive, a very prosperous area at that time, and it remained as a tailor shop for some years until ready-made clothes became more readily available and the custom of having tailor-made clothes began to decrease. At that point, he went more into the cleaning-dyeing business, and that's what he stayed at for the rest of his life.

BOHNING: Where did you receive your early education?

SMITH: My early education was first in elementary school in Manhattan, then later in Brooklyn. My junior high school was Dewey Junior High School, named for an educator in New York City, not for the Admiral. [laughter] Then I went to Erasmus Hall High School in Brooklyn, and from Erasmus Hall High School I went to Columbia College.

BOHNING: During that period, you've indicated that you had no

early interest in science, but that your interest was more in the humanities.

SMITH: This is true.

BOHNING: I understand that part of that was your family influence.

SMITH: It was largely family influence. My father and mother were both self-educated. My father had little formal schooling in the old country. When he came here, he went to high school classes at night for several years to learn English, and really learned it very well by himself. He read everything omnivorously, and so did my mother, and this was what was talked about in the house. As a result, my brother developed an interest in literature very early. I had to read the books they were talking about, otherwise I was left out of the conversation.

On the other hand, I obviously played around with mechanical things. My parents thought I was going to be an engineer, because I developed an early interest in radio. (I think I mentioned this in my autobiographical essay (1).) We had a neighbor who was one of the pioneer radio engineers at that time. We're talking about 1919, 1920.

BOHNING: What was his name?

SMITH: His name was Lipkin. I don't remember his first name. I know that he later went to work for General Electric, but he started out as an independent entrepreneur and had some designs for circuits and equipment, and he ended up working for General Electric. I lost sight of him completely when I was about twelve, which would still be in the early days of radio. I built my first little radio sets thanks to some tips that he gave me, using old cereal boxes and wrapping the wire around and building the taps and all the rest of it. I had things that worked on a headset borrowed from him. My parents realized that I was capable of doing these things, and they finally gave me the money so that I could go out and buy parts and build more sophisticated things. That's how I got started.

I must say, science teaching in the schools was pretty inadequate. I was not aroused by anything that I can remember, either in elementary school or junior high school or even in high school. It was fairly routine teaching out of the books. I don't even remember the names of most of the teachers, except the physics teacher in high school who was quite good. I was not particularly attracted to the physics that they were teaching.

BOHNING: Even though you had this interest in radio, which is related in some respects.

SMITH: Related in some respects, but they never really got to the meat of what modern physics was. You started out in the same old fashioned way, learning about pulleys and levers and this kind of thing, which might have been where physics started at the time of the Greeks, but it didn't tell you anything about what was happening in physics today. Physics teaching, like chemistry teaching, as you know, has changed, in that you now teach what chemistry is about instead of teaching the early chemistry of two thousand years ago.

BOHNING: So chemistry and biology didn't really interest you at that time.

SMITH: Not really. I did well, because I ended up at a good college at that time. But I didn't find them particularly exciting. I did better in other things. I read more widely in other things than I did in the sciences.

BOHNING: Was it just assumed you were going to college? Was that your parents' influence?

SMITH: My parents insisted that we were going to get an education and go as far as we could. My brother went to college with a major in literature.

BOHNING: Did he go to Columbia?

SMITH: No, he went to City College. The family situation at the time was such that it was easier to get him to City College, where it would cost nothing. City College was free. Columbia wasn't very expensive. It was three hundred dollars a year in tuition, which by today's inflationary standards sounds like nothing. I had a good job while I was in college. I mentioned that in my autobiography (1).

BOHNING: Yes, you were a musician.

SMITH: Yes. I think I earned more in my last year in college as a musician than I did as a budding scientist, until I was

finished with my postdoctoral fellowship years. [laughter] That tells you something of the realities about pursuing a career in science as it was then. My graduate teaching assistantship was a thousand dollars a year and free tuition. I could earn that much in two weeks during the Christmas break, which I did. [laughter]

BOHNING: Did you also sell some of these radios that you were building?

SMITH: Oh, yes.

BOHNING: That was also a commercial venture.

SMITH: That was while I was in high school. During the last two years in high school, I had a friend who was just as avid about building these things as I was. His family owned a house with a good-sized basement which he had used as a shop previously. That's where we could build them. We'd borrow the money to buy the parts, put the things together from the latest and best circuits, test them all out. His family had one of our radios. As a result, his family's friends and relatives ordered them. My family got one, and some of our relatives ordered them.

We went our separate ways after finishing high school. He went to New York University and ended up as a lawyer, which was his father's profession. I went to Columbia and I had no time for this, partly because by then I was working as a musician. I had started while I was in my last year in high school, but only the little local neighborhood things on a Saturday night. Nothing much.

BOHNING: Where did that interest develop? Did you have lessons very early?

SMITH: My parents were interested in classical music. They knew nothing about jazz. I thought it would be fun to take up an instrument, but I was too old to start on any of the more classical things like piano or violin. I decided after talking to a friend who was playing the saxophone that it might not be a bad idea. It was an easy instrument to learn. I bought a second-hand saxophone for something like seventy dollars, and I sold it for five hundred dollars about ten years ago.

It's an interesting story in itself about inflation. In fact, I sold both of my saxophones about ten years ago. The inflation of good musical instruments has been just as high as everything else. I took lessons for about two years from a very,

very good, rigorous classical teacher. What it amounted to was listening to records and listening to the radio and being able to improvise and learning the styles and getting some experience playing. I ended up as a professional jazz musician largely on weekends and on summer vacations during my college years.

BOHNING: Did that allow you to pay for your entire college career?

SMITH: No, I still lived at home and I got help at home, because there were times during the year when I was so busy at school that I didn't have much time to do any outside work. There were always slow seasons. The peak seasons were around the middle of December until after the New Year. We were very, very busy in those days. Then, after the New Year's break when final exams were coming along in the colleges, there were no dances, there were no proms. There were no weddings in January and February and March. Things began to pick up again around Easter break. Of course, June was a steady thing. Fortunately, college was over and final exams were over before the first of June, and June was almost a solid month of work. There were times when I played two jobs a day on Saturday and Sunday. Those were the days before canned music really had taken over.

BOHNING: Did you play in a steady group?

SMITH: I played with anybody who would call me. There were some steady groups. I was mostly working through one agency in the late years. I worked largely through the Moss-Hallet Agency, which later was taken over by MCA—Music Corporation of America. That is an interesting anecdote by itself, if you want this kind of anecdote.

BOHNING: Sure.

SMITH: About a year or a year and a half after I stopped playing, when I'd gotten my first teaching assistantship at Columbia, I met Harry Moss on Broadway. I was going to a concert on a Saturday afternoon. He said, "Where have you been?" I said, "I've given up the music business." He said, "What are you doing?" I said, "I'm a graduate teaching assistant doing graduate work at Columbia." He said, "What does that racket pay you?" I said, "I'm getting a thousand dollars a year and free tuition." His eyes popped wide open. He said, "You should have stayed with me; you would be in the big time." [laughter]

The culmination of that story is that more than ten years

later, my wife and I were vacationing in northern New Hampshire. We had rented a cottage on a lake about seventy-five miles from the Canadian border. We knew the area because of friends. When it rained I was writing papers, and in the good weather we were playing tennis and climbing mountains. One day, there appeared an announcement that on Saturday night there was going to be a village dance at Littleton, New Hampshire, which was seven or eight miles away. Mal Hallet was playing with his orchestra. He was a partner of the Moss-Hallet agency. I had worked as an occasional member of Mal Hallet's bands in New York. When it came prom time in June, Mal Hallet had ten orchestras functioning in New York City. He would go from one to the other at fifteen minute or half hour intervals to put in an appearance. [laughter]

We went to the dance and when we got out on the floor Mal Hallet said, "Where have you been? Come sit in and play." I said, "Oh, no. I haven't played in ten years." [laughter] So the connections were still there. I still have, at this late stage of my life, one friend from those old music days who's now long retired as a musician.

BOHNING: Had you ever thought about being a professional musician?

SMITH: No. I never thought of becoming a professional when I saw the lives that the professionals led. It was seasonal. Those who worked the movie theaters were thrown out by talking pictures, which happened during my active time in the music business. To make a success with a good band you had to go on the road and play these one-night stands, traveling from one end of the country to the other by bus. It all ended up in unhappy lives, unhappy marriages and disrupted family life. Everything was wrong. Most of the good people that I knew who did what I did ended up going to some kind of professional school or professional career in other directions. Very few of them stayed as professional musicians, except the classical ones.

There was one group that I played with every Sunday night for some years when I was fairly young, at one of these basketball game and dance affairs in the YMCA. You played for a half hour, then there was basketball practice, they would play the game and then after the basketball game, you'd play an hour for dancing. During the time the basketball game was on I could do my homework. [laughter] I think we got something like six or seven dollars a night. It was a very easy job. This is while I was a freshman and sophomore in college.

The man who played the trumpet with me, Umberto Pennino, came from an Italian musical family and he was attending Julliard. He ended up first in one of the New York Symphony

Orchestras and then with the Toscanini NBC Symphony Orchestra and later with the Philadelphia Orchestra. I lost sight of him after that. A violinist with whom I worked at that time ended up in the New York Philharmonic. He is long retired and I haven't seen him in years. Those who followed a professional career in classical music stayed with it. Those who were essentially jazz musicians, and the saxophone essentially was a jazz instrument, of the people who I knew in college, didn't stay. That was interesting; that was the difference.

BOHNING: Just as an aside, I have a son who is going to start in college as a music major. I'm going to have him listen to your story. [laughter]

SMITH: A number of our biochemical friends have children who have gone in that direction. Howard Schackman is at Berkeley, and he's now professor emeritus. He was president of the ASBMB [American Society for Biochemistry and Molecular Biology] just a couple of years ago. His oldest son Mark went to Julliard and has ended up as a very, very good oboist. He has a group called the Aulos Ensemble that specializes in baroque music. He has done very well. Arthur Kornberg's younger son started out with a joint degree from Julliard and Columbia, but then had some trouble with his hand and gave up the cello. He is assistant or associate professor at UC San Francisco Medical School. So Tommy Kornberg started out in music but ended up as a biochemist/biologist.

BOHNING: As you reflect back on your pre-Columbia days, what was it like growing up in New York City?

SMITH: It was like growing up any place else. You didn't know that it was any different. School was school. You took it seriously up to a point. I took music seriously up to a point. I skipped a number of grades in elementary school and went to junior high school through rapid advancement. I finished high school just before I was sixteen. There were plenty of neighborhood kids in the apartment houses around, so we played ball after school.

I worked after school a good deal through high school, as a delivery boy and in department stores as a wrapper, unpacker, and all that kind of thing. Five dollars a day. This is what we all did; everybody was doing it. This was part of the norm. I've talked to friends who grew up on farms and they worked on farms. In the city, you didn't work on farms, you worked as a delivery boy or you worked at a fruit market or a meat market or whatever. People worked in ice cream parlors during the summer.

My brother, who didn't play an instrument, had a variety of jobs. He sold clothes, he worked as a shoe salesman. He did all of these things. One summer he worked as a street car conductor. He worked as a lumberjack one summer in the Adirondacks. Everybody of that generation was expected to work. This was the norm for second generation immigrants. There was no great prosperity. Besides this, I think the attitude was that work was good for the soul, and I'm pretty sure it's true.

Even though my kids grew up in a very different and more prosperous era, they still worked during the summer. They did something during the summer, and by the time that they knew what university life was, they all got jobs washing dishes in the lab or helping out with primitive experiments and doing all kinds of things. They couldn't wait. They wouldn't just hang around the house during the summer. When they were very young they went to learn how to swim, to type, etc..

BOHNING: Why did you pick Columbia as opposed to City College or NYU [New York University]?

SMITH: I was unhappy about the science situation at City College. City College was overcrowded. The competition was stiff. One of the ideas my parents had was, "Okay, you're interested in radio and science, why don't you study medicine?" I had no real interest or knowledge of medicine, but if you took a premedical course, you could go in various kinds of directions because, in effect, you started doing science fairly early. The competition at City College was horrendous and it was overcrowded. I thought I wanted to do something different.

BOHNING: There were some pretty good people who came out of City College at that time.

SMITH: A lot of very good people came out of City College over the years. I think it's changed now because of the population of New York is no longer so insular. At that time they felt that anything beyond the Hudson River was the far west. Anything north of the Connecticut border was sort of terra incognita. It took a certain degree of sophistication to begin to think about going out of town, plus the expense and the cost of living. At Columbia I could still go to a prestige school and live at home and ride the subway for an hour each way.

BOHNING: You were in Brooklyn at that time.

SMITH: I rode the subway everyday.

BOHNING: That's a long ride.

SMITH: Yes, it's a long ride. In part of one direction, it was crowded and you couldn't do anything. The other part you could read, which I did. I always enjoyed taking some literature or social science courses because I could read the books on the subway. It's not like working in labs. [laughter]

BOHNING: When you started as a premed, you were a biology major.

SMITH: I started as a premed and you had to have a major. I actually took more credits in chemistry than I did in biology.

BOHNING: Why?

SMITH: As I mentioned in my autobiographical essay (1), I was attracted to biology first by one teacher whose course I took in my sophomore year.

BOHNING: That was [James] MacGregor?

SMITH: Yes, MacGregor. You could not take zoology until you had a year of general chemistry. It was a good rule at that time, but I don't know how many colleges enforced that rule back in 1927 and 1928. The general biology that was taught, certainly in the first semester, involved a good knowledge of chemistry because they taught you the composition of living matter with some very simple primitive experiments in terms of understanding that biological phenomena had a chemical basis.

The following year, I took Pop (John Maurice) Nelson's course in organic chemistry. Nelson was a rare bird who related everything he taught in organic chemistry to biological materials. The people in the course who were going to be chemical engineers didn't like it, but those who were interested in biology and the premedical students loved it. He'd talk about carbohydrate chemistry and all the things that went with it in terms of what these things are and what they do in living systems. He didn't teach the biochemistry but always made the connections. He was a superb teacher, really one of the great inspiring teachers. He was unusual as an organic chemist at that time because he was working on enzymes. That was pretty rare for a professor of organic chemistry in the 1920s, and he had started much earlier.

As a result I took physical chemistry and physical organic chemistry and everything else before I finished college and in my first year of graduate school. But I decided I wanted biology because I knew that I could get a teaching assistantship there, and that was important. In chemistry, I wasn't sure what the situation would be. In actual fact, I applied for both and could have had either one, but I had sort of made a commitment to biology earlier, so I accepted the assistantship in biology.

BOHNING: The Depression came midway through this time period. What kind of effect did that have?

SMITH: The effect was that it was clear that I was not going to go out of town for graduate school during those Depression years, because my father's business was hurt. They survived, but it was tough. Certainly, the thousand dollars a year that I was getting meant that I was completely self-sufficient and could even contribute a little bit when needed at home, which became important at that stage.

[END OF TAPE, SIDE 1]

BOHNING: I want to talk a little bit more about your undergraduate career. Your degree was in 1931 in biology. It sounds like you almost had enough to have a chemistry degree as well.

SMITH: I had enough to have a chemistry degree as well.

BOHNING: Did you do any research as an undergraduate?

SMITH: As an undergraduate in the organic course, during the second semester I was excused from doing the regular experiments and helped one of the instructors with preparing a couple of things that he wanted as starting materials for his own research. This was not research, but just making special compounds that he wanted. That was the only real experience I had. The fun of it was that I could use a lot of his apparatus and not just the student apparatus that was generally available. I learned more about good quality distillation apparatus, I learned more about glass blowing and more about how to do more accurate melting points than the kind of primitive methods that were set up in the teaching lab. That was the main virtue of it. But I did not do any other kind of research in my undergraduate years.

BOHNING: You've also commented that during this time it was MacGregor who really interested you in biology. Your interest in evolution was also formed in some respect at this time, and it shows up through all of your work later on.

SMITH: Very much later on. The interest in evolution was very exciting as an intellectual thing. What one could do about it, in terms of trying to understand mechanisms of evolution, clearly would have to come through genetics. I took all the advanced genetics courses during my graduate career and almost went into the field, but realized that genetics was not ready for the kind of chemistry that I wanted to do. It was, in effect, more than twenty years early in terms of the real beginnings of biochemical studies of the genetic material. All of that came very much later.

I was very much attracted to Selig Hecht, who was a member of the zoology department, and was doing what was then called general physiology, but what today we'd call biophysical chemistry. I found this very exciting intellectually.

BOHNING: The other aspect of this is that organic chemistry is a way to approach the secrets of biology. That thinking, to me at least, seems rather unusual for that time period, that the key to biology was really a chemical understanding. Was it Nelson who gave you that feeling?

SMITH: Nelson gave me that feeling first, but there was also a kind of literature that was around at that time in the biological world more than the chemical world. This is one of the reasons why I did not want to take the degree in chemistry at that time. Ninety-nine out of a hundred people who took their degrees in chemistry ended up in industry, including many of Nelson's own students who, while they worked on an enzyme or a biological problem, still ended up in industry afterwards. I had no real interest in going into industrial chemistry.

The impetus and the interest came largely from people like Jacques Loeb and his book Mechanistic Conception of Life (2), his book on proteins (3), and Michaelis' book on oxidation-reduction (4). All of this was in the air at the time, and a large part of it had come out of the German philosophical schools and the trend in German biochemistry at that time. American biochemistry was largely in the medical schools and was devoted, as I'm sure you're well aware, to simply improving or inventing clinical methods. I had no interest in that whatsoever. That's why I didn't go to medical school. Clinical chemistry in the United States at that time was improving methods of urine and feces analysis, and that was very important. I'm not saying it's unimportant. It's still very important today, but it was not

what I wanted to do.

As for Selig Hecht, it was well known that here was a man who was trying to understand sensory physiology by applying physics and chemistry to find out how light impinged on the retina, how it stimulated nerve fibers, and so on. In my senior year I actually sat in on a few of his lectures. I took the course, which was open to both seniors and first year graduate students, as a first year graduate student. That made up my mind. At the same time, I was taking the advanced course in genetics and other things as well, and I was serving for sixteen hours a week as a teaching assistant in biology.

The second year I was a teaching assistant, my assignment was to improve all of the first semester experiments for the beginning students, since I was now the chemist in the department. [laughter] A friend of mine who was the senior teaching assistant and myself introduced very simple enzyme experiments. The student could see in the beginning biology class how an enzyme worked, and he could do some of the things about denaturation, boiling it to kill the activity, and measuring rates and that sort of thing. They were very simple, very primitive experiments, but they were quite successful.

BOHNING: How much of a mathematics background did you have through all of this?

SMITH: I didn't have a mathematics background. It was only after I realized that I was going to go into a field like biophysics and general physiology or even more advanced chemistry that I realized that I didn't have the mathematics background that I needed. I had been poorly advised; premedical students were not advised to take much mathematics beyond advanced algebra. I caught up and I finally took analytical geometry before I got my undergraduate degree. I never took a course in calculus. I bought two good books. One was a standard Osgood calculus (5) which, I suppose, everybody used in that generation.

On the advice of someone, I'm not sure who it was, I bought a book called, Higher Mathematics For Students of Chemistry and Physics (6), by a great Australian named Mellor who later edited a huge treatise on inorganic chemistry (7).

I found that the combination of the two was just wonderful because what Mellor did was to take very simple things in chemistry and physics and show how to apply calculus to them. I was taking thermodynamics at the same time, by the way. Harold Urey didn't want to let me in the course [laughter] because I hadn't had a formal course in calculus, which was a prerequisite. I said, "Well, it's on my head. If I fail, I fail. But I think I can do it." I had started some of the calculus during the summer. I developed just enough interest and excitement in it to

realize that this was a very, very powerful tool in understanding all of these things. I must admit I had never worked so hard in my life, doing the mathematics at the same time as doing the chemistry. However, I found the principles of chemical thermodynamics straightforward, simple and logical.

In fact, my complaint was then, and it has since been rectified, that the rules of how chemistry works were not taught until you were a graduate student. Now it's back in the freshman year, where it ought to be. Chemical reactivity is now taught in the freshman year, like [Linus] Pauling's The Nature of the Chemical Bond (8) and all the things that go with it. We didn't have any of that. What we had in the freshman year was memorizing all the elements of the periodic table and their simple compounds; it was a total bore. I wasn't interested in the Frasch process or the Bessemer process. I wasn't going to smelt iron; I wasn't going to mine sulfur or any of these other things. [laughter] But that's what you had to memorize in the freshman year of chemistry, and that's what high school chemistry was, which I found dull as hell. There might have been people who were attracted to it who wanted to be chemical engineers, and two of my high school friends who also ended up at Columbia did become chemical engineers. That was good for them but not for me. We simply had different interests.

BOHNING: Did you have any other interactions with Urey?

SMITH: I got to know Urey quite well over the years. Urey was not the most inspiring teacher as a lecturer. He was too busy with his own things. He had a tendency to come in unprepared and sort of flounder around with the mathematics and give us a totally different derivation than the one that was in the book. The best teacher of physical chemistry at Columbia was Louis Hammett. He was marvelous because he was a real inspiration. I took half of the thermodynamics from Hammett, and then I took Hammett's physical organic chemistry course which later became his great book (9). That was a thrill, because again, one was learning what this was all about in terms of not simply reactions that you carried out on paper, but what made them go and what the rates were and why it didn't go in another direction. That I found very exciting. I saw Hammett the year I was elected to the National Academy. It was the last meeting he attended. It was quite a thrill that he remembered me.

BOHNING: You were attracted to Hecht partly through your exposure to him as a senior and then continuing as a first year graduate student. Can you tell me something about him and what the biophysics laboratory was like when you started working there?

SMITH: Selig Hecht was a product of the City College of New York. He took his Ph.D. at Harvard in experimental biology with a man named George Howard Parker, who was one of the great pioneer zoologists of this country. He tried to understand how things worked and to apply quantitative methods. Hecht started out in his laboratory essentially doing experimental biology. He was inspired, not only by Parker, but by Jacques Loeb's teachings and his books.

Hecht's early experiments were simply on photoreception in animals. If you shined a light on an animal, it did something. It either went towards it or it went away from it. This was the kind of thing that Loeb had been doing. Hecht carried this a lot further. I'll give you the classical case that he studied on the long neck clam of Cape Cod, Mya arenaria. There was a light sensitive spot on that clam that had been identified long before. Now, if you shined a light on that spot, the clam retracted its siphon. It tried to put its siphon back into the shell. What Hecht found is that you could use a very short exposure. You didn't have to shine the light continuously. Intensity times time was a constant. You used a certain amount of energy to get the contraction to move. He found that that constant was independent of temperature, like all photochemical reactions. Now, we're talking about 1916 to 1919. He also found that there was a latent period, after you shined the light. That latent period was sensitive to temperature. That obviously had to do with a dark non-photochemical process. So, he began to work out ideas in terms of the mechanism of the photoreception process, and he studied this in other animals and then, of course, this got applied to the human eye as well. Here was the application of physical chemical thinking to try to understand a very complex biological process.

After his doctorate work, he went abroad. He worked with [Edward Charles Cyril] Baly, who was a photochemist at Liverpool, to learn photochemistry. He worked at the zoological station in Naples because of the availability of marine animals of the kind that he wanted to study. He learned how to extract rhodopsin which other people had been studying much earlier, of course. The important point is that he could measure the sensitivity spectrum of the human eye at low intensities of light and show that it was essentially identical with the absorption spectrum of rhodopsin. That was the first proof that rhodopsin really is responsible for rod vision of the human eye. This involved spectroscopy, using monochromatic light for studying human vision as well as studying the absorption spectrum of animal rhodopsin. This is the kind of thing that I found very exciting.

I've told a story in my essay about how I did my doctoral thesis (1). Hecht had the custom that everybody who came into the lab would do at least one piece of research jointly with him, a short piece of research just to get the feeling of handling

equipment, how you think about research, and how you do things. I was involved in a piece of research on intermittent stimulation by light of the human eye. I've told the story of how I got into photosynthesis, which was quite accidental. It was a very small and intimate laboratory group. Hecht had one full-time research assistant who was also working for his degree, and there were never more than four or five graduate students in the lab at the same time, and perhaps one postdoctoral fellow. The lab had no more than six, seven, eight people at a maximum. Hecht, having worked in England, had the custom that every day at four o'clock there was tea. Unless you were in the middle of an experiment or teaching at that hour, you were expected to come in for tea and conversation. The conversation would sometimes go on until eight o'clock in the evening but Hecht had gone home long ago. The arguments among the graduate students continued there and then in the cafeteria down the street and back in the lab at night, that kind of thing. It was a very intimate, excellent group of people.

BOHNING: You presented a paper in Leningrad in 1935 (10), which was the result of that very first work that you did with him.

SMITH: That's right.

BOHNING: It was also a belated honeymoon.

SMITH: That's right.

BOHNING: What was it like going to Leningrad in 1935? Was that at Hecht's insistence or suggestion?

SMITH: No. My wife [Esther Press] and I thought we wanted to go to Europe. There was no way we were going to go in 1934 when I was still very busy as a graduate student. She was teaching school, and we had no children, by plan. We were not going to have any children until we were settled somewhere and I had finished my graduate work. We had saved a little money, and these international congresses were held every three years. The preceding congress had been in Rome in 1932. Of course, you always knew three years in advance, and we had that as a goal, that we would try to get to the next physiological congress.

Travel was pretty inexpensive at that time; inflation has hit travel as well. A round trip for both of us for that nine-week trip in Europe was nine hundred dollars. We traveled third class across the Atlantic, and we learned a trick from a friend of mine whose cousin ran a travel agency. The competition among

the steamship companies was such that if you booked, not from New York to Cherbourg, but from New York to Istanbul—they wouldn't book into the Soviet Union—they gave you a reduced fare, and they were responsible for all the train or boat connections to get you to Istanbul. If you made sure to miss the boats, they'd even put you up at a hotel for a few days. By the same token, we booked a round trip back from Helsinki to New York. The upshot of it was that booking through this cousin of a friend of ours, we had very inexpensive travel. In effect, we had three days in Paris on the way from Cherbourg to Paris and then from Paris to Milan for a couple of days, and then we went to Naples because we wanted to visit the Stazione Zoologica, and we had four days in Florence. Worldwide depression? I have still in my diary that we paid three dollars per person to stay in the penzione in Florence for three meals a day and a room, a total of six dollars a day.

The food was simple: continental breakfast, coffee or tea and bread or rolls and jam; lunch comprised a big soup, some kind of pasta or vegetables or something with it; dinner included chicken, meat or fish, something of that kind. Very wholesome food and very simple food. Nothing fancy. Every once in a while if we didn't want to come back for lunch, we'd eat out somewhere and we ate dinner out once in a while. This penzione had been recommended to us by Selig Hecht; he and his wife had stayed there. [laughter] We stayed at a penzione in Naples where he had stayed at one time. These things went on from generation to generation except that the war disrupted all of this. Where he had stayed years before, people would remember. They were delighted to have us come on his recommendation.

As an excuse, we had planned to go to Europe because the physiological congress was there. Hecht had decided he didn't want to go to the congress. He said, "Why don't you present the work?" I had done this together with him and with [Simon] Schlaer. That was quite an interesting experience. We traveled third class through Russia. It was tough. We came in on a Russian boat, which was fun, to Odessa. The hotels were alright. We traveled third class on the railroad. We were young; we could do it. Lots of people have slept in YMCA's and hitchhiked across country. Leningrad was more luxurious simply because we stayed in a fairly new hotel. The government was putting up the whole congress, so they made a good show of this. There were lots of banquets, lots of entertainment, and whatnot.

It was a very exciting first trip in Europe, and it was a very exciting congress. There was no separate biochemistry congress before the second world war. Biochemistry and physiology were parts of the same science. My session was in sensory physiology. I didn't know at the time, but I found out later that Hecht had written to [Lord Edgar Douglas] Adrian who was going to be chairing that session to look out for this young fellow. "Make sure he doesn't get into any trouble during the

presentation." [laughter] I presented my paper, which I had rehearsed very carefully. I had given lectures in the U.S., but it's a different thing before a big international audience. The first question was not a simple question but a statement plus a question from Henri Pirenne, a very distinguished French sensory physiologist who had also worked for many years in the field of vision. He was followed by Walter Trendelenburg from Berlin with a long complicated question in German. Adrian leaned over and said, "You don't have to answer if you don't want to." I said, "I can answer both, thank you." [laughter] Which I did, but in English. It was very pleasing to be able to have survived the experience. I must admit, the preceding afternoon, my wife had gone out with some friends swimming on one of the far islands, the famous stoney island, Kamenoy Ostrov, while I stayed home writing out my speech carefully and going over it again and again and polishing it. It was worth it.

As a reminiscence, in 1975 I was back in Leningrad for the first time, forty years later, at the two hundred and fiftieth anniversary of the Soviet Academy of Sciences. One evening, after some kind of entertainment, we ended up at the supper table with some old friends. Those old friends consisted of Severo Ochoa, now living in Spain [deceased in 1993], who had come from Spain in 1935 to attend that congress, and whom I hadn't known at the time. Alexander Braunstein (now deceased) had also been at that congress. He was one of the most distinguished Russian enzymologists. Vladimir Engelhardt, now deceased also, had also been at that congress. There were a couple of other people at this huge table, but here were four of us who had attended that congress. Braunstein and Engelhardt had known each other at that time but the rest of us hadn't. Forty years later, I was one of the people to represent our National Academy, which was a nice way to return! My wife looked at me, we looked at each other and said, "Would you have believed it forty years earlier?" The answer was no. [laughter]

BOHNING: On this trip, were you cognizant of any political developments going on?

SMITH: Oh, yes. Very much so. Don't forget that Hitler had taken power just a year earlier in 1934. Europe was full of refugees. They were already piling into the United States as well as all over western Europe. There were a number of German refugees in the Soviet Union at that time, many of whom stayed; some of them left subsequently. There was a considerable amount of tension in the air. [Ivan Petrovich] Pavlov, the distinguished physiologist, was the president of the congress and his opening speech was a plea for peace, as a matter of fact. Everybody was well aware of what was brewing or what the potential for war was, because certainly Germany never disguised any of its intentions, and the question was whether you took them

seriously or you thought this was all a bluff. Certainly, I took it seriously. We avoided Germany by going back through Helsinki, Stockholm, Copenhagen, and London. We did not go through Germany at that time for obvious reasons.

BOHNING: You got your degree in 1937.

SMITH: Actually, I finished the work in 1936, but Columbia had a firm rule. You didn't get your piece of paper until that thesis was published, which was not until 1937 (11). [laughter]

BOHNING: It had to be published, not just completed.

SMITH: It had to be published. It had to be published, and you had to turn in seventy-five reprints. [laughter]

[END OF TAPE, SIDE 2]

BOHNING: I wasn't aware of that.

SMITH: I think they've changed that requirement, but in the old days your typewritten thesis was not the fulfillment of the requirements for the doctorate. That was sufficient to have the final oral exam.

BOHNING: Did you have a thesis committee?

SMITH: Oh, yes. I had a thesis committee of five or six people; it went on for about three hours. Because my thesis was in a zoology department on a plant subject, the professor of plant physiology (Sam Trelease) was also on the committee, and one of the other people from zoology, a geneticist (Leslie Dunn), was on the committee. Hans Clarke, who was chairman of biochemistry at the medical school, was on the committee, and one of the people from the chemistry department (Raymond Crist) who taught photochemistry was on the committee. I had taken his course. I knew everybody on the committee beforehand, but nevertheless, they gave me a rough time. [laughter]

BOHNING: Could you tell me something about Simon Shlaer, who collaborated with you during that time period?

SMITH: Simon Shlaer was Hecht's personal research assistant as well as his graduate student. Simon Shlaer had a great gift for equipment. He could build anything. He could design anything. When it came to the intellectual side of science, he was frightened. This was psychological, I suppose, more than anything else. Simon Shlaer went off to Los Alamos sometime at the end of the war. He was there about a year or two years before Hecht died, and stayed there the rest of his life, as far as I know, designing all kinds of special equipment, mostly photographic equipment, or whatever went on at Los Alamos in that period.

BOHNING: When you were starting to repeat [Otto] Warburg's experiments, you commented you had to start from scratch, virtually put everything together. Did Shlaer assist you then?

SMITH: He helped me a great deal. I had to do the work. You didn't get away with anything. This was part of physiology at the time and part of science. You learned how to build your own equipment. Part of building your own equipment was that I took Warburg's descriptions and went to the glass blower and had to convince him how to make the manometers and put a scale on them. I had to build the constant temperature bath, the temperature regulator, design the light source, make the graded light filters and calibrate them. I did all of that. It took months. In the same way, when the published work came along on glass electrodes, I ordered the glass from England, had to blow my own glass electrodes, and assemble the glass electrodes using a type K potentiometer, Wheatstone Bridge, and all the rest of the equipment. You couldn't buy any of these things commercially. The first commercial glass electrode equipment in this country was, I think, available only around 1939 or 1940. That's how [Arnold] Beckman got his start. The first commercial glass electrode assembly in this country, which I remember seeing and using afterwards, was made by the Cambridge Instrument Company, which was British, in a new factory in upper New York State. That's what we had, for example, at the Rockefeller Institute. Beckman's pH meter came along around about 1938 or 1939. I had a glass electrode assembly that I was working with to measure the pH in my buffers back in 1935 and 1936. You couldn't use a hydrogen electrode with carbonate-bicarbonate buffers, which I needed to do photosynthesis. If you put in enough hydrogen you expelled all the CO₂, and you no longer had a buffer. (It's bringing back memories.)

BOHNING: In the work that you did which showed a difference with Warburg's original experiments, you've commented that you really didn't want to tell Hecht what you had found. Yet he reacted differently than you had expected. Could you talk a little bit about that experience? How was that accepted? I think you've

commented that people ignored that for the most part for a while. Is that true?

SMITH: Let me go back to Hecht first. I think part of the student's psychology is that you don't like to contradict the great authority. After all, Warburg's stuff was widely accepted; he had pioneered in a great many of these things. He was long out of photosynthesis, of course, because the photosynthesis work had been done in the early 1920s, and we're now talking about 1932 and 1933, when Warburg's work had taken a completely different turn. He was now isolating enzymes and very important co-enzymes, and all that kind of thing in probably one of the greatest experimental laboratories in the history of biochemistry. Now you suddenly find that you can't repeat exactly what he has reported. What is the difference between the curve involving a first order process with light and dark phases, versus something of the second order? It all depends on the slope of the small part of the curve. The asymptote in this direction is the same, the slope down here is the same. It could be an artifact, due to error, so you calibrate everything all over again and check it all out, and you repeat it sufficiently to make sure that you're right.

At that point I showed the data to Hecht. I think he had become a little bit impatient as to why I hadn't set this thing up for the students any earlier, but finally I told him about it, and he said, "That's great!" He looked at it and he looked over all the data. I showed him all the repetitions and all the rechecking of the calibration of the filters and the calibration of the light source, in absolute units and all the rest of it. He was just absolutely delighted. The fact that my report made very little impression was due to two things. The field was completely at a standstill. The physical side of studying photosynthesis was fine and the pioneer work had all been done. You knew that chlorophyll was the light absorbing source. You knew that it used carbon dioxide and water, and it made some kind of carbohydrate precursor. People always wrote CH_2O in parentheses, question mark, but there was no way of getting at any kind of mechanism at that time. If you disrupted the plant cell and put the contents in some kind of a buffer solution to resemble what was inside a plant cell, nothing happened, basically.

It was not really until 1938 that Robert Hill in England (now deceased—he just died this past year) showed that if you took chloroplasts out of a green leaf and suspended them in the right kind of buffer, shined light on them, that you got reducing power. The system would reduce ferric compounds to ferrous compounds, and it would reduce other compounds also. This was called the Hill Reaction for many, many years. It was the first breakthrough in attempting to study any kind of mechanism (12).

This was a couple of years after my studies on photosynthesis. I suppose the attitude was, and perhaps quite rightly, "So what? If it isn't a first order process, then tell us what it is." The conclusion in my paper that it is more complicated than a simple first order process left people cold. In that sense, I suppose, kinetics of any biological phenomenon leaves one cold unless you can get at the mechanism. The old joke was, you did kinetics when you didn't know what else to do. [laughter] There was no way of getting at the mechanism at that time. We understood nothing, or practically nothing, about oxidation-reduction reactions in general. Whether it was a purely chemical reaction or a biological oxidation-reduction reaction or the most complicated reduction reaction there is. We knew that we didn't really know anything, but we didn't really know how complicated all this was going to turn out to be.

I did know, however, that I was finished with that kind of kinetic study when I was getting ready to leave the lab, and I was anxious to leave the lab. I could have stayed on as an instructor at least for a few more years, but there was no likelihood that I was going to get tenure because the department was not going to expand. It was understood that this was a teaching instructorship in rotation for somebody who got his doctorate degree and needed a few years to get himself established.

I suppose the inspiration for going abroad was the fact that European biochemistry was developing in an entirely different direction. They were isolating enzymes. They were studying intermediary metabolism. They were not like the medical school biochemists here. The zoology department at Columbia had invited John Northrop to come and give the Jesup Lectures. It was Northrop's presentation of studies on crystalline pepsin and its behavior and also on trypsin and chymotrypsin. Here was enzymology, protein chemistry. This was exciting. You now had something that you could get hold of as a pure material and get to study. I realized that what I wanted to get into was enzymology. Intermediary metabolism as such didn't interest me in terms of the steps of the individual reactions, but what was the mechanism of catalysis? What kind of enzymes were they? Were they all simple proteins?

Also at that time, Warburg was beginning to publish his work on oxidation-reduction enzymes, dehydrogenases. Such work had been coming out of [Otto] Meyerhof's laboratory also in Germany until he had to leave. There was no possibility that I was going to go Germany to work. I didn't want to go to work in Northrop's laboratory because Northrop was almost stone deaf, and it was very difficult to communicate with him. The interests of the laboratory were rather narrow, in my sense. Cambridge was very exciting and very attractive. This is where modern biochemistry was flourishing in all its aspects. I talked to Hecht about it and he said, "Wonderful. Put in your applications for a

fellowship." I thought of applying to the National Research Council for an NRC fellowship, and Hecht said, "Well, maybe I've worn out my welcome with the NRC because everybody else who came through this lab who has gone to the NRC for a fellowship has gotten it. Maybe you ought to apply to Guggenheim." I said, "All right." I didn't know any better. So I applied to the Guggenheim, and was lucky enough to get the fellowship.

BOHNING: You had already started some work in that 1936-1938 period at Columbia with chlorophyll and it being associated with a protein.

SMITH: That was in my last year, after my thesis and after my degree. I had done some more kinetic work to finish up some things that were not in my thesis. I had been reading a lot of the literature and wondering where an opening might be to get into some kind of mechanism. As I said in my little essay, it was in the air. This was the period in the 1930s when it was recognized that [James] Sumner's urease was not an artifact, that Northrop's and [Moses] Kunitz's enzymes were not artifacts. These were all proteins. George Wald, who had come from Hecht's lab and gone to Europe, had shown that rhodopsin was a conjugated protein with a vitamin A derivative as the prosthetic group of a small protein. It was also the period that Michael Heidelberger and his cohorts had demonstrated that antibodies were proteins. The first of the hormones were coming along as proteins, not only insulin, which had been done a little earlier, but the pituitary hormones. The lactogenic hormone had been isolated by Abe White in fairly pure form at that time.

Here were enzymes, hormones, and antibodies as proteins. What's the situation with chlorophyll? Reading the literature, it was quite clear that the absorption spectrum of chlorophyll A, which is at three times the concentration of chlorophyll B in the green leaf, has a maximum absorption of around 660 nm. Everybody who'd measured the absorption spectrum of a green leaf in a higher plant, found the absorption maximum to be about 677 or 678 nm. (You're making me remember numbers from fifty years ago. [laughter] Which I do.) This was too big a discrepancy to explain in very simple terms. A few people had suggested that chlorophyll might be attached to protein. But nobody had really done anything about it because this was all highly insoluble material. Unless you took a strong organic solvent like alcohol and disrupted the chloroplast, you couldn't extract the chlorophyll.

In reading over that literature I realized that this was very similar in some respects to what George Wald was describing for rhodopsin. If you took a simple organic solvent in which chlorophyll was freely soluble like ether or petroleum ether, you couldn't extract any chlorophyll from a green leaf, no matter how

much you ground it. But if you added alcohol to disrupt the structure, then it would go freely into ether or pet ether. This sounded to me like denaturing a protein. The question was how to solubilize it. As I've said, I introduced the use of detergents into this whole picture because the use of detergents for extracting insoluble proteins had been invented by Willy [Friedrich Wilhelm] Kühne in Heidelberg in 1878. It had never been applied to anything else but rhodopsin from 1878 to 1937. [laughter] Nobody thought that this was the way to extract proteins. After all, there were plenty of water-soluble proteins. Why worry about those things that were insoluble?

I went to Europe with the idea of not just studying the chlorophyll protein complex, but inducing [David] Keilin to let me try to solubilize cytochrome oxidase the same way. Only he said, "What you're working on is more exciting. Leave the oxidase to me." So there was a footnote that gave credit to an E. Smith (13). [laughter] It didn't matter.

Just a few years ago [1988], Robert Huber and his coworkers [Hartmut Michel and Johann Deisenhofer] got a Nobel Prize for studying the structure of the chlorophyll-protein complex by x-ray diffraction, and have mapped out the complete structure of the bacterial chlorophyll-protein complex using simply a different detergent than the one I used. There's some intellectual satisfaction in being premature by thirty or forty years.

BOHNING: That's not an unusual case in the history of science where you have an idea that can't be followed up because the technique isn't there.

SMITH: The time wasn't right. There was no way of following up. X-ray diffraction of proteins didn't exist. When I was in Cambridge, in Keilin's laboratory, I worked in the big lab with Keilin and his personal research assistant, Ted [Edward Francis] Hartree, who later married one of my graduate students, and Max Perutz. Max Perutz would come in and crystallize hemoglobin. He was studying it and trying to see what he could do with it. He started working on the structure of hemoglobin in the 1930s before I came there, 1937-1938, and he was working on it that entire time. The structure was not solved until basically the simpler myoglobin structure was solved. The structure of myoglobin was presented at a symposium in Paris, at which I was present, by John Kendrew in 1957. Hemoglobin was done almost immediately thereafter. So there we are. It took not only the improvements of the x-ray diffraction technique, but the invention of a good diffractometer for measuring the intensity of the spots, and high speed computers for calculating the voluminous data. If you had to do it by hand, you'd still be at it.

BOHNING: The other thing I wanted to ask you is that when you measured absorption spectra at Columbia, this was pre-Beckman DU days. You referred to the Shlaer spectrophotometer.

SMITH: Shlaer had built a magnificent, very sensitive spectrophotometer for the visual part of the spectrum which did not involve the use of the eye unlike all the matching spectrophotometers which I had used in England. Shlaer had built a very precise spectrophotometer for studying rhodopsin and other visual pigments. It was based not on two Nicol prisms but on a three Nicol prism arrangement, where, in effect, it was sensitive out to about five ten thousandths of an absorption unit. The spectra that I measured were done first in England, and then all over again with Shlaer's spectrophotometer. It was an exceedingly precise instrument. [looking at an absorption spectrum] We didn't even bother to put the points on. [laughter] Nobody has ever made anything more accurate than that.

BOHNING: Which paper is that?

SMITH: This is the 1941 paper from the Journal of General Physiology (14, Figure 1, p. 584). I measured the rate of conversion of the chlorophyll to the phaeophytin by strong detergents like sodium dodecyl sulphate. Look at these kinetic curves (14, Figures 2 and 3, p. 588). Louis Hammett would have been proud of that. [laughter] The effect of pH on rate.

BOHNING: That spectrophotometer was not automatic recording.

SMITH: It was not automatic recording. It was very tedious. If you measured at one wave length, you could get readings every few seconds, in effect, but if you wanted to do a complete spectrum, that took at least an hour to go through, depending on how many points you wanted. It was what's-his-name's automatic spectrophotometer that came along very quickly after that.

BOHNING: Hardy? I think that was the one that GE made in the late 1930s.

SMITH: The one that GE made was based on the one that had been designed at MIT by a man who later became the president of CalTech. Lee DuBridge. Lee DuBridge had designed the first automatic spectrophotometer while he was still at MIT, and it was his model that GE took and built into a commercial machine. It's

funny I couldn't think of his name at first, because Lee DuBridge has been a close friend, whom I met after I came to Los Angeles. We used to see each other regularly; he's not well now.

BOHNING: Still looking at that pre-Cambridge period, you started some association with [Edward G.] Pickels at Rockefeller on sedimentation studies.

SMITH: I did more of that after I came back from Cambridge.

BOHNING: But you did start something before you left for Cambridge.

SMITH: I did some preliminary work in the ultracentrifuge because he had designed the new air-driven ultracentrifuge. Remember, the [Thé] Svedberg instrument was an oil turbine machine which was first developed around 1924 or 1925. It cost a fortune to build and it took a full-time engineer to operate. There were only two in the United States. One was at Wisconsin, which the Rockefeller Foundation built for Jack [John W.] Williams, and the other one was at Du Pont, which they had built for their high polymer studies.

The Rockefeller people had wanted an ultracentrifuge for virus work, and the man who was involved in the yellow fever program had hired Ed Pickels from Virginia to come and design a practical ultracentrifuge at low cost. Ed Pickels designed the air-driven ultracentrifuge at the Rockefeller Foundation, which was housed at the Rockefeller Institute. Ed was not a member of the Rockefeller Institute staff; he was paid through the Foundation. This was all for their virus work. He was free to collaborate, and Hecht had collaborated with him on some work on rhodopsin. I had gotten to know him through that. Then after I came back from England, when I knew more about the chlorophyll protein complex, I collaborated with him by going downtown from Columbia. When I returned after the war started, I spent the first four months in New York to finish up and to do this work with Pickels.

BOHNING: We can talk a bit more about him when we get to that point.

SMITH: You know his history.

BOHNING: I know a little bit about it, yes.

SMITH: He went out, subsequently, to start Spinco, which Beckman took over.

BOHNING: You left in July of 1938 for Cambridge.

SMITH: We left in July 1938 to tour France and to go to the International Congress of Physiology in Zürich, in August 1938. Keilin had said there's no point in coming to Cambridge in late July or August, because nobody would be there. We went to the Congress first, and then came back to Cambridge.

BOHNING: You've commented in your essay about the fact that you'd never had a formal course in biochemistry and that you realized when you got to Cambridge how little you really knew. I'm curious about that, given everything you had been doing up to that point. I guess you felt, in retrospect, that you were a little naive in what you were doing, although maybe not for that time period.

SMITH: I was very naive in many ways. Let me put it this way. The kind of biophysical chemistry that I knew from Selig Hecht in Columbia, I knew very well, but it was very highly specialized. I knew a good deal about protein physical chemistry, and I knew a good deal about photochemistry, absorption phenomena and about the chemistry of absorption in terms of the kinds of compounds that show color. On the other hand, I knew practically nothing about carbohydrate metabolism, and very little about the structure of carbohydrates in general. I knew little or nothing about lipids and lipid metabolism. I knew very little about the general field of amino acid metabolism. Not that the knowledge was all that deep at that time, but there was still a great deal of knowledge. I had no exposure to these fields whatsoever.

My knowledge was good in certain specialized areas of what one today would call some aspects of bioorganic chemistry or biophysical chemistry, while in other aspects of biochemistry, I knew absolutely nothing. For example, I came to Cambridge and discovered that people like Bill [Norman W.] Pirie and others had done very detailed work on the metabolism of sulfur amino acids.

I had known nothing about that work. An emigré from Germany named Ernst Friedmann, who was working in [Frederick G.] Hopkins' laboratory, had done a tremendous amount of work on the metabolism of aromatic amino acids. I had known nothing about that kind of thing.

So there was an area of what we would today call very classical biochemistry that I knew absolutely nothing about. I'd never been exposed to it. If I had taken a standard course in

biochemistry at a medical school, I would have known at least something about these things, but because I had never taken such a course, I didn't know anything about them. I sat in on the lectures in Cambridge, so I got the equivalent of taking the course, only I did most of it at the advanced level right away rather than from the beginning.

BOHNING: Can you tell me a little bit about what Keilin's group was like at Cambridge and what the [Molteno] Institute was like?

[END OF TAPE, SIDE 3]

SMITH: Molteno Institute was a rather unique institution in many different ways. Its history began with an American named [George H.F.] Nuttall, who had gone to Cambridge as a biologist and developed into one of the world's leading parasitologists and stayed in England. This was the migration of that period, the turn of the century. Nuttall was a pioneer immunologist and parasitologist. One of Cecil Rhodes's partners, a gentleman named [Percy Alport] Molteno, a South African, made a fortune in South Africa and came to England to establish his credentials as a donor, as a benefactor, and, I suppose, to aspire to the upper classes of England. One of the ways then and now in which this was done was to be a very generous benefactor of something important. Mr. Molteno gave the money to build a brand new institute for Nuttall. It was called the Molteno Institute for the Study of Parasitology, parasites being very important in Africa. Other South Africans of the period also became benefactors. Cecil Rhodes endowed the Rhodes Scholarships. Alfred Beit, another one of the pioneer millionaires of Africa, endowed the Beit Fellowships of England which were very important in postdoctoral training in science, particularly in the biological sciences.

During the First World War, the big parasite problem was the louse and typhus, because of the trench warfare in France and elsewhere. The leading young parasitologist of France was a Polish emigré named David Keilin, whom Nuttall induced to come to England and work in his laboratory. When Nuttall retired, Keilin became the Quick Professor of Biology and the director of the Molteno Institute. It was in the early 1920s when Keilin was studying parasites that he discovered the cytochromes and recognized what these were. He then proceeded to maintain a dual life. On the one hand, he became a biochemist, self-taught, working in the field of cytochromes and oxidation-reduction enzymes. On the other hand, one whole floor of the Molteno Institute remained devoted to parasitology. He continued to edit the periodical Parasitology until the day he died, having succeeded Nuttall on this periodical that was published by the Cambridge University Press from the Molteno Institute.

Keilin was a warm, wonderful, friendly human being, and so was his wife [Anna Keilin]. We became very close and intimate friends. He was a man of broad culture and education. He was born in Moscow, but his family was exiled to live in Poland, where he grew up and got his education. He went to Paris to study philosophy. As Keilin told the story, which is now an old story because it has often been repeated, he was caught in a rain storm and went into the nearest lecture hall and listened to a lecture in biology. He found it the most thrilling thing he'd ever heard and became a biologist.

There are some things to be said for the relaxed, laissez-faire form of European education where you could go to any school you wanted, do anything you wanted, and eventually pass some exams in the field. You could attend lectures or not attend lectures. He took his bachelor's degree and his Ph.D. in the field of parasitology, and became one of the world's most distinguished parasitologists.

Keilin was attracting two kinds of people. The parasitologists were downstairs and the biochemists were upstairs. He was isolating the cytochromes and studying their importance in cellular respiration, studying other heme enzymes, and isolating other enzymes of importance in biological oxidations. It was a rather unique group of people. At the time I was there, I was the only American. It turned out to be an exceedingly distinguished group of people. His principle long-term assistant, E. F. Hartree, worked with Keilin on the cytochromes and also on other problems. Thaddeus Mann had come from Poland and worked with Keilin on other enzymes. He discovered a whole group of copper enzymes, including the polyphenol oxidases. He discovered the first zinc enzyme, called carbonic anhydrase. Hans Laser was an emigré from Germany who had come from Meyerhof's laboratory and was working on some aspects of cellular respiration.

Most important from my viewpoint was Bruno [Ferenc Bruno] Straub, who had come from [Albert] Szent-Györgyi's laboratory in Szeged, Hungary. Straub was a year younger than I and we became bosom friends very quickly. Straub went back to Hungary in 1939 and retired last year as president of Hungary. He was the transition president. He was the non-party, non-political man who presided over the country during its transition period. He is a close, intimate friend. He made very many distinguished and important contributions in the field of biochemistry. Before the war, he crystallized the first dehydrogenase, lactic dehydrogenase. He isolated flavin adenine dinucleotide independently of Warburg in the same year. Subsequently, he discovered actomyosin and actin in Szent-Györgyi's lab after he went back to Hungary, and a whole series of other important discoveries. He became one of the leading figures in the Hungarian Academy of Sciences. He still is, but I don't think

he's an officer any longer. As I said, he was picked as the neutral figure, a respected, distinguished scientist, apolitical, very patriotic, to preside over the change from Hungary the dictatorship to Hungary the democracy, to put it in simple terms.

Who else was in the lab at that time? Carl Gustav Holmberg from Lund, Sweden, who worked on uricase and discovered that this was a copper enzyme. Jan Jonxis from Holland, who went back to Holland as professor of pediatrics and became a very distinguished pediatric scientist and nutritionist. I think that's about it. All very intimate, all very friendly. The Keilins were exceedingly hospitable people who arranged to see that all their foreign guests got to know each other, entertained them, and got them acquainted with Cambridge society. Keilin used to dine in college whenever there was a feast or a special meeting. He would bring one member of the lab with him as his guest. I can remember going to several with him, at Magdalene College, which was his college, the college of Samuel Pepys.

We became acquainted very quickly with a whole generation of the young people over in the biochemistry department, and Hopkins, the director, was unique. He had a department of fifteen or twenty advanced postdoctoral students and faculty members, each of whom worked on individual problems. Bacteria, plants, animals—it didn't make any difference. It was all biochemistry, a very different kind of biochemistry than existed anywhere else in the world at that time, partly because of Hopkins' benevolence in encouraging people to find their own interests and develop them, and partly because of the breadth of viewpoints. This was a university department. Pirie was working on plant viruses, Marjory Stephenson was working on bacterial metabolism, and so on and so forth. This history has been described many times (15).

It was a very exciting place to be, and additional excitement, of course, was that we had to listen to the radio ten times a day to find out whether the war had started yet. This was a grim period. We arrived in Cambridge a few weeks before Berchtesgaden and a month before the Munich pact. We unpacked, we settled down, and I said, "I'm not moving until I have to move. I've got to get to work." In retrospect, a lot of time was wasted in talking about what was going on. We didn't accomplish anything except that we learned something about each other, and we became very good friends. As a place to learn biochemical science, it couldn't have been a better place in the world, as far as I was concerned.

BOHNING: You had planned to go on to work with Meyerhof in the second year.

SMITH: That's right. In 1939, my brother and his wife had come over for summer vacation because they figured they wanted to get

to see Europe before the war started. They came to Cambridge. We had a car. We drove from Cambridge to London and from London to Dover and from Dover to Calais, and we drove around France for several weeks. The war clouds were gathering in Paris. We were back in Cambridge on the twenty-ninth or thirtieth of August. We had been in Paris up to that time, and everybody was scurrying off the continent to get back to England. We had a car which we weren't going to abandon. There was no sense in trying to get back because people were sleeping on the beaches of Calais waiting to get on a ferry to go back to England. The British, as usual, were spending their summer holidays all over the continent. As soon as we found out that the coast was clear, we left Paris, and drove back to Calais and got on the ferry and went across. My brother and his wife went to London and booked their passage home. We went back to Cambridge, and on the first of September, Hitler invaded Poland. On the third, [Neville] Chamberlain gave his speech to the nation on a Sunday night and declared war on Germany.

The next morning we came to the lab and Keilin told me that plans had been in effect for some time for laboratories to be evacuated from London and to be settled in the Molteno Institute. The labs were going on a war footing. All normal research was basically stopping. If I wanted to stay, I was welcome, but they would not be able to talk about what they were doing. I was an alien, but a neutral alien. Nevertheless, this was war work, and if I wanted to stay I could; if not, it would probably be better if I found a place to go. I had planned to go to Meyerhof some time around December. I was going to finish up what I had been doing with the chlorophyll-protein complex and then go on to learn something about intermediary metabolism with Meyerhof in Paris. By then Meyerhof was on his way to the United States.

I came back and spent several months at Columbia, where I knew that the spectrophotometer and other equipment was available to finish up what I had been doing, and where I could also start writing the papers. Hecht offered me the hospitality and the use of his secretary as well. My wife went back to her teaching job in New York. Then, casting around for a place to go, I decided that a plant protein laboratory might be the right place. I went to work with H. B. [Hubert Bradford] Vickery in New Haven.

BOHNING: During that short period in Columbia you worked with Pickels again.

SMITH: That's right, and that's when we did the sedimentation work (16). That was basically one day a week, or at most, two days a week.

BOHNING: What kind of a person was Pickels?

SMITH: He was a gentlemanly, lively, entertaining Virginian. He had a strong southern accent, a very good, relaxed attitude, and at the same time was a brilliant engineer. He became unhappy at the Rockefeller in the later years of the war, because he was interested in creating new instruments. The attitude of the virologists that he was working with was, "Well, you've now made an instrument that works, just make us another one of the same kind." [laughter] They didn't want any innovations in making new instruments; that was not their interest. He collaborated on a great deal of the virus work, but he already had plans in his head, not for an improved air-driven ultracentrifuge, but for an electrically-driven ultracentrifuge which was later designed at Spinco, and not just an analytical machine, but a preparative machine as well.

I had been in touch with him in 1946 when I was going out to Utah. We had just bought a house but were still living in a motel waiting to move in, and had been in Salt Lake all of four or five days when Pickels and his wife came through, and stopped at the same motel to see us. We had dinner together, we started to talk and he told me all about the plans for Spinco and what he was going to do. I said, "Look, I don't know where I'll get the money but I want the first machine," the analytical ultracentrifuge. He said, "You can't have the first machine because I stopped in Ann Arbor to see Tommy Francis and he's already ordered number one, so you'll get number two." [laughter] That's how you start a company. As soon as he wrote to say that it was well underway and that the prototype was working, we talked about it and we managed to find the money. We got the money out of the NIH, and Ed came himself to install the machine.

BOHNING: What was the arrangement that you had in New Haven? Vickery was at the Connecticut Agricultural Experimental Station.

SMITH: I was finishing up the second year of my Guggenheim Fellowship. What I wanted to learn through Vic was how to prepare proteins, classical stuff, and how to do some amino acid analysis. I think partly what was in my mind was also the fact that I needed a contact with somebody in American biochemistry and I needed to begin to think about what I was going to do in the future. Vic was giving lectures on the history of protein chemistry once a week in the biochemistry department at the medical school. This was late afternoon, so I would quit at the same time he did and go down and listen to his lectures. Usually, it was about a two-hour session. Rather than giving two one-hour lectures a week, he gave a two-hour lecture each time, which was wonderful because I learned a lot about the history of protein chemistry.

I met other people in the department through Vickery, and one of the people I met was Abe [Abraham] White. I had done some gravimetric amino acid analysis and I learned how to do proper Kjeldahl nitrogen and sulfur determinations the way Vic wanted them done. (I had been doing Kjeldahls long before.) There wasn't even a good colorimeter in the agricultural experimental station. Everything there was gravimetric. That was Vic. It changed in later years, but everything at that time—we're talking about spring of 1940—was gravimetric. Abe White had some good colorimeters. In addition to studying these families of plant proteins and doing arginine analysis, I also did tyrosine, tryptophan, and cystine using colorimetric analysis in Abe White's lab. That was the connection. Formally, I was in Vic's lab during that period. I would go down to the medical school once or twice a week in the last period that I was there.

BOHNING: I want to talk about White in connection with Principles of Biochemistry, but we can touch that as a separate issue later on. How did you make the connection with Rockefeller?

SMITH: The connection was made there in a very, very simple way. I was on my second year as a Guggenheim Fellow and I was looking for a job. I was a half-breed or a quarter-breed. I wasn't the proper kind of biochemist for a job in a medical school because I'd never been in a medical school and I didn't have that kind of formal training. I was not, properly speaking, a plant biochemist or a botanist because I didn't have a degree in botany. I'd gotten my degree in a zoology department even though I'd worked on plant materials. I was offered or approached with a couple of possibilities, all of which were, I thought, third rate places to go, where I would have very little freedom to do my own kind of thing. My wife and I made the decision that we would hold out.

BOHNING: Were the others academic institutions?

SMITH: They were academic institutions, but one was to be somebody's research assistant at fifteen hundred dollars a year.

My wife was earning more than that teaching school. We had saved a little bit of money. We weren't rich, but we could survive. Business was coming back a little bit at that time. The war was on, and business had picked up. My parents were even willing to help out if need be. Which I didn't need, actually.

I got to talking with my friend Joe [Joseph S.] Fruton, who was at the Rockefeller working with Max Bergmann. Joe Fruton was a classmate of mine at Columbia. We didn't know each other that well in the first years because he had started out as a chemistry

major right from the very beginning, so he was ahead of me in most of those classes. I got to know him fairly well in my senior year, and then he went up to P & S [College of Physicians and Surgeons] to do his Ph.D. in the biochemistry department with Hans Clarke while I stayed on the campus. During that period we saw each other quite frequently. My wife and I got married in 1934, and we lived on 110th Street. The following year, Joe married his wife and they lived across the street from us. Then, of course, we saw each other a great deal. When my wife and I went abroad in 1938, they came along with us to spend the summer vacation and go to the Physiological Congress in Zürich. We spent six weeks together during the summer of 1938, traveling in France and Switzerland.

I'd been back and forth to New York and I had talked with Joe about the situation. Joe said, "Let me talk to Bergmann. Bergmann might be very interested in having you in the lab for a year or two because you had experience in purifying enzymes in Keilin's lab plus the physical chemical experience. There might be an opening." So there was another fellowship. Initially it was for a year, but then it stretched into two years, during which I got started in enzymology on the peptidases, and that story has been told (17). While Bergmann was away on his summer vacation, I learned how to synthesize peptides from Joe Fruton. I made the first proline peptides and hydroxy-proline peptides and a few other things. It was kind of fun and very useful later on as well.

BOHNING: What was that group like at Rockefeller?

SMITH: That was a marvelous, marvelous group.

BOHNING: There were some pretty stellar people at that time.

SMITH: That was a pretty stellar group of people. Stan [Stanford] Moore was next door to me; Bill [William Howard] Stein was diagonally across the hall; Joe Fruton was downstairs; George Irving was across the hall; Paul Zamecnik was around the corner. There were about six or seven of us. There was one Swiss, with whom I overlapped for some months, named Max Brenner, who later became professor in Basel. Klaus Hofmann had just left the lab to go across the street to work with [Vincent] du Vigneaud. Instead of going back to Switzerland, he stayed in the United States. Of course, he later went to Pittsburgh; he's now retired. It was a pretty distinguished group of people who made their marks in protein chemistry and enzymology. A rather remarkable group of people.

BOHNING: How would you compare that group at Rockefeller with the Cambridge group? Was there a contrast in their style?

SMITH: The Rockefeller group were all trained in organic chemistry, with the exception of Paul Zamecnik, who was trained in biochemistry. The Cambridge group was more diverse in their biological and medical interests. I would say that they were equally distinguished groups, but they went in different directions. The Rockefeller group was very much a chemical group. Zamecnik stayed more in the field of metabolism. I stayed in protein chemistry with a strong leaning on the organic side of it, even though part of it was devoted to biological problems, but so were the others. Fruton was organic and enzymological. Stein and Moore you know. There was a different kind of bias. Keilin had some medical people with him, people dealing more with intermediary metabolism and medical problems. Straub was more the classical enzymologist, phenomenologist, getting at the proteins that did biological things. It was different; equally stellar, but with a somewhat different bias.

In fact, when I think of my own kind of background, it's a curious one. I started out with a major interest in biology, and I then worked more in biophysics. I then went to Keilin, where the activity was more biochemical but with a very biological bias, and then ended up spending two years at the Rockefeller where there was a strong organic chemical emphasis. In a certain sense, I became dilettantish, but I've always liked being a dilettante. I tried never to keep working on the same problem for more than a few years and I drifted as my fancy took me.

[END OF TAPE, SIDE 4]

BOHNING: The United States got into the war during this time period.

SMITH: Well, the United States got into the war in December, 1941. All during the period that I was at the Rockefeller in 1940, (this is an interesting bit of history) the custom was that after lunch you'd look in the library at the new periodicals to see what of interest had come in that day. You would look out of the window of the library at the East River and there were all the lend-lease ships going down the river. You knew that a good many of them would never reach their destinations. They would assemble somewhere off the Newfoundland or Nova Scotia coast and make the trip across to England, or to Murmansk after 1941. You saw the flags of every ship of the allied nations during that period. It was a kind of grim sight.

With the war coming along, the negotiations with Washington went on, and Bergmann decided to get into the problem of the

reactivity of nitrogen mustards with proteins, amino acids and peptides. This was a kind of organic chemistry for which I was not prepared and not fitted. In the meantime, I had gotten an inquiry from Squibb [E. R. Squibb and Sons] as to whether I'd be interested in coming out there as a biophysicist-biochemist to work in their blood fractionation program. That looked very much more attractive to me than working on chemical warfare problems which I knew nothing about. It was not of my kind of chemistry; let's put it that way. For essentially three years, the Bergmann laboratory worked full-time on the reaction of mustards and nitrogen mustards with proteins, amino acids, and peptides. At the end of the war, they published a long series of papers in the Journal of Organic Chemistry (18). Bergmann had died in 1945, and Fruton took the responsibility for getting that stuff published. I went to Squibb and spent four years knee-deep in blood. [laughter]

BOHNING: I remember reading that statement. Experimentally, it was a different experience, dealing with large quantities of materials.

SMITH: It's a different world. You synthesized a peptide and you were glad you ended up with a few hundred milligrams because most of the amino acids that you had to use for making these peptides, you had to purify yourself. Most of the amino acids were not commercially available. In most laboratories, you started out with ten liters or five liters, and you were glad to end up with a few milligrams of an enzyme. In commerce you worked on a totally different scale. It was a marvelous experience to learn all that, and I had a good boss. He was a good teacher.

BOHNING: Who was that?

SMITH: Tillman D. Gerlough.

BOHNING: I'm not clear exactly what your responsibilities were.

SMITH: My responsibilities were three-fold. One was getting into production. We were not yet in production. The methods devised in Edwin J. Cohn's laboratory were largely devised by working on five or ten-liter quantities. We would have to work on a thousand liter scale. Scaling up was not simply a matter of arithmetic or multiplication; you had to devise different techniques for doing so.

Moreover, we started out with a crew of shift super-

intendents who were college graduates who had no experience with any of this. They were largely 4-F; they had some kind of physical incapacity. In one case, there was a man with three children, who was not drafted because they were all very young children. The crew had to be trained. They had to learn how to use a pH machine, and make up a buffer in quantity. They had to learn how to make alcohol dilutions. They had to learn how to handle proteins and work in the cold. All of this had to be set up from the beginning.

I learned how to cut stainless steel pipe. [laughter] I didn't have any experience as a plumber before. I'd built some equipment. I'd done some machine shop work. We learned how to assemble the kind of stuff we needed with three-quarter-inch stainless-steel pipe, because if we waited for the shop at Squibb to make this stuff, we'd be still waiting. They were so busy and overloaded and didn't have enough skilled people. We got the equipment and we cut our own pipe and we made all our own assemblages. We did our own things. We learned how to do all of these things from scratch.

At the same time, we were training a crew. We'd get one unit set up and immediately the Red Cross would start delivering blood, and we'd have to start going through this stuff to learn how to fractionate it and isolate all of the proper fractions that we needed to save, preserve, or prepare in final form as pharmaceutical products. The major product, initially, was serum albumin which was prepared in sterile twenty-five percent solution in the proper buffer, with preservative. This was in a neat little vial packaged in a nitrogen-containing tin can with the proper rubber tubing and the needle and everything else to be used for surgical shock or wound shock.

This was largely for submarine warfare and for landing groups. They couldn't carry whole blood; there was no way of preserving it. It was too bulky. You had to have something highly concentrated. One hundred milliliters of twenty-five percent solution of albumin was the equivalent of one pint of blood in terms of its anti-shock value. We started out with that and we ended up preparing gamma globulin, fibrinogen, prothrombin and other fractions. I obtained experience working on a group of plasma proteins, enzymes, blood clotting fractions, etc.

We were doing the production work, and we were also doing the development work to scale all of this up properly. We were also doing research on some of these fractions.

My wife always insists that the experience at Squibb was the best thing that ever happened to me. She said, "You were a cocky young guy, full of your own ideas, and you knew how to work in a lab." I came to a place where I had to get along with other people and train them. I had to teach. One of the things I found was that I could carry on a lot of different tasks at the

same time. I had a production crew, a development crew and a research crew. By the time I left I had some thirty or forty people working for me. I found that I could no longer go into the lab myself to do anything. It's not what I wanted. I was becoming more and more narrow and specialized.

BOHNING: You certainly must have had close contact with Cohn at Harvard during that time.

SMITH: Oh, yes. I was back and forth during the war many times. Every time we got a new wrinkle, we had to go up and tell him about it. They came down also; it was very close contact. I had actually met Edwin Cohn before, while I was a graduate student, because he and Selig Hecht had been graduate students at Harvard at the same time. Once a year or so when Edwin was in New York, he would drop in the Columbia lab. That's when I first met him. But I really didn't know him well until the war was over. That's when I got to know John Edsall; he's still one of our closest friends. John will be eighty-nine next fall, but he came to the American Philosophical Society meetings in April. He was in great shape, cheerful, lively.

BOHNING: He stops at the [Beckman] Center from time to time.

SMITH: I'm sure. Well, he was rather depressed for a while when his wife died, but he's back in good spirits. He came out to Caltech for the symposium in honor of Linus Pauling's ninetieth birthday in February. We saw him then and we saw him again in April.

BOHNING: Can you tell me a little bit more about Gerlough and what he was like to work for?

SMITH: Tillman Gerlough was born in Idaho. His father was a guide and big game hunter. He grew up in what were then the wilds of Idaho and went to the University of Idaho. He was in his senior year when the United States entered the war in 1917. He was an all-American football player, and went off to the wars, survived, and came back with the rank of Major or Colonel. I could never get him to talk about it but I gather that he was plastered with all kinds of medals. He was, to me, the prototypical wild westerner, since he was the first real westerner I had ever known.

There was no smoking in the plant. I smoked at the time, and I used to go outside occasionally for a cigarette. Gerlough didn't care that much for cigarettes. He was a pipe and tobacco

smoker. He chewed tobacco constantly. He was really addicted. He had a very good English vocabulary, but he also had one of the best four-letter vocabularies I've ever heard in my life.
[laughter]

He was a man who had very little theory, but a tremendously good instinct of how to do things in a practical way. He knew how to solve problems. He had become the head of that division, over the years, simply in terms of experience. This was the division that handled all the protein therapeutic things. It was not responsible for the culturing of bacteria, for example, to make gas gangrene antitoxin, tetanus antitoxin or diphtheria antitoxin, or the isolation of insulin. But in the case of the antitoxins, after the animals were bled, all the preparation was done in that division. The insulin was obtained in crystalline form, but that was standard procedure, and we got the piles of crystals. We had the responsibility of making the solutions, the assays, the sterilization, the filling, all the rest of the handling of any of the protein products at the Squibb lab at that time—the biological products. I learned a lot about all of these things. Gerlough was responsible for that division, and that was the logical place to put the blood program. After all, the antitoxins, the antisera came out of blood.

I learned the practical side of all of these endeavors from him. I also learned all the manipulations you had to go through in order to get satisfactorily sterile products and to be able to package them and ship them off. We had to deal with the suppliers. We had to get top priority to get gum-rubber tubing. Not only was Pearl Harbor bombed, but Malaya had disappeared into the hands of the Japanese. We had to get the right kind of glassware. Everything had to be top priority. I got to know all the Navy people. This was strictly a Navy program at the time. The Army, after all, was going to be fighting on land somewhere where field hospitals could be set up. The Navy and Marines were going to be working on ships of every size and in landing parties.

BOHNING: You also mentioned that you did some globulin work, which was published as part of the research (19).

SMITH: From Squibb.

BOHNING: You also had a key suggestion in the penicillin program.

SMITH: That was pure accident. I had gotten the job at Squibb when they were looking around for somebody trained in biophysics. It was through the head of the division of organic chemistry,

Oskar Wintersteiner, whom I had known before at Columbia. Oskar was a very distinguished steroid and antibiotic chemist. The middle picture on that wall [pointing to picture] is of the first crystals of sodium penicillin behind Oskar when he got an award from the American Chemical Society. Oskar had suggested my name to Squibb because he knew I might be looking for a job. The head of the division at Squibb had come to see me at the Rockefeller to find out whether I would be interested. At the same time he talked to Bergmann and then came in and offered me the job. [laughter] I arrived at Squibb at the beginning of July 1942. I was just getting my own lab set up and we were beginning to get ready for the fractionation of the blood plasma at the time.

Oskar came and asked whether I had time to go to a meeting. I asked what it was about. He said, "Well, you'll hear what it's all about." I came to the meeting and learned about penicillin for the first time. This was a hush-hush research project. They could isolate the active material and it worked on bacteria, but could they accumulate enough penicillin and preserve it? The material was unstable. I listened to all of the procedures that had been tried. They had tested various types of stabilizers. I asked, "Why don't you try freeze-drying?" The engineers looked at me and said, "What do you mean freeze-drying? You can't dry anything that's frozen." I said, "Yes, you can. Water has a vapor pressure at all temperatures even all the way down to absolute zero. If you put the material under a sufficiently high vacuum, it'll stay frozen because the heat of vaporization of the water is going to keep it frozen while the water is evaporating. You will end up with a dry powder." They asked, "How do you set this up?"

I got myself a couple of Cenco high-vac pumps, some glass tubing, and sealing compound to stop the leaks. We pumped and pumped after freezing it in the dry ice-alcohol mixture. The dry powders were then sent for assay. That's as much as I heard until Oskar told me later that the procedure worked. It was simply the fact that the only people who had been using lyophilization, as it was called, were bacteriologists, who were using the procedure as a technique to preserve live bacteria, and protein chemists who had discovered that this was a way of preserving proteins without keeping them frozen forever. You could dry them from the frozen state.

Patents had been taken out for this so-called lyophilization process from the University of Pennsylvania by [Earl W.] Flosdorf and [Stuart] Mudd (20). The patents I'm sure are long gone, of course, but it was the Flosdorf and Mudd process. Flosdorf and Mudd were getting a royalty for every bit of stuff we were preparing on the blood fractionation program. Plus, they sold us the equipment. Flosdorf was the engineer and Mudd was a bacteriologist at Penn. Every time somebody had a problem at Squibb, I got called in. [laughter] I was the problem man.

It was very useful because when I went to tell Squibb that I was leaving in 1946, they wanted to keep me. I told them I wanted to get back into academic work, at least for a few years to find out whether some of the ideas I had about working on enzymes were useful or not. Practically, it was not of any importance in terms of industry, but I wanted to do some of these things on my own. We parted as very good friends, and a couple of years later they brought me back as a consultant because they found that somehow what I had been giving the company as a consultant working there was not being satisfied by the people they hired, one way or another. For the next twenty years I remained as a sort of general consultant for the company.

BOHNING: You commented that this reputation as a trouble-shooter that caused people to ask you to get involved in industrial problems was sometimes to your annoyance.

SMITH: They wanted me to keep working on their problems. I was a member of a different division and I had to keep working on those problems. I had to go to Gerlough at one point and say, "Look, do you want me to work on their problems or do you want me to work on the problems within our division? I can't be in two places at the same time. I simply can't do this." He said, "Okay, we'll cut it off. If they want to ask you a question, that's fine, but to actually get into the lab work and do these things, you can't do that." Occasionally, they would come with a problem that I could solve in the lab in a very simple way.

I can tell you one very simple problem that I got into the last year I was at Squibb, which in retrospect was just ridiculous, but it's the kind of problem that comes up in industry. I taught all those people at the plant how to use high vacuum to preserve proteins. They were making pituitary hormone preparations which came with a buffer and they were drying them in an ampule. Another ampule of saline solution or distilled water went with it, so that the physician who was going to use this could break the ampule, add the distilled water, dissolve it immediately and use it. (Don't ask me which pituitary hormone it was because it doesn't matter.) The fact is that they were doing this, and every time they reconstituted the hormone preparation, there was a precipitate. They couldn't get it clear. This is a product for intravenous injection, and with intravenous injection you can't inject anything with particles. It's got to be absolutely clear. Everything would go into a nephelometer to check clarity. This was part of routine pharmaceutical manufacturing. (I haven't thought about this in many years.)

They were stumped. They couldn't figure out what this fine precipitate was. It had some of the phosphate in it. It wasn't protein, that was clear, because there was no nitrogen. I got them to write down what this was, and very clearly this was a

simple sodium/potassium phosphate buffer, low concentration, made up to the right volume so its physiological salt concentration was right. I took one look at the thing and began to think to myself and remember my inorganic chemistry. The answer is found in the books. If you dry orthophosphates at a very high vacuum, you make them into metaphosphates. You take the water out. You are splitting water out, and these things are insoluble. We ran the control, a very simple control of using the buffer without any protein, and the same thing happened. I said, "Well, don't dry down to the point of less than one percent moisture. Dry it down and figure out the level where it would stabilize at about two or three percent moisture, which is not going to hurt the protein at all. You will not get metaphosphates." It worked. They had been battling this for weeks. I'm not saying that I was all that bright. It's simply a question of memory, that I solved the problem in one day. This is the kind of thing that led to my being called on all the time. [laughter]

BOHNING: I can imagine.

SMITH: That's why I got to be a consultant. [laughter] Over the years, they finally ended up paying me more for a couple of days a year than I was getting when I left there, which is typical of industry.

BOHNING: How did you make the connection with Utah? You were already determined you wanted to get back into academe after the war was over.

SMITH: I had told my friends that if they heard of a suitable opportunity, they should put my name in. One of the people I had told was Abe White. I told Joe Fruton, whom we had seen periodically during the war, and a few other people. Selig Hecht knew that I wanted to get back into academic work, but his connections with pure biochemistry were not that good. He was more in the physiological, biophysical side. One fine day, I got a telephone call while I was at Squibb, from Lou [Louis] Goodman, who was professor of pharmacology at Utah, and whom I had known while I was at Yale, when I was in New Haven. I had met him a number of times. We weren't close, but he knew who I was and I knew who he was. We were on a friendly basis, but pharmacology was not my area. He had come to Abe White asking for names of people who might be interested in coming out to Utah to join a big research project that was going to be devoted to muscle biochemistry and muscular dystrophy. Abe suggested that he call me to find out whether I was interested. To make a long story short, that was the basis of my eventually going out to Utah.

BOHNING: As I understand from what you wrote, it was really being built from scratch.

SMITH: This was the spring of 1946. The war was over in the summer of 1945. People in Washington and around the country were concerned with the research efforts that had been supported by the OSRD [Office of Scientific Research and Development] and other government agencies during the war. The authorization for them was beginning to run out. Scientists were in the middle of all kinds of research problems that were of interest to the medical community and medicine generally as well as other fields. What was going to happen to all of this activity in the absence of support?

One of the clear answers was to develop a research granting agency through the National Institutes of Health. The bill to create a research granting agency at the NIH was introduced by the senior senator from Utah named Albert Thomas. It was introduced with the idea of studying a type of hereditary disease very common in Utah called muscular dystrophy. Thomas had found out about this from the then acting dean of the Utah medical school who was a professor of public health. Here was a unique opportunity to study genetic disorders because of the early polygamy, the fact that Mormon families were largely sedentary in the state, and that muscle physiology was now advancing to the point where some approach might be made. The bill that Thomas introduced was a hundred-thousand-dollar appropriation annually to support a muscular dystrophy program in the state of Utah. It passed by unanimous consent in both houses. It was peanut money, so the president signed it, but it turned out then to be the creation of the NIH research grant program. The NIH asked the people who had gotten the grant to give them back ten thousand dollars for administrative expenses. They had never thought of that.

This grant was under the name of Max [Maxwell] Wintrobe, professor of medicine, as senior investigator, but with the cooperation of Goodman, professor of pharmacology, [Horace W.] Davenport, professor of physiology, and [Leo T.] Samuels, professor of biochemistry. It had four co-directors with Wintrobe as the senior person, with the idea of creating a biochemistry laboratory and a clinical research laboratory to go with it.

[END OF TAPE, SIDE 5]

SMITH: The campus of the University of Utah was established on what had been a part of Fort Douglas. As of now the university has taken over all the rest of Fort Douglas through a series of accretions as the Army was persuaded to give up the idea that

they were going to fight the Indians. There would be some buildings available and a laboratory would be established. If I had gone out to look at this I would have been so discouraged I wouldn't have accepted the job, which would have been a mistake. The fact is we used a temporary building and we were able to order all the equipment and supplies we needed. Eventually we got a good building for all of this, but it took five months. In those five months I wrote up all the publishable work that I had done at Squibb, and even one paper left over from my days at Rockefeller (21).

BOHNING: Did you start teaching at this time?

SMITH: I started teaching immediately. Utah was still on the accelerated program with the idea that since the people who had gone through medical school during the war had gone through in three years, the returning veterans should have the opportunity of acceleration as well. We started to teach some graduate students also. I was teaching in the medical course, and I was teaching a graduate course in enzymology and a graduate course in protein chemistry. It was great fun. I had to learn all of these things over again, and one good way of learning is to teach it.

BOHNING: How did your wife feel about moving to Utah from the east coast?

SMITH: She was well aware of the fact, from the time even before we were married, that when you decide to lead an academic life, it's a migratory profession. Not all the people who get their degrees at an institution can possibly stay there. In fact, the policy very often is not to have anybody stay, but to bring people from the outside. She was well aware of this. Of course, our families thought we were moving to God knows where, out among the Indians, obviously. [laughter] This was a very remote part of the world, but she had no hesitation whatsoever. She knew that while I had my satisfactions in industry, such as they were, that I was not completely happy in an industrial environment. It was not that I was bitterly unhappy, don't misunderstand me; it was not that I resented anything.

During the war it was certainly better than the alternative, being drafted. I was called up all the time, and each time the company had to intervene, and the last time it finally was stopped by the president of the company talking to Roosevelt's personal physician. [laughter] The blood program was not going to flourish or continue if I were drafted. Besides which, they resented the fact that I had to take a day off every time the draft board called me because I had to report to my old draft

board, which was in New York. So that was the end of that. If I had been drafted, I probably would have been down in Bethesda, Maryland. If there had been danger that I would be drafted and the company couldn't get a deferment, what would have happened is that I would have gone into the Navy medical service. They were responsible for this whole program and I knew more about it than most of the people down in Bethesda anyhow, because I was actually in it.

BOHNING: You were also joined by Douglas Brown, who formerly had worked with you at Squibb. Was that the next year?

SMITH: He came out about six or eight months later. Doug had been a technician at Squibb whom I had hired and taught how to run the Tiselius electrophoresis apparatus and to do certain other routine measurements. Every batch of protein that we prepared, particularly albumin, had to be examined in the electrophoresis apparatus to make sure it contained not more than two percent impurity; it had to be a minimum of ninety-eight percent albumin. Most of it was obviously better than that. Other things also had to be characterized.

Doug had been in the Navy, and had received a medical discharge around 1943 or 1944, because he'd had a tumor on his foot taken off, and his heel was shortened. He received a medical discharge and was looking for a job instead of going back to finish up college. When he found out that I was going to Utah, he asked whether there might be a job for him because what he would like to do was work part-time or full-time and finish up his college education and then decide what he wanted to do. He needed the equivalent of about another year and a half of college work. I said I'd think about it and see what the possibilities were. Before I left I was able to tell him that we would have a Tiselius electrophoresis apparatus, and other kinds of physical apparatus. He could take a couple of courses each day, and as long as the time was made up either in evenings or weekends, he would have a full-time job. As soon as we had the labs installed and the equipment arrived, Doug came out with his wife and an about six-month-old baby. He stayed with me there from 1946 until 1963, and then moved with me here to UCLA until I retired in 1979.

BOHNING: That's a long relationship.

SMITH: That's right. He stayed on for another few years after I retired and then decided he didn't want to work for anybody else, and took an early retirement. [laughter]

BOHNING: That's a long period of time to have one person continuing that work.

SMITH: That's right. He's a person who's good with his hands, a superb amateur photographer who has won a lot of prizes, very active in the local photographic societies, and very good with equipment of all kinds, maintenance as well as running it. He didn't feel that he wanted to go through a Ph.D. program; he didn't want to do the book work. It was very good for me because this relationship as my research assistant lasted for essentially thirty-two years. At Squibb he was working for me, but there the relationship was more indirect. I put his name on a large number of papers over the years. I never counted up how many, but probably there are thirty or forty papers where his contribution was sufficiently substantial to justify putting his name on the paper.

BOHNING: That's very impressive. He must have been an impressive person.

SMITH: Still is! We're very good friends and we see each other all the time. They live over in the San Fernando Valley about a half hour away from us.

BOHNING: Rather than at this point talking about some of the research that you were doing, a lot of which has been summarized in review articles that you categorized very nicely in that essay, (although I do want to talk briefly about some aspects of that later), I thought maybe at this point we could pursue your experiences at Utah, and also your move here. As you said, your research had a more logical sequence at Utah than it did in your earlier career. From the Utah period on, things are more in keeping with the times, in terms of the research development.

SMITH: I'm trying to remember in what context I said it because, after all, it's now a good ten years since I wrote that. The point is that each successive new tool that came along got added to the armamentarium of every biochemist and protein chemist. In the 1930s there were very few laboratories in this world that had a good spectrophotometer. By 1950, everybody had a good DU spectrophotometer. In 1934, very few people had a Warburg manometer. By 1950, Warburg manometers were out of date. There were very few Warburg manometers around. They had become commonplace and were succeeded by something else. We got analytical ultracentrifuge number two. Within ten years every major laboratory in the world had an analytical ultracentrifuge and a preparative ultracentrifuge.

When Stein and Moore started to develop their amino acid analysis and their automatic machines, they were, of course, the first, but within a couple of years when Beckman started to make them, everybody had them. We had the first Beckmans, by the way, because the automatic amino acid analyzer was devised by Stein and Moore with the help of my former graduate student, Darrel [H.] Spackman, who was good with his hands and whom I sent there for exactly that reason. We had the first commercial machines.

If you were in protein chemistry, you had to take up every new method and every new piece of equipment, and that's what stimulated the progress. We knew what to do from an intellectual viewpoint. What we needed were accurate molecular weights, accurate amino acid analyses. We needed methods of doing sequence determinations. Later we needed mechanisms of doing three-dimensional structures. We needed methods of analyzing proteins. We needed methods of purifying proteins. As each method came along, every laboratory that was in the know immediately had to take advantage of it. We were in a fortunate period of time when the NIH had the money to grant during this time.

This is what led to spectacular progress, in essence, in the whole field of biochemistry and protein chemistry, and now in nucleic acid chemistry. When I say that the progress became that of the times, this is what I meant. Whereas at an earlier time, one may have had some unique ideas or some unique equipment or method, that didn't last very long. In this period, everything was known by everybody almost instantaneously. The culmination of this is that before, when I would give a talk at the ASBC [American Society of Biological Chemists] as it then was, on proteolytic enzymes, or for that matter on some aspects of protein chemistry, there would be one small afternoon session late in the week devoted to the subject. However, protein chemistry today is a very substantial part of biochemistry and we now have a Protein Society of which I acted as one of the obstetricians to help it give birth a few years ago. Now, as my wife says, I'm a neonatologist helping to keep it going. [laughter] It doesn't need me anymore. They keep me around out of good will because I helped from the beginning. These young people realize that we need to have a smaller society to deal just with the integrative aspects of all of protein chemistry because protein science is no longer chemistry. It's physical chemistry, it's immunology, it's physics, it's everything in the world. The physicists who are in protein science will not go to the ASBMB meetings. The biochemists are not going to go to the crystallography meetings. You have to have a place to bring them together. This is what has happened.

This has been a strength of modern biochemistry. If I may dilate on this philosophy of mine for one minute, I'll give you an anecdote. Late in the 1950s, the NIH decided to set up

training grants. Up to that time they had been giving awards for research grants, and they had also established predoctoral and postdoctoral fellowship programs. This, in effect, was getting too cumbersome. The idea that people were going to try to evaluate every predoctoral applicant from all over the country as well as postdoctoral applicants, was beginning to get out of hand. The notion was to establish training grants so that institutions would get support for training graduate students or postdoctoral fellows and they would do the selection in terms of their own standards. Why should NIH bother with this?

I was asked to serve on the first committee on training grants for the entire spectrum of NIH activities. Clearly this was just the beginning, and after that first year it broke up into specialized panels. I was one of the first members of the training grant committee on biochemistry. One of the things the NIH asked us to do was set up criteria as to what represented a good track for a training program in biochemistry. I guess there were ten or twelve of us on the committee. We went around the table and people said, "Well, a beginning graduate student certainly ought to have courses in organic chemistry, physical chemistry, and this kind of thing." We discussed what the content of the courses ought to be.

Suddenly in the middle of this I burst out laughing. Herb [Herbert E.] Carter, who was chairing the meeting, said, "Something's bothering you." I said, "What's bothering me, Herb, is the fact that there are only two people on this committee out of a dozen who have degrees in biochemistry. This is the strength of biochemistry." Herb Carter and Al [Albert L.] Lehninger were the only two people on that committee who had actually gotten a Ph.D. in the field of biochemistry. All the other people there had come from biology or organic chemistry or from physical chemistry. Dave Rittenberg was a student of Harold Urey's in physical chemistry; somebody else was in organic, and so on, all around the table. I said, "The whole strength of this science has been the diversity of people who came into it with different technical and intellectual backgrounds, and that is what has made the strength of the field. That's what has got to continue. I think that we ought to let every department of biochemistry set its own criteria. If they've got a bright student who has learned a lot of physics but doesn't have much organic chemistry, I'd say, 'Take him.' Let's cut out the nonsense of dictating what the course contents ought to be." That was the end of that discussion.

I think this is what I mean by what is in keeping with the times. This is still true today. There's been a swing over now into a more biological and biochemical kind of approach with less organic chemistry, and perhaps even less physical chemistry, except on the part of the x-ray crystallographers and the NMR specialists and all the people who are getting into it from that end. It doesn't matter. The pendulum will swing in terms of the

way the fields change and the way methods become available. Up until now, or up until very recently, x-ray crystallography was the only way of doing three-dimensional structure. Now NMR can do a hundred residues in a protein.

There's a paper in this week's Science where they're talking about being able to get up into the hundred and fifty, two hundred residue range with NMR, which is a lot cheaper (22). Once you have the equipment, and you don't need all that much equipment, it takes a lot less time. All of this is made possible by high speed computers. If we didn't have the computers, we couldn't do any of this today. This is the way it's going to go.

When I say it was in keeping with the times, that also brings me to another aspect of this (because we're not going to go on too much longer or I won't have any voice left). I decided when I retired I was going to give up the lab because, in effect, the kinds of methods that I was using to do protein structure were becoming antiquated. If I were to stay active as a biochemist with anybody else having any interest in seeing what I was doing, I would have to re-gear the lab one hundred percent. Every method that I was using, some of which we had developed, was now being superseded. It was so much easier, so much was different, I would have to start all over again. There was no point to it. I'd had fifty years in a lab. That's enough.

The fact is that you have to have a perspective on how the science is developing. Today people are doing amino acid sequences of proteins by isolating a little bit of the protein, getting a small part of the sequence, attaching that to something else, making an antibody, using the antibody to fish out the section of DNA on which this protein is being made, cloning it and getting the DNA sequence, checking it to make sure that it's the right thing. You then have the whole damn sequence in short order with very little labor, but with a whole new set of techniques that are partially biological, partially chemical. Well, this is a different world. First we had to get the techniques for doing the sequence. We had to prove that you could do all of this and that it made sense to do all of this. This is a different world. I don't have to compete in this world any longer. I competed in other sets of worlds earlier. Let the young people have this new world. That's essentially my philosophy behind this.

BOHNING: How quickly did Utah develop, since you started there when it was virtually brand new?

SMITH: It had been going as a four-year medical school for about two years when I came, and it developed very well. It's had its bumps like other places, and the first big hurdle in the early

years was surmounted, thanks to the NIH. The grant policy was generous, and the NIH, like all government agencies, wants to put some money in every state so that you get the support from the House of Representatives and the Senate. We were the only medical school in what was called the intermountain west, between Colorado and the West Coast and between Canada and Mexico, at that time. Now there are medical schools in Arizona and New Mexico. There's no school yet in Wyoming; it is too small. There's no medical school in Idaho. There are now new medical schools in the Dakotas. There's a small medical school in Nevada; they don't have the population to become large.

Utah signed agreements with all of these states to take in their medical students. The NIH was anxious to see this develop. You need the support of the west if you're going to get legislation through. [laughter] We were the beneficiaries. I make no bones about it. It was real. The school grew, the quality grew, old people retired, and new people came along. Every school makes mistakes in appointments, but they made a lot of good appointments. Today it's really flourishing, particularly since they've gotten the local support. They've got good new buildings, good new facilities, a good library. Jim [James Chipman] Fletcher as president did a good job when he was there. He later went back to NASA. I think it will continue. They've made mistakes. They have a current president who is retiring next week. They've made some disastrous mistakes with cold fusion, [laughter] but the university will recover.

BOHNING: When you arrived there you were young and you were new and there were other new people coming in, yet there was an old guard present. How did that interaction take place? Did the old guard adjust to the new changes?

SMITH: Some of the old guard resented it, but most of them didn't. We had one man in biochemistry named [Harold C.] Goldthorpe who had been the professor and chairman of the department when it was a two-year school. He was a very nice man. He had done some old-fashioned nutrition research fifty or sixty years before. For years, he had been teaching practically alone, with the help of one assistant. There was no opportunity for research, but he didn't resent it. We got along very well, and we gave him subjects to teach that were within his knowledge. Clearly, he would never teach modern enzymology or protein chemistry. Within the department of biochemistry, he was really the only holdover. The others were all people who had come after it was established as a four-year school.

In the clinical departments, there weren't any old-timers. The two-year school didn't have any clinical departments, except for pathology. The first head of a clinical department was in surgery, and he was responsible for bringing Max Wintrobe out in

medicine, and then other people came. I wasn't there at the time, but of course, I knew the history. Let's remember that at that time there were something like seventy medical schools in the United States. There are now about a hundred and thirty.

BOHNING: So it has doubled in the last forty or fifty years.

SMITH: Let's say almost fifty years, because there are not going to be any more.

BOHNING: That's quite a change. I hadn't thought about that.

SMITH: Some of them had been two-year schools that got to be four-year schools. Look at California. California, before the war, had the University of California at San Francisco, University of Southern California, and the College of the Medical Evangelists over in San Bernardino. The University of California alone now has five medical schools.

[END OF TAPE, SIDE 6]

BOHNING: You started out as associate professor of biochemistry and also research professor of medicine. You were making rounds with the physicians at one point to try and see the relationship between biochemistry and medicine on a more practical level.

SMITH: Actually, what happened was, since I didn't have a lab in September of 1946, Max Wintrobe said, "Why don't you come down and give us a lecture once a week on what you think is interesting and important that is happening in biochemistry that would be of interest to the clinical staff? You've been involved for four years with plasma proteins, antibodies, blood clotting, albumin, and important proteins. There's a lot you could tell us that we don't know about." So I started to give these lectures and got a good audience. It developed into a number of collaborations with people in the clinical departments because we knew how to do things that they were interested in.

Grand rounds in a medical school are not bedside rounds. Grand rounds means once a week you take important and interesting cases for teaching purposes and you bring in the patient to demonstrate certain physical characteristics or signs, and the patient leaves. Then you show the x-rays, the results of the laboratory tests and other signs or symptoms. Then you ask the students and the house staff what they think is wrong. What is the situation? What is the diagnosis? How do you treat it?

Grand rounds are a teaching device. Max said, "Why don't you come to grand rounds? We have an interesting case of this, that, or the other coming up next week. I think you'll be able to contribute something in terms of the basic biochemistry." Which I did. (I've forgotten what those cases were at this point.) I found that I was learning something about what the problems were in medicine in terms of the applications of biochemistry.

I attended grand rounds for a good part of that year and I was on call so that whenever they had an interesting case that was in my special area of interest, they would invite me to come to grand rounds to participate. Over a period of two or three years, I did this maybe three or four times a year after the first year, and then it gradually petered out for a very simple reason. I had postdoctoral fellows in my lab who were trained in medicine who now could do this just as well as I could, if not better. They knew more medicine than I did, and they were all learning the biochemistry. It was good for them. Today you don't need this. We've got more than one generation of physicians in internal medicine today who are well trained in biochemistry. It's a different world.

Biochemistry has become part of the language of medicine. There are certain aspects of biochemistry we don't really teach in the first year anymore. They're taught in the department of medicine. You teach the general language and you teach the basics. The applied aspects are better taught in pediatrics, medicine, or surgery or someplace else. Acid-base balance and electrolytes are no longer taught in a biochemistry course. It's either taught in a physiology course or it's taught in the department of surgery. They are the ones who use it. They are the ones that have to deal with the problems of kidney failure, kidney function, transfusion and similar problems. They know more about these things than we do. It's a different world.

BOHNING: Let me pursue that a little bit. You said earlier that most biochemistry departments were in medical schools. Is that pretty much still the case?

SMITH: No.

BOHNING: I think at Case Western it still is. This department still is.

SMITH: Yes, but our department here is only part of biochemistry on this campus. Before I came here, in the summer of 1962, I was interviewed to see if I was interested in the position of chairman of this department, which was then called physiological chemistry. There was also a division of biochemistry in the

chemistry department on the campus. The division of biochemistry in the chemistry department taught undergraduates and had a graduate program. This department taught medical students and had a graduate program. I was not totally enthusiastic about coming here, partly because the space wasn't all that adequate. Even though there was going to be space available two or three years hence, I wasn't ready to wait two or three years and give up two-thirds of my research program to move. I was not unhappy, let's put it that way.

After I got back to Utah, I got a telephone call from a friend of mine named Paul Boyer who was then at Minnesota. It turned out that the chemistry department had invited Paul to come as head of the division of biochemistry in the chemistry department. Paul said, "We'll be driving back through Salt Lake City. Can we stop and talk?" I said, "Of course, Paul." We knew each other; we were good friends. Paul came to Salt Lake City, and we spent two days talking and one evening socializing, letting our families get to know each other. We decided that we'd both come or neither of us would come to UCLA. The arrangement would be that the chemistry department would be responsible for teaching undergraduates; our department in the medical school would be responsible for teaching medical students and dental students since the dental school was just beginning. We would set up a joint graduate program. There was no sense in having two rival competing programs. We would give joint courses with joint requirements and we would set up an appropriate kind of program with the training grants and everything else. When we discussed this with the people at UCLA, they said, "Of course, nobody told us about this problem." It turned out that the previous head of the biochemistry division had wanted to be the head of the medical school department, but the medical school brought in somebody else.

Our joint program has worked exceedingly well. A graduate student can start in either program. If he likes the research and wants to work in somebody's lab in the other program, he's allowed one switch. You can't oscillate. [laughter] If you want to work with somebody over there, fine; vice versa, fine.

In the meantime, several years later, we recognized that the biology here was getting kind of old-fashioned and that something had to be done about it. A committee was set up to establish molecular biology. I was asked whether I would be the head of it, and I said no. I had enough administration, and I didn't want to build a new program. I felt it ought to be done by somebody who was younger and who would be willing to put the energy and effort into it. I couldn't do that and be chairman of the medical school, which was still building, at the same time. I agreed to be chairman of the advisory committee on molecular biology, and we induced Paul Boyer to become director of the Institute of Molecular Biology, which was set up not as a department, but as an interdepartmental institute involving

members from biological chemistry, chemistry, biology, bacteriology, botany, and so on. In fact, Paul and I served on the committee that recommended combining botany and zoology into a single department of biology.

Biology pledged six new appointments to molecular biology. These people would get their salaries and their titles in biology, but would occupy space in molecular biology, which was a very nice new building. Several members of our department moved over there where they felt that the work they were doing was more compatible. Graduate courses are taught jointly. The teaching program in molecular biology and biochemistry is essentially one program. You can take your degree in any of the individual departments, or in molecular biology.

Other schools have learned a little bit from this, but there are some schools where there is a separate department of molecular biology. In Berkeley, they have now combined practically all the biology and biochemistry in one department, a super-department, with a whole bunch of divisions. It has taken them twenty years longer than it took us, but they were well established and in an established place it always takes longer to break down the barriers. There is now superb biochemistry and molecular biology on a lot of campuses where there are no medical schools, or separated from the medical school or integrated with the medical school. Yale, for example, now has a department of biochemistry and biophysics which includes the people in the medical school. Some people are located in one place, some people are located in the other, but it's one department. At a university like my alma mater, Columbia, where the medical school is physically remote, you have to have separate administrative units. The subway does not make it that easy. At San Diego their departments are all totally integrated on one campus. This is now more common than it used to be.

We're getting back to what I learned from Frederick Gowland Hopkins, whose picture is over there. [laughter] It's all biochemistry. You've seen my bibliography. I have worked on problems in microorganisms, plants, and animals—to me it's all life. That's the way it should be. What we have learned from bacteria, we could never have learned by studying mammals, in order to develop what we now know about the genetic systems. It could only have been done first in bacteria. There are still problems in plant biochemistry that will teach us a great deal about living organisms and their relationship to us as mammals, that we won't learn in any other way. The problems of plant biochemistry in terms of agriculture have stayed as important as they ever were.

I still have to explain to my wife about ripening fruit. If you get unripe fruit and you want it to ripen in a hurry, you put it in a plastic bag. Don't seal it too tightly; make sure there's enough oxygen in there. The hormone that fruits make is

called ethylene. Ethylene is what comes out of our gas taps. Nevertheless, fruits make it, and they make it in the most peculiar and unpredictable way possible. Do you know the pathway? From an amino acid, methionine, by a combination of anaerobic and aerobic processes. Absolutely crazy. Nobody would have been able to predict that. People are working very hard now to get all the fruits in a field to mature at the same time to cut harvesting costs. That's the way to do it.

BOHNING: I am curious about this relationship with the medical school. As you said, some of the subjects are taught by the physicians themselves.

SMITH: Certain subjects have shifted into the clinical years.

BOHNING: That cooperation between the practicing physician and the biochemist over the years—has that been a pretty good combination?

SMITH: There have always been periods of cooperation, periods of tolerance, periods of armed neutrality, and periods of warfare, and this will go on in every university and every department for every school in the university. Forever. I think it depends on personalities, and it depends on the way a school is run. I have found that many of the problems can be solved with money. Some of the problems are problems of turf. You have a curriculum committee who ought to decide who teaches what, when and where.

If all the biochemistry were to be taught in the biochemistry department today, you'd need two or three years to do it. You can't do it. Aspects of applied biochemistry that are very important should be taught in a clinic; they don't have to be taught in biochemistry. You can't teach the structure of an amino acid at the bedside. A student has to know what an amino acid is to begin with. He has to know something about what a protein is and what DNA is. Of course, a lot of this is now undergraduate work. At a certain level you are moving up the scale, and at a certain level you are moving down the scale. Students come in knowing all about DNA as genetic material, but they don't know the structure of adenine. If you ask them to write the structure of ATP and how it functions, they wouldn't be able to tell you. But at least they've heard of it and they know something about it.

This question of graduate teaching and professional teaching is partly a matter of turf, and partly a matter of getting things straightened out. As I said, you can always solve it with money. I solved one problem here when I came that had never occurred to people. I said, "My alma mater's done this for years." People

kept coming to me because they wanted a biochemist in their department. It is very important to have good biochemistry in medicine, surgery, and so on. "Will you give him an appointment?" they asked. I said, "Why does he need an appointment in biochemistry? Why can't you make a biochemist a professor of surgery?" There's no law that's written in the bible that a man has to have an M.D. to be professor of surgery. You need a license to practice surgery. That's different. To hold a professorship, you don't need this. At my alma mater, Columbia Medical School, Michael Heidelberger was professor of medicine (immunology). He didn't have an M.D. anymorth the an I do, and Michael is now a hundred and three, by the way, my oldest friend. Michael has a degree in organic chemistry. If Michael Heidelberger could be a professor of medicine, why can't so-and-so be an assistant or associate professor of medicine?

Our department of surgery has non-M.D. professors, one who is a very distinguished immunologist and another, a very distinguished bacteriologist—both Ph.D.'s. This is the way to do it. You need that person? You want him devoted to the problems in your department? Fine. He could attend our seminars, and he could come to our lectures. But he's not a member of the department of biochemistry. We can't put him through the teaching program that we have to go through. He has different obligations. The same is true with radiology. You can have any number of biochemists in every department. This has taken a certain amount of education. We've done it here. Many schools have done so also. I don't know how many, but I don't have to be concerned about the world anymore. I have to help solve problems here.

BOHNING: I was going to ask you in a more general sense how you found administrative work, since when you came here you were an administrator more than you had been in the past.

SMITH: As I said before, my wife thought the experience at Squibb was very good. I learned how to delegate. It takes a little while to find out who the people are in the department who can do certain kinds of tasks. You appoint a person and say, "Look, you take care of this. You take care of that. For certain things we need a committee." You pick out the most competent and responsible people in a particular area to do the jobs for you. I know the department does not do it any longer, but it was a custom which I instituted, to have lunch together in our departmental library every Wednesday. We all have to eat lunch. If we have problems to talk about regarding the department, the school, the students or anything else, we can talk about it at lunchtime. If we don't have anything to talk about, we can talk about science. Or we can just talk about baseball or football or whatever the season is, but let's meet together at lunch every Wednesday. We would get a report on what

is going on when we needed it. It turned out that most of the time there is something to discuss, and we did meet every Wednesday. Now I gather that they have a staff meeting only once a month. I don't like that. People get too remote from one another. The more you bring people together, the better is the department.

I found that I could operate this way very well by having some capable people who could take care of the admissions of graduate students. If you have a new appointment to make, you appoint a committee. You advertise the job. You appoint the committee to do the preliminary scanning and come in with their recommendations. You pick out the ten best people, look them over, and then pick out the best three. You don't need a whole department or the chairman looking over two hundred applications. It makes no sense. Besides, people develop more of an interest in the department, more devotion to the department, if they know they're a part of it and they're being consulted on major issues. Since every appointment and every promotion has to be voted on anyhow, why should the chairman have to do all this work and present it cold turkey to a department? Let them be involved in it right from the beginning. That's the way I think it should be done.

I found that being chairman took a certain amount of time, but I also had a very good vice chairman. We shared all the work. If he weren't available I'd pinch hit for him, and if I weren't available he'd pinch hit for me. There were no secrets. There was no "I'm the boss" kind of thing. This went very well. He succeeded me as chairman of the department, and then he took early retirement. After five years he said, "It's time to enjoy life." [laughter]

BOHNING: What do you do to enjoy life outside of all these other activities over the years?

SMITH: After retirement, the first thing I devoted myself to was getting out of town for two and a half months. I had told the dean that I didn't want a lab, but that I wanted an office and access to a secretary. I didn't want to be on the same floor as the department, so that no one would feel that I was looking over his or her shoulder. I moved up here, two floors away from the department. This used to be a division of the history of medicine. Today it's a combination of family medicine and some of the history of medicine.

BOHNING: I saw a history of medicine sign down the hall.

SMITH: That's right. There are no labs here, so nobody has to

worry about throwing me out because they need the lab space. The first thing I did when I retired was to get out of town, as I said. We went to Europe for two and a half months. I had a couple of meetings as the excuse, and I wanted to visit some friends and give some lectures. We had a great time. With as much traveling as I've done and as much as we've lived in Europe off and on, we have friends all over the world now, including former postdoctoral and graduate students. It was a kind of homecoming.

When I returned, we started work on the seventh edition of the Principles of Biochemistry. A few months into the planning when we were getting ready to start, Abe White died suddenly. I was asked to take over as senior author and coordinator, and then the year after that Phil Handler died. So in effect, I had the brunt of it with some younger colleagues and we turned out these two volumes. We decided to split it into two books instead of one. The first book is called General Aspects in Biochemistry (23), which is very useful for an undergraduate course or a beginning graduate course. The second volume is called Mammalian Biochemistry (24). It speaks for itself; it's specialized.

After we finished this, two of my younger colleagues decided they didn't want to do another edition. It was too time-consuming. They'd rather work in the lab; they've got a lot to do, and they're still enjoying it. That was fine. Bob Hill and I were sort of lukewarm about it, and finally I said, "Bob, if you want to carry on, you can have it." [laughter] He decided not to do so. So the seventh is the last edition. The first edition was published in 1954 (25). We started in 1950. The last edition was published in 1983. It had more than a thirty-year life. It's still selling, more abroad than in the United States today. It's still a useful book, but it is dated in many ways. I have no desire to do it again. I'm not teaching anymore. I don't need the money and I don't need the work.

I've served on a few committees in the university. I had the privilege of taking on those committees that are either amusing or fruitful. I don't have to do any of this. I've served on some committees of the ASBMB. I was sort of the memory and the conscience of the Society for a while, particularly on the finance committee. For about a dozen years we built up a good reserve nest egg so we could do all kinds of things without worrying about funds, and we stayed ahead of inflation. For the last six or seven years, the Protein Society has occupied a certain amount of time. The young fellows were very enthusiastic, but they had no idea how to set up a legal society and get incorporated, get tax-exempt status, begin to build reserves, and begin to build the right kind of organization and procedures. All has gone well.

Leisure: I don't come in at eight or nine o'clock in the morning. I come in when I feel like it. In the summertime I

usually come in around ten because I ride my stationery bike for about a half hour every morning and my wife and I go swimming. Then we have showers and breakfast and then I walk over. I go home whenever I feel like it. If there's a seminar or lecture that's interesting, I'll stay for it. I've done a certain number of book reviews. I haven't done much lecturing recently, but I've given some lectures off campus. Hobbies: I listen to a lot of music and do a lot of traveling. We go to the National Academy meetings. I'm not on any Academy committee at the moment, but those committees kept me pretty busy for a long time. I go to the Philosophical Society meetings. That's about the size of it.

BOHNING: Are both your sons involved in chemistry or biochemistry?

SMITH: My oldest son is chairman of the chemistry department at the University of Massachusetts at Dartmouth. My younger son, after a Ph.D. in physics, decided to go into medicine, and he is now here as an assistant professor of pediatrics. He is a neonatologist. It is the kind of thing that he likes because it involves being a specialist in infectious diseases, respiration, biochemistry, etc. It involves problems in the newborn, and particularly, the problems of the prematurely born. They are doing wonderful things today in keeping them alive. His field of research is basically cellular immunology, rather than biochemistry. He knows a lot of biochemistry. He does not like to admit it, but he does.

BOHNING: I don't know how much more time you have.

SMITH: I think I'm going to give you about five or ten minutes, because my voice is giving out, and we do have to go to a retirement reception.

BOHNING: I understand.

[END OF TAPE, SIDE 7]

BOHNING: One of the things we have not discussed is the details of your research.

SMITH: That is all part of the published record, as far as I am concerned.

BOHNING: The combination of what you have written on it and what other people have written on it is important. It has been reviewed and integrated with other work in the field. It does conveniently fall into certain categories. I have thought of looking at how each category originated, some of the people that were involved, and maybe some general comments you have, but not to go into any of the specifics. We won't have time to do that today, but if I'm ever back at UCLA, if you felt like pursuing that for an hour or so, we could do that.

SMITH: Sure. I'd be delighted.

BOHNING: We have talked about Principles of Biochemistry. Maybe you could talk a little bit about how that all came about. You told me how it ended, but we didn't talk about how it started.

SMITH: It began while I was in New Haven, in 1940, during that seven or eight month period at the last part of my Guggenheim Fellowship. Abe White and I kept bemoaning the fact that the textbooks in biochemistry were hopeless at that time. Some time during the war years, when he came to visit us in New Jersey, we talked about the fact that maybe someday we would have the time to do a textbook. He could deal with the more physiological aspects and intermediary metabolism, and I could do the chemistry and biochemistry of proteins, enzymes, oxidation-reduction reactions, et cetera.

Obviously, during the war we were both too busy. At the end of the war, I was moving to Utah and he was getting out of war research and back into fundamental biochemistry. It was quite clear that this wasn't going to be an immediate prospect. Then sometime in the early part of 1949, at a meeting of the ASBC, Abe said, "You know, it's quite obvious that we two are never going to do a book alone. Why don't we bring in four other people?" He made an outline suggesting how to divide up the work so that we could get the job done in roughly a year or two without impinging too much on our time, and we'd have a reasonable textbook. These were all knowledgeable people who wrote well. I said, "All right, that sounds fine. You get in touch with all the other people." It was his idea; he was the senior person.

We decided that we would have a meeting at the Committee on Growth which was the research granting agency of the National Research Council administering the monies of the American Cancer Society at that time. It met in Washington early every December to review research grant applications. Abe was on one panel, I was on another, DeWitt Stetten was on a third panel, and Philip P. Cohen (who had been at Yale) from Wisconsin, was on another panel. Phil Handler came up from Duke, which was not very far

away. We started to talk about the project and made some preliminary outlines. Everybody was very enthusiastic. Two months later we were exchanging outlines of what we thought ought to be in our sections, in order to coordinate the projected contents. Many subjects can be in two or three different places, so you have to decide on a single place. You can't cover a subject more than once.

Sometime later, Phil Cohen said he was head over heels in building up the department and his own research. There was no way he was going to be able to take the time to do it, so he pulled out. The man who was going to do the nutrition, who was at Vanderbilt, Bill Darby, decided he couldn't participate because he had a number of prior obligations. At that point, the four of us met in Atlantic City, as usual, for the ASBC meeting. We said, "Having come as far as we have, the four of us can do it without the other two." After all, dividing up those other two parts wouldn't be that much more difficult. Besides which, Abe and Phil had both worked on amino acid metabolism, which was what Phil Cohen was going to handle. Abe and Phil had also both worked in the field of nutrition. They could handle that. So we reassigned subjects. I took on a little more, they took on a little more, and that's the way it went.

I had not met Phil Handler before. I had met DeWitt Stetten earlier, casually, because he had been a graduate student at P&S while I was down on the campus of Columbia. He was Abe White's age and older than I. He, in fact, had gotten an M.D. before he took his Ph.D. in biochemistry. We became very close friends. We worked very intimately. Very early on we decided that despite the fact that each of us had a preliminary assignment, we were exchanging every word and every chapter and rewriting and deleting and adding and rewriting, so we could not identify in the book anywhere what each one had written. This was going to be a communal task, and we were all responsible for each and every section. We all read proofs of every chapter, every word in both galleys and pages. It made a lot more work, but it made a hell of a lot better book, I can tell you that. Stetten pulled out after the second edition because he became the associate director in charge of research at one of the NIH institutes, and felt that he simply had no time to continue.

BOHNING: What kind of impact did it have when it first came out?

SMITH: It had an impact on the teaching of biochemistry in the best medical schools and in a lot of undergraduate courses in biochemistry. The old-fashioned professors of biochemistry didn't like it. There was too much chemistry; it dealt with things that were not properly within the province of the medical student, like chapters on the genetic aspects of biochemistry. All this stuff on nucleic acid structure was very interesting,

but it had nothing to do with teaching medical students. [laughter] It had a chapter on evolution that was certainly unnecessary to medical students. The first edition didn't do badly, let me put it that way. It didn't do as well as we had hoped.

In the meantime, an explosion was happening, and we decided we'd better get the new edition out in a hurry. The second edition came out in 1959 (26), and that was an enormous success.

A third edition came out five years later (27), and even more successfully, a fourth edition (28). I think, in retrospect, that the third and fourth editions were probably the best editions we did. They were very up to date. They encompassed the modern viewpoint of biochemistry better than anyone had done up to that time. We all were still actively teaching and putting our best efforts into it.

The fifth edition (29) got to be a little verbose, and was not as well edited, partly because by that time Phil Handler had become president of the National Academy and was really bogged down. The only real time he could devote to actual writing were the summers at Woods Hole. The rest of the year he could try to read some literature and keep up, but he was not living with it from day to day. He got so far behind that, in effect, Abe White and I had to take over a lot of his writing assignments, and I took over the heaviest part of it. At the end of that edition, I said, "Gentlemen, if we don't get help for the next edition there ain't gonna be one." [laughter] Everybody agreed. There was no question about it; the three of us couldn't do it alone any longer.

We met in Minneapolis, as I recall, at an ASBC meeting, and we spent three hours talking about whether we should do a new edition. We talked about all the pros and cons and then we went out to dinner. On the way back from dinner, we met a whole bunch of people in the lobby, friends of ours, heads of departments of biochemistry from all over the country. They all looked at us and said, "Ah, these guys are plotting a new edition." Our answer was, "Well, should we? Do you think we ought to do a new edition? Do you want a new edition? Do you think it's worth it?" Everybody insisted that we had to do it. Well, if the response is that enthusiastic, we're going to do it, but we have to get at least one and maybe two additional people.

By that time Abe White had retired from Albert Einstein and had gone out to Palo Alto to be a director of a new division at Syntex, with an adjunct appointment at Stanford. That was also one of the reasons why I got bogged down with that fifth edition. Abe suggested bringing in Bob [I. Robert] Lehman, who knew the field of nucleic acids and was a major contributor to that field. He would be able to handle all of the chemistry and biochemistry very easily, and do it well. He wrote very well. I said, "Wonderful." I had handled all of that in the previous five

editions. I had kept up with that whole nucleic acid field. I had a background in genetics, so that the language was not unfamiliar, but keeping up with that literature!

The other logical choice was very easy. Bob [Robert L.] Hill had come to me as a postdoctoral fellow and spent seven years in my lab. I sent him to Duke to be an associate professor under Phil Handler. He came to me as a postdoc and then was an instructor and assistant professor. He had been doing independent research while he was still in my lab. Then he moved to Duke and later succeeded Phil Handler as chairman of the department of biochemistry. Bob was the obvious other one to bring in. That's how the sixth edition got done (30). It's a good edition. The seventh got split into two pieces, and we kept Phil's and Abe's name on the covers, but they did nothing in terms of actual writing. That is the saga. Within a very short time, I lost a lot of my closest friends, and I'm the survivor. As Maurice Chevalier once said on a similar occasion, "It's better than the alternative." [laughter]

BOHNING: With that, let me thank you very much for taking this time this afternoon. I've enjoyed it. It's very fascinating.

SMITH: It was an era when the science of biochemistry came to maturity. It's been a fantastic experience to have been in it during this period. As I said in that essay of mine, if I remember, that it was great fun because within a short time you knew everybody in the field. Now you don't. Now you know a few people in your own specialty, and there are so many that you can't know them all. The point is, you knew everybody all over the world, for that matter. Even if you'd never met you knew each other, because you knew their writings. This was quite an experience. We are still enjoying it in that sense. We look forward to enjoying more of it. I still enjoy reading the literature and seeing what's going on. I keep up pretty well. I don't try to cover all topics in the same way that I once did. It's hopeless. But I know the major trends. I am going off on Friday to the Protein Society, and we'll have dinner on Friday night, an executive committee meeting all day Saturday, reception Saturday night, and I've got to chair a scientific session Sunday morning.

BOHNING: It doesn't sound like that part has changed at all. [laughter]

SMITH: That hasn't changed at all. Sessions close at noon on Wednesday. We'll be back Wednesday night. I'm still on the board of a small foundation that gives away money, which is always fun. I don't do any industrial consulting anymore because I've had enough of it. I've made a very strict policy, which is

that I'll go away to something alone for one night only, but for more than one night I don't go anywhere without taking my wife. After fifty-seven years, we're still getting along beautifully. I can't ask for more.

BOHNING: That's marvelous. You've commented, again in your essay, about her support throughout your career.

SMITH: There are some wives who will support and some wives who don't.

BOHNING: Yes, I know.

SMITH: She's been very supportive. She always laughs and reminds me about every four or five years that before we got married I warned her that full professorships were very rare and I'd be lucky to get a good associate professorship somewhere. [laughter] We would live reasonably well, but we would never be rich, we would never do this, and we would never do that. She says, "Boy, you have been so wrong." [laughter] Not that we are that rich, but there is nothing we really want that we lack. The book helped. Not that we made that much money out of the book, but we did from the investments that the book made possible.

When I first started to consult for Squibb in 1949, we decided that we would not spend that money. That would be invested as future education expenses for our sons, so that they could go to whatever college they wanted to. Utah was not my idea of a good undergraduate educational institution at that time. You can do good graduate work anywhere if you have a good professor at a good lab. Undergraduate study is different. A state university has to take in everybody because it is state law. At that time (I don't know what it is now), one-third of the freshman class had to take bone-head English or bone-head math or both, and that is not the most stimulating kind of atmosphere. We put away that money, and it turned out later on we didn't need it. I was getting a high enough salary and enough income out of the book that we could cover it. Those early investments have paid off, so we don't have to worry.

BOHNING: On that, I'll thank you again. I certainly appreciate your time.

[END OF TAPE, SIDE 8]

INTERVIEWEE: Emil L. Smith
INTERVIEWER: James J. Bohning
LOCATION: University of California, Los Angeles
DATE: 17 March 1994

BOHNING: The last time we talked, one thing we did not do is discuss much of your science, although we had taken you through Utah and brought you here to UCLA. I thought today we might review your work in the way in which you have outlined it in your memoir (1), using the categories in which you conducted your research. I know that a lot of this work has been reviewed, but I thought we might look at it from the standpoint of how it originated, the people who were involved, and where your support was coming from, as opposed to going into the specifics that are already in the scientific papers.

The first category, starting in 1946, is the peptidases. You've said that came from your work with Bergmann; you were looking at the role of divalent metal ions and hydrolytic enzymes. Could you provide any more details about how you got into that particular area and why?

SMITH: I think I have covered in my autobiographical memoir why I went to Bergmann's laboratory and what I did there. It left many intriguing questions hanging during the war, when I couldn't do any of the peptidase work. Of course, no one at Bergmann's laboratory could follow it up because they were involved in research on the biological action of nitrogen mustards during the war. Bergmann died before the war ended and the laboratory broke up so that people went in different directions. What I had realized from the work that I had done in Bergmann's laboratory was that metal ions, like magnesium and manganese, were needed for the activity of certain peptidases. It was unlike oxidative enzymes, where it was known that elements like copper and iron could change valence, and that could be understood easily in terms of their being receptors or donors of electrons.

What was the need for a metal ion in a hydrolytic reaction? At that time it was known only that magnesium was required by certain phosphatases and that even magnesium or manganese was required by certain peptidases. That was the extent of our knowledge. While I had been in Keilin's laboratory in Cambridge before the war, he and [Thaddeus] Mann had discovered that carbonic anhydrase was a zinc enzyme, which again was an element that didn't change valence, but was essential for a hydration or a dehydration reaction. The enzyme converted carbon dioxide and water to carbonate and vice-versa. So the question is: what role

did metal ions play in these hydrolytic reactions and how universal was this, and how universal were these enzymes? Initially these enzymes were known only from intestinal mucosa, where it was thought that their primary role was in completion of digestion of proteins and peptides to finish off what the proteinases didn't do in liberating free amino acids. It was already well-known that in digestion only free amino acids are absorbed into the blood, and that our tissues build proteins from free amino acids and not from peptides.

When I came to Utah, I started on two lines of work. One was to see whether the peptidases were present in all tissues, which was determined soon. Second of all, my students and I tried to purify a number of these enzymes to see what we could find out about the nature of the enzyme, and try to think about what the metal ions did. I came up with the notion that the metal ion was involved in complexing on the one hand with the enzyme, and on the other with the substrate. The exact notions at the time in 1948 and 1949 were pretty naive, but nevertheless it stimulated the whole field. Soon came the realization that there were a vast number of enzymes in nature that were non-oxidative and in which ions of manganese, magnesium, and zinc were involved. Subsequently, a lot of others were found, even bizarre ones like nickel which is in the active site of urease, which had been the first enzyme actually crystallized. Nobody had discovered the nickel until very recent years because nobody thought of looking for it.

So we now have this array of metal ions that participate in a vast number of different enzyme reactions. We came up with the notion, which was first published in 1949 (31) that the metal ion might bind by complexing to carboxyl groups or amino groups, and at the peptide bond, but at the same time it did not explain the specificity of these enzymes. One enzyme had been called leucine aminopeptidase because it required a free alpha-amino group in the substrate. Although leucine peptides were the most sensitive, the enzyme actually hydrolyzed a large number of different peptides. Provided the side-chain was non-polar, the size of that non-polar group determined the rate of action by the enzyme. If there was a polar group on the side chain attached to the alpha-carbon involving either a carboxyl or an ammonium group, the rate of reaction of the enzyme was very slow indeed.

So we came up with the hypothesis, which was fairly obvious, that this non-polar side-chain also had to bind to the enzyme, presumably through non-polar forces, and that ions would disturb this reaction. This agreed with the Bergmann hypothesis of a three-point interaction between enzyme and substrate, in order to explain the specificity for l-peptides rather than d-peptides. It also satisfied the requirements of explaining the relative specificity of the substrates. We attributed the side-chain interactions to van der Waal's forces or hydrophobic forces as they're now called. That basically was the beginning of this

research.

BOHNING: Who were some of the people who worked on that for you?

SMITH: One of the people was a graduate student named Darrel Spackman, who got his Ph.D. with me and subsequently was a post-doctoral fellow with Stein and Moore in New York. He participated in the design of the automatic amino acid analyzer. He was exceedingly good with his hands and clever with manipulation. He had several opportunities to go elsewhere, but he worked at the Rockefeller Institute until the machine became commercially available. It was made first by Beckman instruments and Spackman subsequently went to work for Beckman instruments. He then went to Seattle to another research job.

Another person who participated in this work was W. J. Polglase, or Jim Polglase, who was originally an organic chemist. He did a great deal of the synthetic work in making many of the peptides that we used in these studies. He subsequently went back home, when the opportunity became available, to the University of British Columbia, Vancouver, where he later was chairman of the department. He is now retired. They were the two principal people who were involved in the early experimental work in Utah.

I should note that in my first years at Utah, I synthesized many peptides with my own hands.

When I had been invited to the Cold Spring Harbor Symposium to give a talk in 1949, Rufus Lumry had just come to the lab and we had gone through the ideas with him. He was the one who decided to do some calculations to see whether van der Waal's forces and interactions would explain much of the specificity. Indeed, you do get the same kind of curve for the strength of the van der Waal's interaction as you do for the series of homologous peptides in terms of their interaction with a hydrophobic pocket. He was a co-author of a paper that was presented at the Cold Spring Symposium at that time (32). Lumry went on to become professor of physical chemistry at the University of Minnesota, where I think he's retired now too. We're talking about work done in the late 1940s, so it's forty-five years ago.

In later years, a number of other students and post-doctoral fellows contributed to some of the peptidase studies.

BOHNING: What was your source of financial support?

SMITH: The support came from the National Institutes of Health, primarily, and that was through a fairly generous grant that

supported the laboratory.

A big change in work began to take place in the early 1950s. [Frederick] Sanger had presented in 1949 in the same Cold Spring Harbor Symposium his first work on determining amino end-groups and a partial amino acid sequence of insulin. Work had also been presented on amino acid analysis where two things were now becoming clear. One was that an attack on the amino acid sequences and the structure of proteins was becoming feasible. Second, that amino acid analysis, which used to be laborious and required huge quantities, was now getting down to the micro-scale work, mainly because of the work of Stein and Moore, and that this would aid in determining and understanding structure of enzymes and other proteins.

The result was that in 1952, when Ted [Edward O. P.] Thompson got his Ph.D. degree with Sanger in Cambridge, he came to my laboratory at my invitation. I had a grant from the Rockefeller Foundation to support Thompson and his wife. He introduced the Sanger methods of doing end-groups and of separating small peptides by paper chromatography and paper electrophoresis in the laboratory. At the same time we began to set up the column chromatography for doing the Stein and Moore separation of amino acids for quantitative analysis. We realized that since we had the leucine aminopeptidase in a fairly pure form, it was quite clear that a protein of over two-hundred thousand molecular weight was not going to be subject to amino acid sequence studies at that stage of history, plus the fact that the quantities that could be obtained of these animal peptidases was so small that we wouldn't be able to do much anyhow. The methods at that time required fairly large amounts of protein.

So we began to think about other proteins to study, which would give us the kind of information we wanted. It was for that reason that I hit on the notion of studying the plant proteinase papain, since the crude dried latex from papaya was available in large quantities. In our hands we learned how to crystallize it and purify it fairly easily, so we could prepare grams of the substance at a time. We knew that its molecular weight was fairly low, and we measured it again fairly carefully. We were dealing with a single peptide chain in the twenty-thousand range rather than something in the two-hundred thousand range. So we began to study the specificity of papain, mechanism of action, kinetic studies, and also at the same time (1952-1953) began structural studies on the enzyme.

BOHNING: We'll see more of this, but you have been witness to radical changes in experimental methods in biochemistry from the early days.

SMITH: Everything is methods. [laughter]

BOHNING: When these new sequencing techniques were available, or when the new chromatography techniques were available, how rapidly did they take hold, and how rapidly were refinements made?

SMITH: They took hold exceedingly rapidly, and the refinements were just steady. I met Sanger at the Cold Spring Harbor Symposium in 1949, and we became very good friends at that time. In 1951 he came up to visit us in Salt Lake City, and it was through him that I induced Thompson, who was from Australia, to come and spend a year or so at our laboratory before going back to Australia. It was Thompson who came to our laboratory to introduce the fluorodinitrobenzene method of doing amino end-groups of proteins. Within the first week that Ted Thompson came to the laboratory, and since we had all the pure amino acids available, Thompson, Mary McFadden (a graduate student) and I synthesized all the dinitrophenylamino acids in one day, and recrystallized them the next day or the day after. [laughter] This was simply a campaign to get everything ready to start doing the work. We had the wherewithal, he had the technique, and we went ahead and got everything ready.

At the same time we set up all the tanks (we designed and had built them ourselves) to do the kinds of paper chromatography and paper electrophoresis that we needed for identifying all of the dinitrophenyl or DNP-amino acids, and for isolating and separating the small peptides that you could get by partial cleavage of enzymes and proteins. We started to do this work just as fast as it was introduced. Since Moore and Stein were close friends of mine and I had worked in Bergmann's laboratory across the hall from Bill Stein and next door to Stan Moore, I went to see them every time I visited New York. So I was thoroughly aware of everything they were doing, and as soon as the methods were available, not only did we use them in our laboratory, but I sent them my student [Spackman] to participate in their work in developing the automation for the instrument.

This is another way of saying that the field of protein chemistry was very small at the time. There were a limited number of people in it because the big excitement of biochemistry in that era was intermediary metabolism, thanks to two things. C-14 became readily available. Everybody was labeling compounds to see what happened during the metabolism of an amino acid, a carbohydrate, or other important natural products. All the pathways of synthesis and degradation of amino acids in a variety of species, of carbohydrates of all kinds, of lipids, everything was being worked on simultaneously in every active laboratory in the United States. So the big excitement was really metabolic biochemistry at that stage of history.

Those of us who were interested in mechanism of action of enzymes and in protein structure were in a very limited number of laboratories. There may have been half a dozen in the whole country that were devoted essentially full-time to such studies. We were doing enzyme studies as well, but not with C-14. We were making synthetic substrates and studying specificity, which is a different kind of endeavor. Whatever was happening in the protein field was rapidly communicated from one laboratory to another and everybody was up to date. Everybody shared techniques, in essence, because it was the only way to make progress at the time.

BOHNING: Who were the other players besides your group and Stein and Moore?

SMITH: There was Sanger's group, of course, in England. [Claude] Fromageot in Paris. Pehr Edman, initially in Sweden, and then in Australia when he got mad at the Swedes for a variety of reasons. Our laboratory, Stein and Moore's laboratory, Fruton's laboratory in New Haven, [Christian] Anfinsen at the NIH, Hans Neurath in Seattle. That was it. C. H. Li was studying protein hormones at Berkeley. On the physical side there were many people involved, but I'm talking about the organic structural side. Those were the leading players. Starting in the late 1940s and early 1950s. Within a decade, there were many others, and students from the various labs were going around the country starting their own laboratories. This is what happens. It grew exponentially for quite a long time.

Now the old methods are almost out of date. People in a sense are determining protein sequences by studying the nucleic acid sequence, and now that the techniques exist for doing the sequence of DNA and of amplifying the DNA and the synthesis of the corresponding protein, you don't need to do it by the methods we used. That's one of the reasons I stopped work when I retired, because I knew that if I were to continue I would have to change fields completely. The methodology that we had been using and that we had helped to develop was now hopelessly out of date.

BOHNING: It was at this time that genetics was really beginning to change. As Arthur Kornberg has said, it changed from an obscure branch of biology to chemistry. At this time was there still a concern over the role of proteins in genetics?

SMITH: That had been answered. As far as I was concerned it had been answered with the work in the middle and late 1940s. It had been answered by the work of [Oswald T.] Avery, [Macyln] McCarty,

and [Colin M.] MacLeod at the Rockefeller. After all, I had left the Rockefeller in 1942 and I knew what was going on. When they published their work in 1944 (33), it was quite clear that the genetic information in the type-specific pneumococci was in the nucleic acid. That was amply proved.

In fact, I can recall a long argument with Arne Tiselius, who was chairman of the Nobel committee, why the Nobel prize had not been given to Avery for that work. What it reflected was the fact that Tiselius, although a very nice man, was essentially a physical chemist and naive about biology. He didn't realize the importance of this work. Then Avery died shortly thereafter, and there was no way of giving the Nobel Prize to his younger collaborators. That argument with Tiselius took place at the time of the IUPAC meeting in 1951.

Moreover, in 1950-51 I began collaborating with my co-authors in writing The Principles of Biochemistry (25). Since I was regarded as more the chemist-geneticist of the group, since after all I had been trained in biology and had taken all the advanced genetics at Columbia, I was given the task of writing up the chemistry of nucleic acids and the genetic implications. The information regarding the structure of nucleic acids, including all of the [James D.] Watson and [Francis] Crick ideas, and the description of all of the work of [George W.] Beadle and [Edward L.] Tatum, fell on my shoulders. The book went to press in 1953 and it came out in 1954, the first textbook of biochemistry that had all that information in it. The chapter was called "Evolution, Genetics and Metabolism."

Now, for an anecdote that will amuse you. When this book was submitted to McGraw-Hill in manuscript, the editors were horrified, at least the senior editor was, and it was regarded as far too long and complex for an elementary textbook. They proceeded to send the book to two older senior biochemists, who felt the book was very good but it was much too long and much too difficult. One of the suggestions they both made for shortening the book was to leave out that chapter on "Evolution, Genetics, and Metabolism," which always gives me much to laugh about in later years. [laughter] They regarded it as unnecessary. That is the part of biochemistry that has expanded the most in the last forty years.

BOHNING: How did you manage to keep it in?

SMITH: We said, "Gentlemen if you don't want the book, send the manuscript back. There are three other publishers banging on our doors, [laughter] who will take whatever we give them." They said, "Oh, we'll publish it, we'll publish it." [laughter] They didn't regret it. So that tells you the story, that we were aware of what was going on. I had met Francis Crick in 1952, the

first time I went to England after the war; I was a prodigal son returning. My old professor David Keilin in Cambridge arranged a big party to meet some of my old friends as well as to meet some of the younger people. I remember very well his words introducing Francis Crick to me and vice-versa, saying something like, "You two probably talk about as much and as fast as anybody I've ever known. Let's see who can out-talk whom." [laughter] Francis and I became very good friends from that point on, and we agreed about many things and disagreed about some things.

BOHNING: Could you give me some more details about your arguments with Tiselius about the Nobel prize?

SMITH: I had felt there were two fields that the Nobel committee had overlooked. Although Tiselius was in the chemistry section, this could be either chemistry or medicine, depending on which one you wanted. The committees do get together and talk about the awards. There were two things that I had argued with him about. One was genetics, which they later rectified by many rewards. The other one, I felt, was the contributions of Michael Heidelberger in immunology. In fact, Avery could have shared the prize with Michael Heidelberger for discovering type-specificity of the pneumococcal and streptococcal organisms being due to polysaccharides and not due to protein. It was Avery who recognized type specificity in pneumococci, helped to develop the antiserum of all the different types, and turned over the materials to Michael Heidelberger who isolated the carbohydrates and continued working on them off and on for the rest of his life. It was a major achievement, both in chemistry and in medicine. Of course, the antibiotics made the antisera out of date later on, but that had nothing to do with what came earlier. In fact, today the polysaccharides are all back in action, being used for immunization, rather than worrying about antibodies to cure the pneumonia after it takes place. Probably, more than anyone else, Heidelberger and his students made immunology a quantitative science and helped to establish that antibodies were proteins.

[END OF TAPE, SIDE 1]

SMITH: In other words, what I'm saying is that the Nobel Committee is not infallible. They don't pretend to be, and they've made some serious mistakes. One could make a substantial list of mistakes that they've made. They've made fewer mistakes in commission than they have in omission. I think the mistakes that they've made in commission have been more in medicine than in chemistry, where they've made a few really terrible blunders. But in chemistry, I think practically everybody who has received the prize deserved it, but there were perhaps more who deserved

it who didn't get it.

BOHNING: As an aside, what were some of the blunders that they made in medicine?

SMITH: There was a Portuguese surgeon who did lobotomies to cure insanity. Sure, if you take away the brain, you're no longer insane. This was hardly a valid treatment for mental disease. That was one big blunder. Another big blunder was the recognition of somebody who found that if you got malaria it counteracted the effect of tuberculosis. We now know that this is due to the high temperature. It had nothing to do with the tuberculosis or malaria. There were a number of other things of that kind in medicine, fly-by-night important discoveries. Recent awards in medicine on the whole have been pretty good. It's some of the older ones that were pretty ridiculous.

On the other hand, in chemistry, biochemistry, whatever you want to call it, the omission of the proof and the characterization of antibodies, which was largely Michael Heidelberger, was rectified when they later gave the prize to Rodney Porter and Jerry [Gerald M.] Edelman in medicine for the chemical nature of antibodies for the determination of amino acid sequences. But that was derivative in a certain sense. Once you learned how to do the amino acid sequence of proteins, why reward antibodies more than any other kind of protein? So that was really secondary. Of course, the nucleic acid work was recognized with Watson and Crick, but again it took years before they gave the prize. After all, the original paper was 1952 and it was some years before the Nobel people were sure that was important. That was a real blunder. I think one of the major blunders was the fact that my old professor who discovered the cytochromes and did so much to unravel the complexities of biological oxidations in respiration, David Keilin, never received it. This was a real injustice. But there were others.

BOHNING: In Avery's case, had there been nominations proposed to the committee?

SMITH: No way of knowing but I would assume so. All I can say is that I nominated Moore and Stein three times before they got it. [laughter] Many more people will be nominated than will ever receive it, which is as it should be. You expect that. But they finally got it. In fact, I was furious when the Nobel Prize for medicine was announced before the chemistry prize that year. (It usually is; they all have their dates set.) They announced the Nobel Prize in medicine to Porter and Edelman, whose work depended entirely on the work of Moore and Stein. I was just absolutely furious. I was ready to get on the telephone with my

friends in Sweden and lambast them when the chemistry prize was announced and it turned out to be Moore and Stein. But, they gave it to them and Anfinsen for the ribonuclease work, rather than the methodology. It didn't make any difference.

BOHNING: From what you said it sounds like the Nobel committee is not a mix of ages and experiences, but the senior type of individual.

SMITH: I'm well aware of what it is. By statute, in medicine it is the full professors of the Karolinska Institute, which is the medical school of Stockholm, who vote. As some of my friends have told me, "You can't give the prize to biochemists every year. You have to make treaties with internists, surgeons pathologists and pharmacologists as to who's going to get it in a given year. Sure you can give it to biochemists every year, but you would have problems persuading the others." So that's part of the politics.

The other part of the politics is that the chemistry prize is given by the chemistry section of the Royal Academy of Sweden. Physics is given by the physics section. I think the chemistry section has only twenty members. Unless this has changed (and it very well may have), there used to be an equal number of organic chemists, physical chemists, inorganic chemists, analytical chemists, and biochemists. So again, you have to make treaties as to whom you are going to honor this particular year. You can't give it to a biochemist every year or to an organic chemist every year. What the analytical chemists do in participating in this I'm not sure, because I don't think anybody's gotten the Nobel prize in analytical chemistry for a very long time. [laughter]

BOHNING: The only one I can think of is [Jaroslav] Heyrovsky for polarography.

SMITH: That's a long time ago [1959].

So that's the way the Nobel committee works. I've known various people in the chemistry section. In fact, for a long time the chairman of the chemistry section was my former post-doctoral fellow, Bo Malmström, who just retired last year from Göteborg University. He said it is a very difficult job. You get an awful lot of nominations and you've got to haggle. The Committee has to decide here and now who's going to get it. Then the Nobel committee set up this firm rule that a prize cannot be shared by more than three people. Sometimes this becomes a very difficult situation.

BOHNING: At that same time, you also started doing some work in immunoglobulins.

SMITH: The immunoglobulin work was actually an outgrowth of some things that I had started at Squibb. The work at Squibb had largely started for two reasons. One, I was involved in the blood fractionation program which had been developed by Cohn and Edsall and their group at Harvard and in the production of the immunoglobulins. The human immunoglobulin fraction was used mainly for passive immunization; first against diphtheria and tetanus, and second of all it was used against hepatitis. In the course of that work we had prepared a lot of immunoglobulins and the section that I was in at Squibb was also preparing horse antitoxins.

One of the people at Squibb, August Holm, had a bright idea. It had been known for a long time, since the work of Paul Ehrlich, that milk contains antibodies. A newborn calf has no antibodies, but after it suckles, these antibodies are in the bloodstream of the calf, and therefore they are protected. It was known that human infants don't make antibodies right away after birth, and that the human infant does obtain some antibodies from its mother by placental transmission. Placental transmission takes place in humans and primates, but it does not take place in ungulates. In cows, sheep, and goats, antibodies are transmitted via the first milk or colostrum, whereas in other species, depending on the type of placenta, antibodies are transmitted from the mother's blood into the infant's blood.

Holm had the bright idea that if we could immunize cows, you could collect these milk antibodies which could be used for feeding human infants and protecting them against certain common diseases like diphtheria. So an experiment was set up with five cows. I was asked if I would purify the antibodies from milk, which I did, using some of Cohn's methods and some other methods. We had pure antibody fractions from milk, and while I was at it I purified some from the horse and from sheep as well. I had a whole battery of these things. I had enough help to do this, which you can get in industry. The project was not very practical because it was much too expensive. Nevertheless it was interesting, and it gave me some fun purifying some proteins.

We also had on hand from the days before antibiotics and the sulfonamides, the various rabbit antibodies for different types of pneumococcus. We also had the specific pneumococcal polysaccharides, which had been prepared at Squibb. In fact, during the war years an experiment was carried out at one of the army camps, I believe in North Dakota, where pneumonia was endemic. They used the polysaccharide antigens to see how effective they were in immunization. They did the usual experiment of immunizing part of the camp and not immunizing the

other, and the immunization was so successful that the pneumonia totally disappeared, because once you rendered half the camp immune the carrier rate dropped, and the epidemic stopped. You don't have to immunize everybody to stop an epidemic.

People lost interest in this after the war because penicillin became available, and other new antibiotics were discovered. Sulfonamides were ancient history by then, ten to twelve years old, but penicillin became available on a large scale only after the war. Now, pneumococcal antigens, which are all polysaccharides, are being used again to immunize older people, people who are susceptible for whatever reason.

In any case, when I left Squibb, I asked my boss, "Can I take these preparations which nobody wants?" He said, "Of course." So I took all the pneumococcal polysaccharides with me. I took all the rabbit antiserums reactive with these polysaccharides with me. I took all this other stuff that I had prepared, and samples of various other things. When Michael Heidelberger found out that I had the world's supply of pneumococcal polysaccharides, (and we had been friends before), I gave him part of my stock.

That's how the antibody work started. We showed, that if we took, for example, a specific pneumococcal polysaccharide (repeating the Heidelberger experiment) you could precipitate the antibody for this specific type. The precipitate was washed by centrifugation several times to remove non-antibody proteins. It didn't matter that the polysaccharide was there; you could do an amino acid analysis. We showed that the amino acid composition of different antibody proteins differed. We showed that the end groups were mixtures of different types. But at that time I didn't start in to do any structural work because we knew that those antibodies were large molecules. We got into this field because we had the raw materials. We had an ultracentrifuge and we could study the physical properties. We had an electrophoresis apparatus and we could do the charge properties. And we could do the end-groups and amino acid analysis. At about that time, we became heavily involved in the study of smaller enzymes, like papain, the subtilisins, the cytochromes, and others, so we dropped the antibody work. Rodney Porter and Jerry Edelman went on to study them. You can't do everything.

BOHNING: It sounds like except for the size limitation...

SMITH: We were in a good position to do it.

BOHNING: ...you just had a wide open choice of all kinds of things at that time.

SMITH: The reality is that I was interested in the enzyme problem. I also loved to study problems for which you can have a quick assay—an enzyme that can be assayed in a couple of minutes. When it comes to antibodies, it becomes a much more difficult situation. Later on, what happened is that once the lab became well known as a place that was active in protein structure and was actually accomplishing something, we were bombarded with requests from people who wanted to come to our lab to learn the methods. That's why we branched out into a variety of other small proteins to study, because we had the people on hand.

BOHNING: That was another question I was going to ask you. How readily you were able to attract qualified people to work with you?

SMITH: That was no problem. When the work becomes well known people are attracted, if they're interested in the field and in learning the methodology.

BOHNING: What about the networking of people who were working in those early days, especially when it was a small group—the exchange of students and people. How much of that went on?

SMITH: Well, it always goes on. In every field. It went on to a large extent, not necessarily between the people who are in the field already, but between people who wanted to get into the field. For example, when Ted Thompson went back to Australia in 1952, from 1954 or 1955 on until I retired, there was always at least one Australian in the lab, from either Melbourne or Sydney or someplace else. So the connections were established with Australia and a steady succession of people came. This was all new to Australia, of course, but Australia has had a strong tradition of interest in protein chemistry because their leading export for a long time, and may still be for all I know, was wool—a very important protein. The wool research laboratories of Melbourne, Sydney, and elsewhere were stocked with people who were trained in Europe and the United States. Thompson went back to the wool research laboratories in Melbourne, but then later became professor of biochemistry at the University of New South Wales in Sydney, from which he retired just a few years ago. I had a number of people from his lab who came to work with me, as well as from other laboratories in Australia. So that is the way these things happen.

In England, a number of people came to my lab from Oxford, from London, from the laboratory at St. Mary's Hospital Medical School, where Albert Neuberger was professor of chemical

pathology, and Rodney Porter was there also before he went to Oxford. I had at least three or four people from St. Mary's who came either through Neuberger's laboratory or Rodney Porter's laboratory. Rodney Porter was a very close friend, and I supplied the pure papain for his work of chopping up antibodies. So the ties were all there. As I said, Sanger's second graduate student (Thompson) came to work in my laboratory. I don't know how many came from England, how many came from Australia, from France, from Italy.

In some instances, people came from laboratories where there was no tradition of protein chemistry. Today there certainly isn't an important department in this world that doesn't have people who are working on either nucleic acids or proteins or both. This was certainly not true forty years ago when the big interest was still intermediary metabolism. Then everybody had C-14 and worked on metabolic pathways.

BOHNING: When did intermediary metabolism decline in terms of interest?

SMITH: Well, it's still here. It's just gotten smaller and more specialized. I think historically, one can say, initially intermediary metabolism was concerned with the most general pathways. In other words, how do you make glucose, how do you break it down? Every organism uses glucose in one way or another, and the related transformations of other sugars into glucose or fructose are general. The same twenty amino acids are, after all, the building blocks of all proteins. The same four nucleotides go into DNA. So the pathways of working out how you make each of these amino acids, or nucleotides, and how you break them down, is general for all organisms, except those organisms that can't make certain of them. We can only make half of the amino acids ourselves; the other half we have to get from our food.

So these were the first problems of intermediary metabolism that loomed large in the world of metabolism to biochemists. Lysine is important, tryptophan is important, alanine is important, glucose is important, glutamic acid is important. So all of these pathways were the first to be worked out. Then you get into specialized situations, such as what happens in different microorganisms? What happens in plants? Do plants use the same pathways for making, let's say aspartic acid, as does E. coli, or that we do? Those are the specialized aspects. That goes on, and will continue to go on, because there are special and important things that happen in different species.

For example, in plant biochemistry, it has been known for a long time, and I don't recall how it was discovered, that ethylene will make unripe fruits ripen. It was also known that

it requires oxygen. So you could store green bananas, for a long time in an inert atmosphere of nitrogen and they won't ripen. Whenever you want them to ripen, let in the oxygen, and if you add a little bit of ethylene, you'll really speed up the process. It was much later that it was discovered that ethylene is the ripening agent that is made by plants. It is a plant hormone.

I don't think anybody would have predicted fifty years ago that ethylene is made from methionine, a sulfur-containing amino acid with an S-methyl group, a thio-ether. What has that got to do with ethylene? But that's the way that plants make it. Nobody would have anticipated it. But people were studying the synthesis of ethylene as a plant hormone, and finally they worked out that it's a two step reaction—one aerobic and one anaerobic—that ends up with ethylene. So intermediary metabolism will never die; these specialized pathways will continue to be studied forever, because there are special circumstances, special organisms and so on that have to be studied for practical reasons or for theoretical reasons. But the major push for the main substances of all living organisms was really finished around the late 1960s or early 1970s. There are still plenty of unsolved problems. There are still specialized aspects of these problems, but other things have come into the picture.

Another way of saying it, as a philosophy of biochemistry, the old problems don't disappear. It's just that with new discoveries you have new and exciting fields that develop. So the old fields are still around, they're still flourishing, but to a lesser extent. Fewer people are working on them, but on more specialized organisms or organs or tissues the new fields have loomed very, very large indeed. So that's why biochemistry or molecular biology or whatever you want to call it, since I regard both as the same thing, has become the total language of all of the biological sciences. This is where we are.

BOHNING: Who were some of the people who worked with you on the immunoglobulins? We didn't really talk about the individuals who were responsible.

SMITH: The physical studies I did myself, with the help of my technician who ran the electrophoresis and the centrifuge. That was Doug Brown. He was a technician who was trained originally by me at Squibb, and whom I brought to Utah because he wanted to finish his undergraduate work. He took what courses he needed, provided he made up the time on weekends or evenings, so that he would be entitled to full-time pay. After he finished his bachelor's degree, he decided he didn't want to go on to graduate school. He stayed with me for the seventeen years I was in Utah, and then moved to Los Angeles with me. He continued to work for about three or four years after I retired, since he's younger than I am. He's now retired. He did all the work in running all

the electrophoresis and the ultracentrifuge and the other kinds of physical methods in which I had trained him.

Much of the other work on the antibodies was done by a graduate student named Mary McFadden, who did the end-groups of the rabbit antibodies and was responsible for some of the amino acid analysis as well. Since I had recognized that all of the antibodies contained carbohydrate, we decided to look at the carbohydrate and to determine where the carbohydrate was attached to the protein. Some of that work was done by another student named Chris Nolan, also by a student named John Rosevear, and a post-doctoral fellow who did some of the carbohydrate work named John Rothfus. At that point we decided to drop the problem. We got what we wanted out of it, and we showed that the carbohydrate was attached to aspartic or asparaginylnyl residues. The sequences around that attachment are essentially homologous in all the different species: bovine, equine, human, and rabbit. As it turns out, the carbohydrate site has nothing to do with the antibody specificity; it has to do with the attachment of the complement, a recognition site for cells that attack antigen-antibody complexes.

[END OF TAPE, SIDE 2]

BOHNING: You worked in the lab yourself, but did you ever reach a point where you no longer did so? I've talked to a number of people where there's a point, sometimes very early in their career, where they are no longer working in the lab. I had the feeling that Harlan Wood, even the day I was there, was still out in the lab with his students. I wondered what your situation was?

SMITH: My situation was that up until the time of the second edition of The Principles of Biochemistry (26), I worked in the lab. When I first came to Utah, I started out with one technician; later, I had one or two post-doctoral fellows and a student or two. As long as the number of people that I was responsible for was about five or six, and I had no real administrative responsibilities other than running my own lab, I put in a fair amount of time in the lab myself.

Beginning in 1949 or 1950, I was asked to serve on an NIH study section, which meant three meetings a year and a lot of applications to read. I had to travel to Washington three times a year. Then in 1950-1951 we started work on The Principles of Biochemistry, and I was still able to get into the lab a fair amount. But I no longer could carry a problem that required my attention every day. So frequently I was the one who did the organic synthesis of peptides and derivatives. I could do a couple of reactions and then let material crystallize in the

refrigerator for a couple of days. In fact, sometimes it was better to leave a preparation a few days rather than trying to work it up right away. It could sit for a week or two; it still didn't make any difference.

It was sitting there under an organic solvent, well-stoppered. Then when I found time, I could go on to the next step or steps. To carry on enzyme purifications with my own hands became impossible from the early 1950s on simply because they were too unstable. But doing organic work, or doing analytical work of some kind was still feasible. Doing enzyme assays was still feasible because I could let things accumulate.

By the time we got into the second edition of The Principles of Biochemistry, which I guess was in the mid-1950s, I was working every night and every weekend on the book, and the literature was literally exploding at that time. It was the golden age of intermediary metabolism. Then came the point at which the lab was also expanding, in a certain sense because of our successes. The more you publish, the more people want to come; the more people who come, the more you publish. It got to the point around 1954-1955 where I had about a dozen people. At that point I said, "Enough is enough."

From that point on I never had more than ten people in the lab, including post-docs, technicians, and students. I always had two technicians. Doug Brown worked for the whole laboratory, and after we came to UCLA, for the whole department. He did all the ultracentrifuge work and all the electrophoresis work for everybody. I always had one full-time person running the amino acid analysis. I required all the post-docs and graduate students to do the analysis at least once or twice themselves, so they knew what it was about, but I regarded it as silly for a talented post-doctoral fellow to spend time doing routine analysis for several hours every day. They ought to be spending their time doing creative work rather than doing routine analyses or routine running of an ultracentrifuge or electrophoresis apparatus.

So we always had at least two technicians in the lab, and the rest were students and post-docs. Ten became my upper limit, so that I could see what was going on everyday. Whenever I was in town, I certainly made the rounds every single day, and talked to everybody in the lab. When the number of people gets above a certain size you lose touch.

BOHNING: How did you feel about making that transition?

SMITH: It was gradual. There was no real way to avoid it if I were going to continue with my obligations. One of my

obligations was the book. If you do it once, and it's a failure, you say, "Okay," you wash your hands, and to hell with it, forget about it and never do it again. But what do you do if it's a success? The publisher is after you for one thing, and you have an obligation to your co-authors on the other, and financially it was useful. It helped to pay for some college education for my sons. It helped to put away some money for the future, because certainly at that time, in Utah particularly, the salaries were not all that generous, and the retirement situation was pretty poor. Things have improved since. We had a success on our hands, and from that point on, we basically had to do a new edition every five years.

BOHNING: Just as an aside, I discovered that in our collection of the Principles of Biochemistry we have one edition which all of you have signed. I think it came from the publisher.

SMITH: Very likely. We signed slips and they pasted them in. In retrospect, I think the most revolutionary and the most important edition was the third one. By then we had been so successful, and had done such a good job, that there were imitators all over the place. That's what happened. The field exploded. There were a lot more students, a lot more places at which biochemistry departments expanded enormously.

BOHNING: When did [Albert L.] Lehninger come out with his first edition (34)?

SMITH: It was certainly after our second edition, and maybe after our third. Lehninger did a good job. He also used our edition very heavily in writing his. He wrote very well, and it reflected his general interests. Ours was a more diverse kind of interest because we had different people with different interests. He gave us plenty of competition, but on the other hand, our sales didn't suffer all that much. Basically, the field expanded. What surprises me is that even our seventh edition is still selling a few copies, mostly abroad. It is still going on, even though it's out ten years. [laughter]

BOHNING: Is it that long ago?

SMITH: It came out in January 1983.

BOHNING: We may have discussed this last time, but it is probably somewhat of a record for longevity for a textbook of this nature. Thirty years or so, and that many editions.

SMITH: Yes.

BOHNING: I would think it has got to be hard to keep the interest going for that length of time.

SMITH: Obviously, we're finished with it, partly because my original co-authors are all gone. The younger people we brought in, particularly for this last edition, decided it wasn't worth the time. Partly, I suppose, because it's too difficult now; every field is exploding so much. I don't think there's any book that is going to satisfy the market anymore. My colleagues downstairs don't use a book. They use their own mimeographed outlines; the way they teach is quite different.

BOHNING: Do you think there might be a book on proteins, a book on nucleic acids, etc.?

SMITH: Part of what used to be called biochemistry is now taught in the clinic. A large part of physiology is now taught in the clinic. We're talking about teaching medical students. Graduate student teaching is entirely different. There is no satisfactory book for teaching undergraduate biochemistry. My older son teaches undergraduate biochemistry and he says, "Every book is terrible." Students want a book. But you have to pick and choose and then you spend a fair amount of time correcting mistakes.

In a way, this is a measure of our success academically in that salaries have become fairly adequate. Nobody wants to bother writing a book. Books are expensive now. I don't know what the situation is going to be in the future. Probably for general chemistry it's easier, because you've got tens of thousands or hundreds of thousands of people who take general chemistry every year. There can be a few books that are successful, and they don't have to be revised that often because elementary general chemistry doesn't change that much.

BOHNING: My experience is that the general chemistry texts are revised often because the publisher wants to be able to sell new copies.

SMITH: They don't want the second-hand ones around. We used to kid the publishers that they wanted a self-destructive edition. It will explode spontaneously, or become unreadable after X years. [laughter]

BOHNING: That's a good way of putting it.

Getting back to your research, how did your work start on cytochromes?

SMITH: I had been interested in the cytochromes ever since I was in Keilin's lab. After all, he had discovered the cytochromes and their role in respiration. Cytochrome c had become available in pure form before any of the other cytochromes. It was a very small protein. Emanuel Margoliash was one of the first people to apply modern chromatographic methods to the purification of cytochrome c in Keilin's lab, when he was a post-doc from Israel. This meant that you could obtain pure cytochrome c very easily.

I first met him at that time, in 1955. He went back to Israel and was very unhappy because he had a job in cancer research, which was getting nowhere at the time, as cancer research wasn't progressing anywhere at that time. He wanted to get into modern biochemistry. He was in Israel only by a curious set of circumstances. His parents had lived in the United States, and his two older brothers were born here, but his father was in the importing business and decided to move to Cairo to export rugs from Cairo. The family business was in buying rugs all over the middle east. So Emanuel Margoliash was born in Cairo, of all places, even though his parents were actually American citizens. He was educated partly in Cairo, and then at the American University in Beirut, where he obtained his master's degree in chemistry and his medical degree. When things were happening in that part of the middle east he migrated to Israel. He was completely tri-lingual. The schools that he attended in Cairo were French; that was the tradition. American University schooling was in English. His English was flawless. He also knew some Arabic. So he talked to me about coming here, and we arranged a post-doctoral fellowship for him to work at our lab for two years. In effect, he wanted to learn modern protein chemistry.

He came with the notion that there was an inhibitor that people discovered in agriculture (I've forgotten the name of it now) which strongly binds to catalase. Because it very strongly binds to catalase, it is very effective as a herbicide against certain weed plants. He thought of making this herbicide with C-14 and binding it to the active site of catalase and then seeing where the heme group was attached to the catalase. (This is all interesting history as to how things happen.)

When he came to the lab I said, "This is silly, for two reasons. Why tackle a protein of a couple hundred thousand molecular weight, when all you're going to get is a little piece, and what are you going to know after you find out where it's

attached? Second of all, my friend Walter Schroeder at Caltech has already started work on the complete sequence of catalase." Which of course, Margoliash didn't know. Everybody knew what others were working on, and if possible you avoided what anybody else was working on. So I said, "Look. You're the one who isolated pure cytochrome c. How about working on the sequence of cytochrome c? It's nice and small." He said, "Why don't we work first on the heme attachment sites?" I said, "It's silly. You try to do the whole thing. We know how to separate the peptides. You do chymotryptic digestion. Don't do a tryptic digestion, there are too many lysines in there. You'll get tiny little peptides. You want bigger peptides." He said, "Okay."

So we started out that way. After all, we had all the enzymes, we had all the techniques, so he could just go ahead and use them. We started out doing horse heart cytochrome c, which was basically done in about a year and a half. We were just about finished with the chymotryptic peptides and were ready to start on the tryptic peptides when we had a visit from Hans Tuppy from Vienna, who had been Fred Sanger's graduate student. I had met him earlier. It turned out that Hans Tuppy had a graduate student named Gunther Kreil, who was working on the tryptic peptides from cytochrome c. With what he already knew, and with what we knew, we could put together most of the complete sequence. We agreed to let Gunther Kreil get his Ph.D. and finish up the tryptic peptides and see where we were. We would withhold publication until he caught up with us. This was in the winter or early spring of 1960-1961.

In 1961 I was going to an international conference on biochemistry in Moscow and we sent off an abstract, slightly weasel-worded, but indicating that we would present the complete amino acid sequence of cytochrome c. On the way there, my wife and I stopped in Vienna to spend a few days with Hans Tuppy. We got the rest of the sequence and put it all together, (we had corresponded by mail and had it all set out) and we presented it in 1961. Then we published three simultaneous papers in Nature.

Our first paper was by Margoliash and me on the amino acid composition and the chymotryptic peptides (35). The second paper was Kreil and Tuppy on the tryptic peptides (36), and the third paper combined the two for the complete sequence as a joint effort (37). Then, of course, the complete versions we published separately (38). So that's how it got started.

Margoliash decided not to go back to Israel; he wanted a career over here. We arranged that he would go to Montreal to work at McGill University for two years, so he could fulfill the legal requirements of having been a scholar out of the country for two years, and then he could apply for readmission to the U.S. Then he came back to the United States where he worked at Abbott Laboratories for a number of years. So that's the history.

We then went on to study other cytochromes because of my early interest in the evolution of proteins. Back in Connecticut in 1939, I had isolated a whole family of seed globulins from the curcurbitaceae. These were oil-seed proteins from pumpkins, squash, cantaloupe, cucumber, honey-dew melon, etc., all related in the same family. They all store nitrogen in the form of storage proteins. I isolated all of them and determined the composition in terms of arginine, cysteine, tyrosine, and tryptophan. I showed that they were all homologous (39). The sequences were unknown, of course, at that time.

So here was a family of proteins that obviously had derived from a common ancestor. That was my first foray into the evolution of proteins. The cytochrome story was quite obvious. We did human cytochrome; we did dog. We did a number of other species, and after doing a few mammalian species we branched out. It is quite clear that cytochrome c originated very early in aerobic life because it is homologous whether you look at the protein from higher plants or from higher animals, and tracing it all the way back (40). Here is a protein that is at least as old as the ancestral species before the divergence of animal and plant life, which means that this is as old as mitochondria, about a billion and a half years.

BOHNING: That evolutionary interest stayed with you for a long time.

SMITH: Oh, yes. But later I dropped the work on the cytochrome c for the simple reason that it began to become taxonomy, and was no longer of interest as protein chemistry.

BOHNING: Where was your support coming from at this point? Still from NIH?

SMITH: NIH, Rockefeller, and earlier I had some support from the American Cancer Society.

BOHNING: This was still a time when the support was still pretty easy to come by?

SMITH: Very easy to come by. Let's take a break.

[break]

SMITH: This is an anecdote that has to do with the library. It

has nothing to do with science. I was talking to the former librarian, Whit [Whitfield J.] Bell [Jr.], who's now writing a biographical history of all the early members of the Philosophical Society. Some years ago, I was asked by people here at UCLA to give a short talk about the history of the Philosophical Society and the American Academy of Arts and Sciences, when new members were being honored at a reception. Since I was, at that time, the only member of both who happened to be available, I was asked to give a little of the early history. So I read some of it, and discovered that the first woman who had been elected to the Philosophical Society was a Russian named Ekaterina [Romanovna] Dashkova, as a foreign member.

I asked Whit Bell whether he knew anything about her, and he said, "I can't find out a damn thing about her." I said, "Do you have a copy of Alexander Herten's memoirs (41)? He was the great Russian patriot and author back in the nineteenth century." He said, "No." We looked in the library, and there was no mention of Herten. I said, "You know, he wrote a long essay about Dashkova, which I have read. I happen to have the four volumes of Herten's memoirs, including all his occasional papers, translated into English." He said, "Fascinating. We would love to have it." I said, "Okay. When I get home I'll send it to you." So I sent it to him. He wrote back, all excited. He said that as soon as it arrived he sat down and read the whole long essay. So I wrote back and said, "Look. I have a number of other things in the history of science and biochemistry. Why don't I send you lists; you pick out what you want, and I'll send them." So I've been doing this now for a couple of years. I send them lists, and they check off what they don't have. In a couple of cases I've been able to give them first editions when they only had seconds. [laughter]

BOHNING: That's wonderful. That's how many collections are built. You can't just go out and buy some of these things.

SMITH: I happened to have, for example, half a dozen books in English on the history of alchemy. It was interesting to me. I don't read Arabic, but there have been many scholars, particularly in Britain, who wrote about alchemy because they could read Arabic, which I don't. Since I had satisfied my interest in alchemy, I was glad to donate these books. It turned out that they didn't have four of these volumes.

BOHNING: That's amazing. As an aside, one of our board members came down from New York to one of our meetings. I saw him come in the door with a New York Times, and he had a picture frame stuck inside the New York Times under his arm. After the meeting, he said to Dr. [Arnold] Thackray, "This is something

that's been in our attic. I think you should probably have it. My father bought it at an auction in the 1930s." It turned out to be Isaac Newton's family tree, written in his hand. [laughter] It's been appraised at five to ten thousand dollars.

SMITH: I should hope so. [laughter]

BOHNING: It was just stuck in a newspaper, not even wrapped, and he carried it down on the train.

SMITH: That's the best way to carry it. Nobody would assume that it was valuable.

BOHNING: Why don't we continue on with the next area. In 1962 you started on the subtilisins. You had a Japanese come to your laboratory. He actually suggested it, didn't he? Is that how it got started?

SMITH: He came over to learn our methods. By the way, Hiroshi Matsubara has just retired as professor of biochemistry and dean of science at Osaka University in Japan.

He had come to learn our methods, so I put him to work on the sequence of human cytochrome c. In very short order, he had completed the work. He suggested that we study a proteolytic enzyme on which he had done some work in Japan. He thought we might have a look at it from a physical and chemical viewpoint. This was subtilisin.

Now the subtilisins were originally discovered in Copenhagen, Denmark. I knew the whole story, because these people were all friends of mine. Linderstrom-Lang, who had been the director of the Carlsberg Laboratory, had been working on ovalbumin, the protein from the white of the hen's egg. Ovalbumin makes nice needles as crystals. Lang found a batch of ovalbumin that had obviously become contaminated by bacteria, and there were no longer any needles. Instead there were plates. Linderstrom-Lang proceeded to call it plakalbumin, instead of ovalbumin. It was worked out that the proteolytic enzyme from these contaminating bacteria had cut off a piece of ovalbumin, and the ovalbumin had gone into a new crystalline form. So they proceeded to isolate the enzyme from what was Bacillus subtilis and gave it the name subtilisin.

[END OF TAPE, SIDE 3]

SMITH: The isolation and crystallization of subtilisin had been done by Martin Ottesen, a very close friend of mine, who succeeded Linderstrom-Lang as the head of that laboratory. When Hiroshi suggested that we work on this, I said, "Ottesen's working on it. I'm not going to interfere." I immediately wrote to Martin Ottesen and asked if they were planning, or were actually working, on the sequence of the enzyme. They said, "Absolutely not. We're not doing anything with the sequence; moreover, in addition to the Japanese strain, we can supply you with as much as you want of two other strains in crystalline form. The Novo company is making them in large quantities because they're being used in another way." These were the subtilisin Carlsberg and subtilisin Novo.

Now what were they doing with them? Subtilisin was being added to laundry detergents to digest the proteins that weren't being washed out by ordinary detergents. The enzyme was being prepared in hundreds of gram quantities, and we were supplied with all we needed.

Hiroshi started out with BPN', which was the bacillus proteinase neutral (BPN) from Japan. After we did the molecular weight by sedimentation-diffusion measurements and did the end-group analysis and started on the isolation of peptides, Hiroshi had to return to Japan. We carried on with the other post-doctoral fellows, and finished its sequence and started work on the other two varieties. We ended up doing the sequences of four of these enzymes. Two of them turned out to be identical. Whether the Danes stole from the Japanese or the Japanese stole from the Danes, I remain neutral. [laughter] But when two enzymes, supposedly independently isolated in Japan and Denmark, turn out to be absolutely identical, it raises some questions.

Now the fascinating part of the subtilisin story is that here is an enzyme that has the same mechanism of action as trypsin and chymotrypsin from animal tissues, is inhibited by many of the same inhibitors, contains the active triad of serine, histidine, and aspartic acid, but turns out to have a totally different amino acid sequence. It means that you have a beautiful case of independent, parallel evolution. The enzyme mechanism evolved independently and in exactly the same way from different amino acid sequences, different folding properties, and different stability. The reason why subtilisins can be used in laundry detergents is that they happen to be very resistant to denaturation by sodium dodecylsulfate, which is the ordinary laundry detergent these days.

Let me finish up the subtilisins with just one further comment, which is in my autobiographical statement (1). I think the importance of it turned out, in our minds, to be the following: subtilisin Novo and subtilisin BPN', which have almost identical kinetic and physical properties and are almost identical in size, differ only in that there is the deletion of

one residue, in one of them as compared to the other, but they differ in about forty percent of the sequence. That means that most of the structure on the outside of the protein can vary all over the place, as long as it doesn't affect the three-dimensional structure, the substrate binding site, or the active site of the enzyme; it doesn't matter what happens elsewhere. This was the first case of that kind to arise. As long as there is the proper backbone for folding, and you make the proper conjunction of residues in the active site for specificity and for enzymic or catalytic activity, it doesn't matter what you have in the rest of the sequence. This, of course, is now the lesson that people are following-up synthetically in trying to make artificial enzymes by these methods.

We're coming into a new type of synthetic organic chemistry, of making enzymes, but not necessarily by duplicating the exact sequence because you don't need to do so. Put in the easy residues where you don't need that kind of specificity. Do the difficult residues where you have to put them in. People are making all kinds of chain-folding experiments using alanines and leucines and things which are easy to handle synthetically because they don't have highly reactive side-chains. Things that have highly reactive side-chains like histidine and tyrosine and tryptophan are going to give trouble. They have to be handled more carefully, and the yields are always lousy.

That is now the new importance of the subtilisins, and subtilisin is now a large industry. Most of it is being made in Copenhagen by the Novo company. They are also making huge quantities of amylase to go with it. Starches don't wash out well with detergents, so they add amylase to digest the starch down to smaller oligosaccharides which wash out into water very easily. The combination of things that you spill on a tablecloth that you want to remove are protein stains with starch or lipid. The detergent will take care of the lipid. To get rid of all the proteins and polysaccharides you need some enzymic help. This is now a whole new industry, which was very useful for me, because I was a consultant to Proctor & Gamble for ten years on the properties of subtilisins and other enzyme studies.

BOHNING: Prior to that time then, was it felt that the entire sequence had to be the same?

SMITH: Nobody knew. The largest series of proteins whose functions had been studied were the hemoglobins. All animals that have red blood have hemoglobin, and the properties of hemoglobins differ in different classes of animals. Do the animals live at high altitudes or low altitudes? A parasitic worm has a high affinity for oxygen, whereas organisms with high demand have a low affinity for oxygen and it is readily released. It was known that all these hemoglobins have very different

properties, but how much of it was due to the functional differences which are essential, and how much was random, was not known.

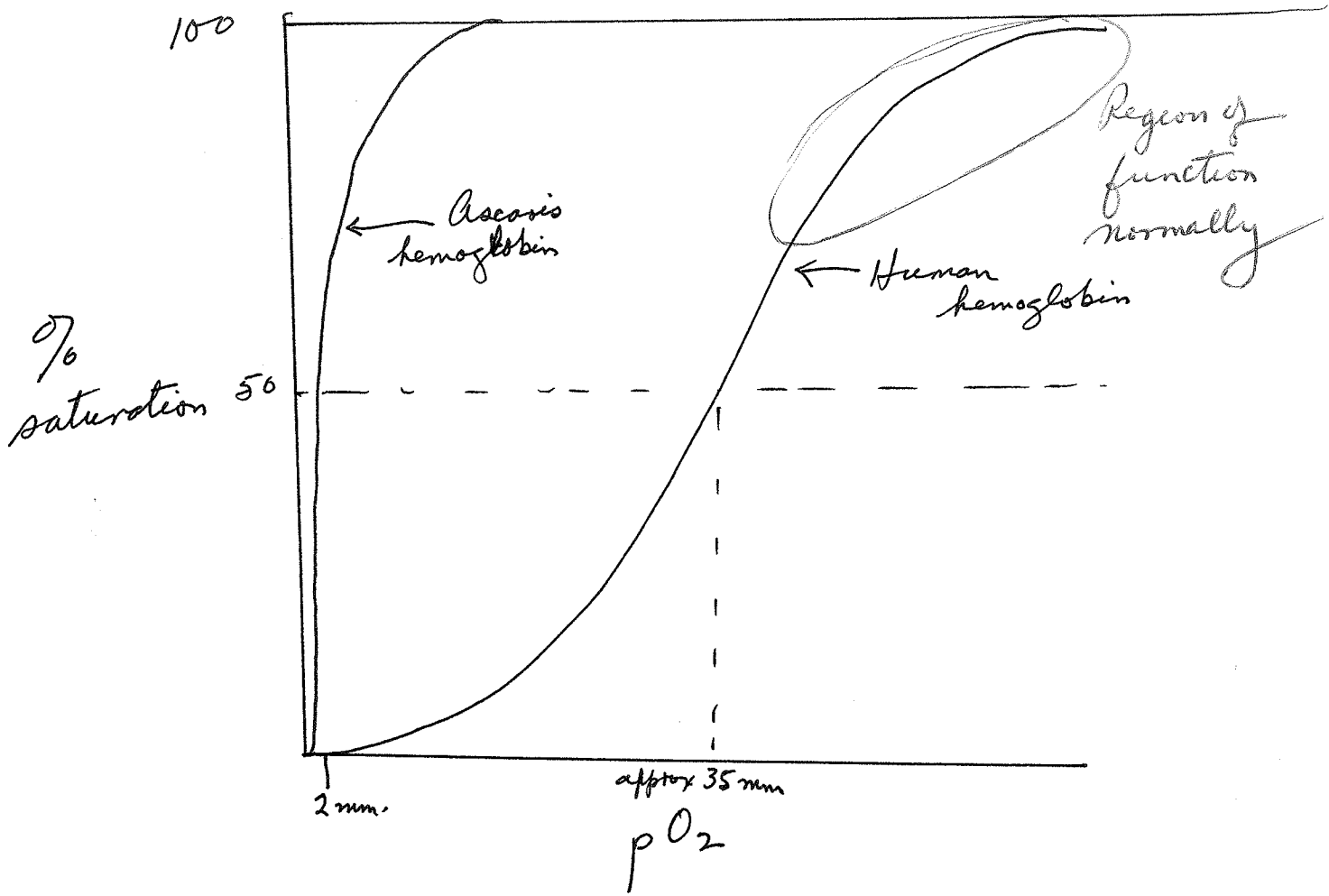
In fact, in the last PNAS, Proceedings of the National Academy, there is a fascinating paper (42). Human hemoglobin has an "S" shaped curve—this is partial pressure of oxygen and this is percent saturation. In the lungs we put on a full load of oxygen, in the muscles we take it off down to here. It goes back and forth in the circled region [see diagram, following page]. You wouldn't want the hemoglobin to have a higher affinity for oxygen or it would never release the oxygen when needed. So this is the area in which it functions. The parasitic intestinal worm Ascaris—a round worm—has an oxygen binding curve with a very high affinity for O_2 . It gives up its oxygen only in extreme situations where there is little oxygen available.

Why does Ascaris hemoglobin have such a high affinity? It turns out there is a difference of one amino acid residue near the active heme where the oxygen binds to iron. The iron binds to a histidine nitrogen (as well as to the four heme nitrogens) and in Ascaris hemoglobin, the iron is loosely hydrogen bonded to another residue, whereas in human hemoglobin, the sixth coordination space in the iron is essentially vacant. It is due to a difference in this region that makes the difference in affinity. The rest isn't the same, but it doesn't matter. This has just been worked out by X-ray crystallography. By changing this residue into the one that occurs in most mammalian hemoglobins, it no longer has this high oxygen affinity; it now has a more normal oxygen affinity like that of human hemoglobin.

This is what we're still learning. You follow what I'm saying.

BOHNING: The histones are next. That started in 1967 when [James] Bonner from Caltech asked you to get involved, if I remember that correctly.

SMITH: That's right. I met Bonner at the National Academy Meeting. Bonner was an old friend, and still is. He suggested we have a look at the histones. He convinced me that he had pure material for a study of the sequence and we agreed. We worked simultaneously on both the one from bovine thymus, which was the standard material, and from pea seedlings. It turned out that the small protein (Histone 4) differed in only two amino acid residues. It is the most conservative of all known proteins, comparing an animal and a plant protein. This is the key to the fact that the histones are crucial for maintaining chromosomal structure, very conservatively so. As we now know, histones occur in a four-fold complex with four different kinds of histones. They form a very important tight core structure on



which the DNA is wound. So we did the histones of two different types—Histone H4 and Histone H3. It was interesting in terms of the evolutionary history more than anything else. We never got involved in the functional side of the histones, because that essentially was Bonner's problem and those of other people. We weren't going to go into that kind of study.

BOHNING: Someone has attributed to you the comment that "we are all brothers under our histones."

SMITH: Yes. This happened in a very curious way. Before this work had been published, I had been invited to give the Ciba Foundation lecture in London on the basis of our work on cytochromes and other proteins. I gave this lecture on the evolution of proteins starting from the beginnings of our studies on the cytochromes, the subtilisins and others. When I came to the histone story, which nobody in the audience knew, there was actually a gasp from the audience that there were two almost identical proteins, with only two very conservative amino acid substitutions as the difference between the animal and the plant protein. I thought up spontaneously, that "obviously, we are all brothers under our histones," and the audience broke up into applause. [laughter] "We need not feel superior." It got quoted in Nature at the time (43).

BOHNING: Who was working with you at the time?

SMITH: Bob [Robert J.] DeLange. Bob DeLange had worked with me as a post-doctoral fellow on subtilisin Carlsberg. He was just finishing that up when the histone possibility came along, and I asked him whether he would be interested in taking a look at the structure with me. We drove over to Caltech to discuss the problem and then started work on it. Bob DeLange stayed on and worked on the histones, and then independently as a colleague he remained in the department, working on many other problems. Incidentally, he came as a post-doctoral fellow after working with [Edmond] Fischer and [Edwin] Krebs at Seattle, who got the Nobel Prize two years ago. They owed me one because I had sent them as a post-doctoral fellow Chris Nolan, who proceeded to work out the sites of phosphorylation on their enzymes. [laughter] That's the way the world is.

BOHNING: You commented about the increasing number of people wanting to come here. What made your group so attractive?

SMITH: I can't say that. I don't know that. I think that all of the people who were active in the protein field at that time

also became very popular. I think that's really part of the story, because I think that people were flooding into all of the laboratories that were successful in doing protein structural work at that time.

BOHNING: Did you have any uniqueness compared to the other groups?

SMITH: I think that all of the major methods rapidly became commercially available to everybody. In the early 1950s there might have been a gap of a year or two. By the 1960s I don't think this was true any more. For example, when we started to set up two-dimensional paper chromatography, we had to design and have tanks built to our specifications. Then tanks became commercially available. When we started to do paper electrophoresis on a large scale we designed and built our own equipment, except we bought high-voltage power packs, of course. Within a year or two, such equipment was generally available commercially. In fact, after our jerry-built home-made equipment began to wear out, we just discarded them and bought whatever we needed.

I don't think it was a matter of methodology any longer. As far as doing column chromatography was concerned, or using fraction collectors, everybody bought the same things. There were different ones on the market. We had some of the early ones. Amino acid analyzers kept improving year after year with lots of competition. We certainly had been successful with a number of proteins, but so were other people, and they were busy. Hans Neurath had a big full lab going. Stein and Moore obviously had a big full lab going. We did. Others did. I had international connections through my early students, having had somebody who went back to Japan to become an outstanding investigator, or to Australia, or to London, or to England generally. They would send their students. It got talked around, I'm sure.

BOHNING: You had already decided not to go beyond ten. You wanted to limit your group as well.

SMITH: That's right.

BOHNING: Were you involved in any of the aspects of the commercialization of these techniques? Did you consult with companies who were involved?

SMITH: I left Squibb in 1946. In 1949 they tried to get me back

as head of a division and I said no. But they hired me back as a consultant. I remained as a consultant with them for twenty-five years on general biochemistry, not just on proteins or enzymes. It obviously was useful and fruitful for them because they continued the relationship for a long time. I not only helped them with a number of their internal research problems, but I also helped them in hiring people. Sometimes I helped them by telling them to avoid mistakes. When people would come from the outside with research problems, I would be consulted on whether the problem was worth following up. Sometimes you can save a company a lot of money if you say no. [laughter] "Don't waste our time."

When the subtilisin work came along, we published our first paper (44), a preliminary note in the JBC giving the sequences of two subtilisins at the same time. That had never happened before. I got a call from Proctor & Gamble; they wanted to talk to me about subtilisin. Could they ask me some questions? I knew what they were after. So I agreed that I would be willing to consult with them, but my fees were steep. I knew exactly what they wanted. They sent a man out here, and they wanted to know how to stabilize the subtilisin in detergent. I could tell them right off the bat. I saved them tens of thousands of dollars of labor, and a hell of a lot of time. In any case, they still do a good business with BIZ, which is their brand of subtilisin plus amylase plus other things. I consulted then with them on a variety of problems for about ten years; then I got tired of traveling and said, "Enough is enough."

BOHNING: What about the companies who were making the equipment that was being used in these techniques? Did they ever contact you?

SMITH: They contacted me, but much of our improvements were minor. We were not the originators. Moore and Stein had originated the automatic amino acid analyzer, and they built the first really successful fraction collector at Rockefeller. We improved on a number of these things and a number of procedures, but we were not the creators of any of those methods. Compared to many other laboratories, but not exclusive with us, was the fact that we always had on hand six or eight pure proteolytic enzymes which we could use for degradation of proteins or peptides. We had prepared these ourselves before they were commercially available. Later they all became commercially available, but we had prepared carboxypeptidase, trypsin, chymotrypsin, papain, leucine aminopeptidase and so on. We had a battery of enzymes. When Emanuel Margoliash came to our lab, he never prepared a single enzyme. [laughter] They were all available. He could use them. So could other people. Of course, this is what made it easy. Somebody came into the lab and had all this stuff available.

BOHNING: Who were the companies that became the big players in commercializing and making these available so that you didn't have to make them yourself? Sigma?

SMITH: Sigma was one. Worthington Biochemical, which subsequently got bought up by somebody else, made trypsin, chymotrypsin, carboxypeptidase. Charlie Worthington had been [Moses] Kunitz's technician at the Rockefeller when these things were all first purified. When Kunitz retired, Worthington went into business. Somebody put up the money. I've forgotten who took it over.

Later on, a lot of these things became available more cheaply from Europe. For example, the first bovine glutamate dehydrogenase that we used, we made ourselves, but later on we bought it from Germany. It was available in gram quantities; it was cheaper to buy it than to make it. We checked the purity, but that's about all we did. In the early days we prepared many amino acids, or we bought them from American suppliers, and in later years all of this stuff was available from Japan much more cheaply.

BOHNING: Why didn't the Americans pick up on doing this themselves, before the Japanese or the Germans?

SMITH: Cost. We're talking about before the period before inflation in Germany, when things were a hell of a lot cheaper. You never know how things were going on behind the scenes. For example, in 1976 I was at a symposium in Riga, Latvia, then part of the U.S.S.R. I visited the Institute of Organic Chemistry and discovered that the main support for that institute was making important organic chemical synthetic precursors for the German chemical industry. The Germans were farming it out to a place where it was cheaper to make many compounds. The Institute at Latvia was doing very well out of it because they were getting foreign currency to buy all the equipment they needed. As far as the U.S.S.R. was concerned, there was more shortage of foreign currency than of domestic currency, and if you could sell all of this stuff abroad, you could pay a certain amount back into the academy coffers, but much of it you could use yourself to buy your own equipment.

Later on I discovered that one of the big laboratories in Moscow was making recombinant insulin and selling it to the Japanese. Human insulin. A lot of these things go on that we don't know about. Something comes in with a label, but you're not aware of where it was actually made. It's like buying anything from Hong Kong. The chances are ninety-nine percent it

was made in China, not in Hong Kong. Before 1973, if it was made in Hong Kong it could come into the United States, but if it was made in China, it couldn't come into the United States legally. [laughter] So the world of commerce has its own rules.

[END OF TAPE, SIDE 4]

SMITH: I asked one of my friends in China in 1973 (but whom I had known before), "How did you manage to keep your lab going, and all the people in the institute functioning, at the time of the Cultural Revolution, when many of the people in the science institutes and in the universities were being sent out into the fields?" He said, "It was very simple. We set up a factory to make chemicals and biochemicals. We were supplying all of the necessary materials for the clinical laboratories in the hospitals. Since we didn't have the foreign currency to buy things from abroad anyhow, we'd have to prepare all our own biochemicals, like our own amino acids, enzymes, coenzymes and so on. In that way I could hold my laboratory together. We built a new factory, a four story building, to make chemicals for everybody in China." As far as I know, that factory still functions. When I came back from China in 1973 I had his price list. [laughter] Later on, they were selling supplies to other countries. They were supplying much of Southeast Asia with these chemicals. For all I know, they may have even been supplying the Japanese. Who knows?

But don't forget, the Japanese have always had a big fermentation industry. After all, soy sauce is fermentation, and a major ingredient of soy sauce is monosodium glutamate. When I was at the Rockefeller, we used to buy our glutamic acid in the form of monosodium glutamate from Ajinomoto, which they isolated from their soybean fermentation. The way we got glutamic acid from monosodium glutamate was to add hydrochloric acid to it, precipitate it with alcohol to get rid of the sodium ion, and there we had it. Today, you'd put it through a column to get rid of the sodium ion, but in those days we had pure glutamic acid coming from Japan. We're talking about 1940. So the Japanese had their fermentation industry, and their sauces were prepared by using aspergillus, a fungus whose proteolytic enzyme hydrolyzed the soybean protein. The amino acids were all there.

You want to isolate them? These days you just put them on a column and isolate all of them. Then they discovered that the so-called mushroom flavor is inosinic acid, which is after all a derivative of adenylic acid. That's what artificial mushroom flavor is, inosinic acid, as they sell it. It's all Japanese.

So the industrial side of all of this has played an important role, and I'm sure the institutes in the Soviet Union are making even bigger deals now to survive. They make chemicals and they get money from it.

BOHNING: But didn't the Japanese activity that you're talking about really start after World War II?

SMITH: It started before World War II. As I said, we were buying monosodium glutamate in 1940 when I was at the Rockefeller, and the war started in December 1941.

BOHNING: What effect did the War have then?

SMITH: It cut off the supplies, and there were then American companies making many of these things. Japan got cut off during the war.

BOHNING: What happened after the war?

SMITH: Japan flooded the market. They had cheap labor and the fermentation industry. The fermentation industry in this country was interested in big money, like making penicillin, or streptomycin, or the equivalent.

How did Pfizer become such a power in the antibiotic business? Pfizer was a small business in Brooklyn, New York when the Russians published their way of using fungi to make citric acid. Citric acid is the important ingredient in making soda pop. Soda pop in the old days, when I was a child at least, consisted of carbonic acid, with a little citric, and a little phosphoric acid. Plus, sometimes, a little citronella from lemon peel to give it a lemon aroma. That was lemon soda. When the Russian fermentation chemists learned to inhibit the fungus so that it accumulated huge amounts of citric acid, Pfizer picked this up. They were in the fermentation business making citric acid for the whole soda pop business in the United States. But they had the aerobic fermentation facilities needed to make penicillin. That's why they were dragged into the penicillin business in 1941 or 1942. That's the story. From then on they were a pharmaceutical company. I don't know if they still make citric acid.

BOHNING: Let's return to your research. In the glutamate dehydrogenase work, you were looking for something different again.

SMITH: We looked for something different again. Now that we had the techniques and the methods for studying smaller proteins, it

was time to go on to something bigger and of a different kind. At that time, the amino acid sequence was unknown for any dehydrogenase. I picked glutamate dehydrogenase partly because it was easy to prepare, partly because it was easy to crystallize, and partly because it is one of the key enzymes in all organisms. It is a very crucial enzyme. It is the only dehydrogenase that works on an amino acid in mammalian systems. There are other dehydrogenases in various microorganisms that work on amino acids, but in general in mammalian metabolism, l-amino acids are degraded by transamination to make the alpha-keto-acid, and the amino groups are transferred to alpha-keto glutarate to make glutamate. Glutamate is the one that's then dehydrogenated. The product, alpha-keto glutarate, which is a component of the Krebs cycle in mitochondria, is then oxidized or it is again available for transamination in both cytoplasm and mitochondria. So in that sense glutamate is the central amino acid in all of mammalian metabolism. That's why we started our study of the enzyme.

We also knew that it had four peptide chains and that each chain had a molecular weight of about sixty thousand. We had been dealing with proteins in the twenty to thirty thousand molecular weight range; now we were going to make the jump to peptide chains of double the size. It was evident that the four chains of glutamate dehydrogenase were identical.

By the time we were well along in our studies, we realized that other laboratories were also studying dehydrogenases. A group in Cambridge was studying lactic dehydrogenase, another group was studying triosephosphate dehydrogenase, and so on. But that's basically the story.

BOHNING: This also continued your evolutionary interests.

SMITH: The evolutionary story came a little bit later. An important point about mammalian glutamate dehydrogenase is that it was known from work before we started that the enzyme is very strongly regulated in its activity. ATP or GTP strongly inhibit glutamate dehydrogenase. ADP or GDP strongly activate it. This is predominantly a liver enzyme, although it is found in other tissues as well. Our livers are activated to destroy amino acids when energy is in short supply when you need to make the triphosphates. You conserve amino acids when energy supply is plentiful, principally being derived from carbohydrate or lipid metabolism. Here we had an enzyme in which we could think of three different kinds of sites to investigate—the active site where dehydrogenation would take place and transfer the hydrogen to the coenzyme which would be NAD or NADP, the site where the triphosphate binds to inhibit, and the site where the diphosphate binds to activate. These are called allosteric sites because they are not at the active site. They change the conformation of

the enzyme to increase or decrease activity. So this presents a different kind of challenge than simply studying a proteolytic enzyme which is not regulated. By the time we had finished the sequence, we had done some labeling, so we actually knew one of the inhibitory sites, and had a suspicion as to where the activating site was, and this became an interesting story in itself.

The only reason that I went immediately on to study the chicken enzyme is that one of my colleagues in the chemistry department is an X-ray crystallographer. The mammalian glutamate dehydrogenase gives terrible crystals; the small needles are utterly unsuitable for crystallographic study. But the chicken enzyme looked as though it would give good crystals. So we said, "We'll take a look at the chicken enzyme because this will help the crystallography." It turned out it was fairly easy to do the chicken enzyme, because it is so homologous to the bovine enzyme. By the time we had finished, it turned out that the chicken enzyme crystals were no damn good either. So we dropped it.

Then we went over to Neurospora, because Neurospora, like many microorganisms, unlike vertebrates, has two different enzymes that work on glutamate. They have an NAD-specific enzyme which clearly is involved in energy supply, because NADH specifically is oxidized in the mitochondria through the cytochrome system to produce ATP. The other type of dehydrogenase is a synthetic enzyme, because most plants and most of the organisms that make their own glutamate use the NADPH enzyme. In other words, they used the reduced form of the coenzyme to supply the hydrogen for the reduction of alpha-keto glutarate and ammonia to make glutamate. That's the synthetic pathway. For example, E. coli, which makes its own glutamate, has only the NADPH enzyme. All organisms that have only one glutamate dehydrogenase that is used synthetically use the NADPH enzyme. It is a generalization for all dehydrogenases that those that use NADPH are synthetic; those that use NAD for substrates supply energy through the ATP mechanism. That's why we started to study both. It turned out the NADPH enzyme is small and is homologous to the vertebrate enzyme. The NAD enzyme of Neurospora is quite different.

So we ended up doing both, which took a long time, and of course that was the work that I was doing as I was scaling down the laboratory, getting ready for retirement. That was our last job.

BOHNING: Who was working with you on that?

SMITH: The two people principally who worked on the NAD enzyme were Brian Austen, who was from England, and who's back at St. George's Hospital in London as a research biochemist, and Maggie

[Margaret E.] Haberland, who is now in our department of medicine as a research biochemist in the division of cardiology.

The role of glutamate, why mammals have an enzyme that works on both, is a good story in itself, but it has nothing to do with us. That's metabolic biochemistry.

BOHNING: How much contact did you have with undergraduates? Did you have undergraduates working in your group from time to time?

SMITH: We would occasionally have a summer student come in who usually had some good training in chemistry, but generally working with one of the people in the lab, not directly with me. I had no real contact with undergraduates here at UCLA, except occasionally when I was a guest lecturer for somebody in one of their courses. At Utah I also had very little contact with undergraduates. I really didn't teach undergraduates from the time I left Columbia in 1938.

BOHNING: I have a number of questions relating to what I'll call your "extracurricular" activities. But before we look at that, is there anything else along the lines that we've been discussing that you would like to add?

SMITH: No, I think the scientific information is all in the reviews. The personal information I think you got pretty well before. I think that covers it.

BOHNING: In terms of some of your extracurricular activities, there are three in particular I was interested in. One goes way back, and that's the International Union of Biochemistry and your activities in a number of places there, especially international conferences. Do you have any comments about those years?

SMITH: I got involved first in 1957 or 1958. I had been appointed to the U.S. National Committee for the International Union of Biochemistry, which was made up of representatives nominated equally by the biochemistry division of the ACS and by the ASBC. These were the two different organizations of biochemistry in the U.S. It was done through the National Academy, who always appointed one additional member. The chairmanship was the senior person from the group to succeed the previous chairman from the other group. It so happened that the turn came of the representative nominated from the ASBC, and the senior person was Connie [Conrad A.] Elvehjem. He became president of the University of Wisconsin and resigned. He had no time to spend on the U.S. National Committee, so I became

chairman of the committee.

As chairman of the committee I automatically became a delegate to IUB at the next general assembly, which was going to take place in Moscow in 1961. In the meantime—the history is an amusing one—the last previous congress in chemistry in the U.S. was in 1951, during which we were embarrassed by the fact that our state department refused to give visas to a large number of Europeans to attend the conference. This was the [Joseph R.] McCarthy period. We in biochemistry had made up our minds that we were not going to hold a congress in the United States until this situation changed, even though by that time we were by far the dominant country in the world in biochemistry. The previous congresses in biochemistry had been held in Cambridge, Paris, Brussels, and Vienna. This all started after the war, because prior to the war biochemistry was included in the physiology congresses. A separate union was set up after the war when the physiologists didn't invite biochemists to the first post-war congress.

So the question was whether things were changing now that John Foster Dulles was dead and Christian Herter had become Secretary of State. It was the last days of the Eisenhower administration. We decided that we could have a congress in the United States if there was a clear indication that there would be no problems with visas. One day when I was in Washington, together with the foreign secretary of the Academy [Harrison Brown] and a couple of other people, an appointment was arranged to meet with Secretary Herter. We got along very well, because I reminded him that his uncle, for whom he was named, had been the founder of the Journal of Biological Chemistry, and that in reading the minutes of the early history of the JBC and its expenditures, his nephew had been paid some money for helping to wrap and mail the first issues of the JBC. [laughter] He laughed like hell. [laughter]

Of course, he knew what we were coming over to see him about, and we then presented the problem. It had been a terrible embarrassment for us and for our country, to go through a situation where a very large number of distinguished scientists from various countries had been kept out of the United States in 1951. It wasn't the Russians who were kept out. It was people from France, many of whom had joined the communist party during the underground, like Jacques Monod. It was people like Pehr Edman in Sweden who had circulated the petitions to stop above-ground nuclear testing. Anybody who signed those petitions had been blacklisted by our State Department. We had a long list.

I was on the executive board of the biochemistry section of the ACS and I had been responsible for organizing two symposia in 1951. It was the twenty-fifth anniversary of IUPAC and the seventy-fifth anniversary of the ACS. The first week was ACS. The following week was IUPAC. They were consecutive meetings. I

organized two symposia, one for the ACS and one for IUPAC. The sole responsibility as a member of the executive committee was to work, to organize a symposium.

The symposium on the ACS side was no problem. They were all Americans. For the symposium that I organized on the IUPAC side, two of the people that I invited were blacklisted including Edman. I got a telephone call, "You've got to fill up the program." I said, "Like hell I'm filling up the program. I'm not going to fill up the program. I'm going to get up there and announce why our speakers aren't coming." In the case of Pehr Edman, I pointed out that Pehr Edman had been a post-doctoral fellow in the United States for a couple of years, working at the Rockefeller, and was now not allowed back, and explained the reason why. So that's the way I and others dealt with the problem.

I explained all of this to Mr. Herter, who obviously knew nothing about it. He said, "I assure you that any qualified biochemist who wants to attend the biochemistry congress in the United States will be given a visa, even if it's only a limited visa for the time of the congress." I said, "That's all I can ask. I can't ask you to change laws. I can ask you to make it feasible." So we held the first major congress in the United States after the McCarthy period.

I went to Moscow in 1961 and invited the congress to be held in the U.S. in 1964. We signed contracts for I don't know how many thousand rooms in the New York Hilton and in the Americana, which were still holes in the ground. [laughter] It was the only way we could get enough space in mid-town Manhattan at that time.

Previously, we had looked all over the United States. It was the only place where there were enough beds and enough hotel space for a congress of this size. It was going to be in New York, and there were two brand new hotels going up where we could hold the entire meeting. We signed the contract and went to Moscow with a letter of invitation from the Mayor of New York City and the Governor of New York State. It was accepted, and that was it.

Then came the time to plan the meeting in New York, and I appointed Stanford Moore as chairman of the local organizing committee. He was on the spot and could do it. We appointed the committees to select the invited speakers and to arrange things. The most amusing part of the story was to arrange the finances. Europe was still pretty poor at that time. Japan was still pretty poor at that time. Most of the world was still recovering from the war years. We knew that the only way we would get any young people at the meeting was to pay travel, and to try to get inexpensive space for them to stay. We had a meeting of the executive committee of the congress to decide how we were going to handle finances. I wrote the applications to the NSF and the NIH. We also decided we wanted to do some reasonable entertaining. The travel help for invited speakers was easy; we

could use NIH or NSF money for that, because that was for the benefit of American science, that we have distinguished speakers from around the world.

The younger people couldn't be justified in any way. So Mel [Melvin] Calvin, bless his soul, came up with a bright idea. We were meeting at the Academy in Washington and Mel said, "Let me call Max Tishler," who was research director at Merck, "and explain the situation." Mel Calvin came back twenty minutes later and said, "Max Tishler has agreed to serve as chairman of the finance committee, if he is allowed a free hand to appoint the members of the committee himself." We said, "Of course." Later on we found out what Max had done was to appoint as members of the finance committee the research directors of all the major pharmaceutical and chemical firms in the United States. He called one meeting and explained what the situation was as to why this was the first chemistry congress since 1951 and the first biochemistry congress; he assured people there that there would never be another one in our lifetimes.

[END OF TAPE, SIDE 5]

SMITH: He explained the situation, and said, "We've got to have entertainment. We've got to make it a good show. We've got to make up for lost years. On behalf of Merck & Co. I am authorized to start the ball rolling with a contribution of \$100,000." [laughter] Whereupon a number of chins dropped, [laughter] and they all said that they had to go home and see what they could come up with. We ended up with over two million dollars. There were quite a few companies that came across matching Merck, others with \$50,000, or \$25,000, all the way down the list. On that basis we were able to hire the Boston Symphony for a concert at Philharmonic [now Avery Fisher] Hall. We couldn't get the New York Philharmonic because they were touring somewhere in Europe, but we got the Boston down from Tanglewood. We opened up the Metropolitan Museum in New York. We arranged ten banquets simultaneously for the ten major symposia we organized. We had proteins, lipids, amino acids, all the topics. Each topic had a banquet. I was the host of the protein and enzyme banquet. These were all at expensive private restaurants. We ran a good show. That's what this all paid for. Plus the fact that we gave all student applicants who were qualified, round-trip excursion fare from home-base to New York and return, plus a per diem which allowed them to stay at inexpensive hotels for which we made the arrangements. So we had a lot of younger people. Everybody says this was the greatest congress ever organized. Nobody has ever done the kinds of things we did. The next congress, by now titled International Union of Biochemistry and Molecular Biology, will be in San Francisco in 1997. Ironically, the chairman of that organizing committee is my former post-doc Bob [Robert L.] Hill, who watched me and Philip Handler go through all of this

because he was in my lab and then with Handler when we did much of the preparation for the congress of 1964.

In 1961 or 1962, Harrison Brown, who was then foreign secretary at the National Academy, decided to create an advisory committee on all international organizations and programs through the Academy. He appointed me a member of that committee because of my experience with the IUB. After a year or so, he made me chairman of the committee because the previous chairman, Al [W. Albert] Noyes [Jr.], had decided to retire from international work. Al Noyes had been the editor of the JACS for many, many years. We became very good friends, and he said, "You have all the younger contacts, and I know all the has-beens. You take over." So that's how I got involved in international affairs and that lasted for a long time.

BOHNING: In the 1951 meeting, when you refused to fill the gaps, and made the public statement as to why the people weren't there, were there any repercussions?

SMITH: Other people did the same thing. A few people filled the gaps. There were no real repercussions that I heard about. It was an embarrassment, and that was it.

BOHNING: I was just curious about whether the State Department had heard about it.

SMITH: When I later became chairman of the advisory committee on international organizations and programs, we tried to get the Chinese from China to come to our meeting in 1964. We wrote letters inviting them, but we never got any answer from our Chinese friends. In fact, when we sent out the letters from my office here, they were returned by the post office as "undeliverable." That's what happened to mail addressed to China at that time. So we took the same letters and put them in new envelopes. I mailed them over to a friend of mine in London and asked him to put British postage on them and send them to China. We had the names of six or eight leading Chinese, three of whom I knew because two of them had worked in Cambridge in Keilin's laboratory. The third one had worked with another friend of mine in Cambridge. So they all got invitations. I was told when I went to China in 1973 that they got the invitations but there was nothing they could do about them.

In 1972, Mr. [Richard M.] Nixon decided to open up China. In the meantime, we had been agitating to try to get the Chinese involved, with no success, but finally in 1973 things did happen.

BOHNING: I wanted to ask you about that trip to China because you met with Chou En-lai at that time.

SMITH: Yes. In 1970-71, we had created in the Academy, with the cooperation of the American Council of Learned Societies and the Social Science Research Council, a committee called the Committee for Scholarly Communication with the People's Republic of China. This was wishful thinking. We had a letterhead, and we had a mail-drop at the Academy to let the Chinese know that whenever they were ready, we were also. We tried to get in touch in various ways. For example, on a trip to Sweden I talked to Arne Tiselius, who had been invited by the Chinese and had made a tour of China. I told him to write the Chinese and let them know that whenever they were ready, we were ready to open negotiations and either meet on neutral ground or they would be welcome here. They got the word. I also had done this with a friend of mine who was then the director of the Ciba Foundation, who had been to China. So they got the words. They weren't ready, but we were available.

In the meantime, I was chairman of the advisory committee on international affairs, but I refused to serve on the China committee because it wasn't doing anything. There was no point in my being attached to the committee. In fact, the man we had as chairman of the committee was a China scholar from Columbia. In 1971 he died suddenly, and Harrison Brown asked me to take over as chairman because he thought a chairman from the social sciences was the wrong message. The Chinese would be more sensitive to that than to a natural scientist. It looked as though the Cultural Revolution was receding a little in China, because the word had come around that some Chinese were visiting Europe. So I said, "Okay." Then in 1972 we got word that a full-fledged Chinese delegation was planning to visit France and Canada. In the meantime, Kissinger had made his trip to China, and there was talk about Nixon visiting China. So we wrote to the Chinese, inviting them, if they were going to be in Canada, to come and visit us in the United States. After the Nixon visit, we got a reply saying, "Yes." So I flew to Washington, and they came down from Canada. We had a reception for them at the National Academy, and they visited laboratories in New York, Boston, and Chicago, and then out to the west coast. In the meantime, I had to get back to teach, so after I saw them in Washington, I flew home. Then in their final stop in San Francisco, my wife and I flew up and stayed in the same hotel with them. We made the trips together to Berkeley and Stanford.

That's when they arranged to invite us to send a delegation to China. Harrison Brown and I very carefully selected a delegation that would appeal to them. There were a few people from the humanities and the social sciences, but mostly natural scientists. We picked George Harrar, the retired director of the Rockefeller Foundation, who had created the green revolution; he

was one of the world's great agronomists. We selected Glen Seaborg; we knew the Chinese were interested in atomic energy and its uses. We selected Carl Djerassi, who was one of the inventors of the pill. The President of the Social Science Research Council and the President of the Council of Learned Societies were invited. Then we invited a number of people who would be useful to us, like Max Loehr, who was the retired curator of the oriental art collections at Harvard who had lived in China for nine years doing art history work. We invited Al Feuerwerker, who was professor of Chinese history at Michigan and whose wife was Chinese. We had on our delegation six or seven people who spoke and read Chinese. Our delegation of seventeen or eighteen people went over to China. We spent a month there, basically from May fifteenth to June fifteenth, 1973. It was in the course of that meeting with Chou En-lai that we agreed on a scientific exchange program. That's history.

BOHNING: What was your feeling as you talked to him or interacted with him?

SMITH: Very exciting. He was undoubtedly one of the brightest people I have ever met in my life. We followed protocol. I would speak in English and it would be translated into Chinese. He would speak in Chinese, and it would be translated into English. While the translations were going on, he and I were speaking in English, as we sat next to each other. He spoke English with a very strong accent, a rather guttural accent, but he clearly understood every word because when the translator, Nancy Tang, who was a graduate of Vassar, didn't say precisely what he had said in Chinese, he corrected her. [laughter]

He made it very clear that they were ready for scientific exchanges, but were not quite ready for exchanges in current history and the social sciences. He said it would come, but not yet. There was no problem whatsoever with archeology, anthropology, ancient art history, or any of the sciences. "You work out the details with my colleagues. But the other things will have to wait a bit." He was already a pretty sick man at that time. As we now know, he was dying of cancer, and he died a year or so later.

While the translations were going on, he asked me to identify all the people by face from our delegation. So there came a point when he was talking about some point of history or science, that he was looking directly at that person. He talked about them. He had the full dossiers memorized of every single person on the delegation. After this was all over, he escorted my wife and me out to the door of the Great Hall. On the way, he dispensed with the translator. He knew that I had been involved in this committee for a long time. He knew that I was friendly with the two biochemists who were in Shanghai and in Peking. He

knew that I had written to invite people to attend the congress in New York in 1964. He knew the whole history of my committee.

He said something to the effect of, "You must be very pleased now that this has come to pass. It's been a long time, hasn't it?" I said, "I am very pleased. I've waited a long time. It's a great satisfaction to bring China back into communication with the world of science and with the hope of peace in the world." Then he stopped, and he looked at us, and he waved his hands and he said, "But you must admit that President Nixon has done one good thing." I said, "I agree." He said, "But Watergate!" [laughter] The hearings were all taking place at that time, and we knew about them only because Harrison Brown had a short wave radio and would report to us at breakfast every morning what was happening; otherwise we were out of touch. But Chou knew about it. My final words were, "But that will make no difference to our Academy, and to our committee whatsoever, regardless of what Watergate leads to. We are ready to continue our work indefinitely." He grabbed my hand with both of his and said, "Thank you. Thank you so much. Very good to hear." That was the last we saw of Chou En-lai.

There's Nancy Tang with Chou En-lai and me.

BOHNING: That's a good picture.

SMITH: A Chinese photographer took that picture. Here are pictures of some of the people with whom I have spent my life—this is Max Bergmann, Selig Hecht, with whom I took my degree, David Keilin who was my professor at Cambridge, which is a picture that I took.

BOHNING: That's a good picture.

SMITH: That appears in a book of his which his daughter edited after he died (45). She has the negative. This is H. B. Vickery, with whom I worked in New Haven. This is another picture of Selig Hecht which appeared in Time magazine. Here's my late friend Oskar Wintersteiner with the first crystals of sodium penicillin. Otto Meyerhof. John Edsall. Abe White. Claude Fromageot from Paris. Phil Handler. Bill Stein and Stan Moore. Willy Kühne, the man who first used detergent to extract a protein. He used bile salts, which he discovered, to extract rhodopsin from the eye. He also discovered myosin, the contractile protein in muscle. A very remarkable scientist. Stein and Moore again. Then my surviving co-workers in 1971—Phil Handler and Abe White, when we were having an author's meeting at the National Academy in Washington.

BOHNING: That's a great shot with all of you together during that working session.

SMITH: That was taken by Phil's son. And Frederick Gowland Hopkins, more than anybody else, the founder of modern biochemistry.

BOHNING: That's an excellent collection.

[break]

SMITH: There is another story which I think is historically interesting. When we arrived in Beijing, I was asked if I would be willing to give a talk. I had been aware of the fact that they might ask me, so I had brought slides with me, appropriately. We were planning on being in Beijing for nine or ten days, and every day they kept postponing when I would give my talk. Finally they set a date, which was about a week after we had arrived there.

In the meantime, I had been interested in trying to visit the biophysics lab, because I knew about one of the people who was there, whom I had met at the International Conference of Biochemistry in 1961. That was the last time the Chinese had attended an international conference, because it was at that congress that the IUB had admitted Taiwan. They refused to participate later because of Taiwan. Our policy in the Academy was that we admitted scientists from every country, regardless of politics. For example, both North and South Korea, East and West Germany, etc., were members of many scientific unions. The Chinese withdrew from IUB. I met one of the Chinese in Moscow because he had worked in Keilin's lab. After I left Cambridge I received all the reprints from Keilin's lab, so I knew about his work.

Finally, they said, "Today we'll visit the Institute of Biophysics." So I said, "Fine." I came to his laboratory and we said, "Hello." I looked around the lab, and I asked what he was doing. The answers were marvelously evasive. "We are planning to work on so and so. We are also planning to work on so and so. We are intending to do this." Not that they had been doing it. It was quite clear that all of the bottles were clean and full of water. The constant temperature bath was stirring along, but there was nothing in it. There wasn't a used thing in the laboratory. They had been waiting to bring him back from the farm so that he could act as my interpreter when I gave my talk. There was nobody else there who knew enough biochemistry to be able to do so.

Later on I found out from him that he had been out on the farm indeed. They had brought him back for a few days and got him new clothes. After he was back, they never sent him back to the farm again. He told everybody I saved his life. We've become very good friends since then, and in our second visit to China in 1980, we had dinner in his home. Some years later, he and his wife were guests in our home.

I gave that talk, and with interpretation and with questions, it lasted three or four hours for a rather small group of people. The atmosphere was curious. People were afraid to say anything; the Cultural Revolution was really not over but its worst phase was done.

When we arrived in Beijing, we had been given a long list of things that we might want to visit. Everybody had different institutes and things they wanted to see. It turned out that George Harrar and I were the only two who wanted to visit the Institute of Botany. We arrived at the Institute of Botany, and as is the custom in China, standing on the sidewalks waiting for us were three or four of the senior people from the institute. We were introduced and shook hands—our interpreter was with us. In Chinese custom you are first taken in for tea. In conversation they told us about the institute. We went through the main building. It was a traditional kind of botany place. There were a lot of leaf presses, a lot of geology, history of plants. We were then going to go into some out-buildings where they had work going on in plant biochemistry and physiology. About a hundred yards away I saw a familiar figure that I hadn't seen since 1932 or 1933, a man I knew at Woods Hole with whom I used to play ping-pong. In fact, he really taught me how to play ping-pong. He was the most distinguished plant biochemist in China, and the former head of the Institute of Botany. He refused to go along with the Cultural Revolution. The Chinese are rather formal, and except for close relatives, don't embrace, or hug. They don't do what Frenchmen or Europeans do in general. I said, "Pei-sung" and he said, "Emil!" and we rushed to each other and we threw our arms around one another. Everyone looked pretty startled.

We explained that we were old friends, and we hadn't seen each other from about 1932 or 1933, when he went back to China, to 1973. Forty years. He told me what he was doing in the lab, and he was actually working. They never sent him out to the farm, because he was already not a young man. He had been kicked out of his professorship at the University and demoted. Every time we were alone, he would say, "I'll be all right. Don't worry about me. Send me reprints. Send me books. Tell people to send me reprints. If I don't answer, don't worry about it. I'll get everything; just be careful what you say." Somebody would join us immediately. When we were back there in 1980 he was in all his glory. He had been restored to a nice new apartment. He was an honored figure when the Cultural Revolution

was over. He died a couple of years ago. He was in his late eighties or early nineties.

When we went down to Shanghai finally, after a big tour, I was met at the railroad station by Wang Ying-lai, whom I'd also met in 1961 in Moscow, who was the head of the Institute of Biochemistry. He immediately said, "I want you to give a lecture. Not tomorrow, but the next day. Eight or nine o'clock." I said, "Fine." I decided to talk about the evolution of proteins, a good general topic in which I can bring in protein structure, biological activity, changes of function, etc. I lectured from nine o'clock until about twelve-thirty, and then we broke for lunch. "Would I come back in the afternoon and answer questions?" I said, "Of course." At two o'clock we started in again.

It is very easy to judge an audience when you speak in English and then wait for the translation. I could understand how many understood English, because they laughed at the jokes. [laughter] And then those who laughed when the Chinese translation was made. I had actually discovered this trick years before in Europe. The first question from one of the Chinese was, "Professor Smith, you first became famous for your work on proteolytic enzymes, but you haven't said anything about proteolytic enzymes. Have you stopped working on proteolytic enzymes?" So I explained a little bit about some of the subtilisin work and some of the other things. With translation and what not, it takes quite a while to go through this. Next question. "Professor Smith, you showed us all of this beautiful work on sequences of so many different proteins, but you didn't tell us how you did it." I discovered this was the real problem. Intellectually they could grasp everything you had to say, but they had no idea about the methodologies. They were completely cut off. So, with a certain amount of prompting, I talked until about six o'clock mostly about methods. The next year they sent a delegation to the U.S., including my lab, to observe and take notes on the methods. This is the real problem of cutoff. You can read the journals and understand the ideas, but until you see it done, or know how it's done, you have no way of appreciating an experimental science. The theoretical physicists and the mathematicians have an easier time.

BOHNING: So they did have access to the journals.

SMITH: Oh, yes. They had access to the journals.

[END OF TAPE, SIDE 6]

BOHNING: Do you have anything else about that China period?

SMITH: No, I thought that would be enough.

BOHNING: It's very interesting. You've also been active in the ASBMB.

SMITH: It used to be the ASBC. In order to preclude the formation of a separate society of molecular biology, we decided to co-opt the situation; the international union has done the same thing.

BOHNING: What has been the relationship between the ACS division of biochemistry and the ASBMB?

SMITH: Close. There is a very large duplication of the membership, but there are a certain number of bio-organic chemists, for example, who are in chemistry departments, who are loyal to the division and are not necessarily members of the ASBMB. To make sure that there is no rivalry, the division of biochemistry of the ACS only meets in the Fall. It never meets in the Spring to conflict with the meeting of the ASBMB. I am a member of both, obviously, and so are most people. The ACS people tend to be more organic, more mechanistic, more on the physical side.

BOHNING: Are there any particular activities at the ASBMB? You've been involved there for a long time.

SMITH: Earlier, I was a member of the publications committee and also on the editorial board of the Journal for a decade. The thing that I've been involved in most recently, since my retirement in fact, is that I'm a member of the finance committee. I'm still a member of the finance committee for another year. I decided one more year is enough. I will be through on June 30th, 1995.

BOHNING: That's something like twenty years?

SMITH: Something like that. I suppose that I'm the memory and the conscience of the committee, [laughter] because there have been many treasurers and other people on the committee have also turned over quite a bit. I guess the only person who has been pretty constant, as an ex-officio member, is Herb [Herbert]

Tabor.

BOHNING: That's right, because he's been editor of the Journal...

SMITH: ...all that time. He took over as acting editor when Bill Stein became ill in 1969. After Bill realized he could no longer do it, Herb became the editor-in-chief. Herb shows no signs of slowing down or giving up, but is the editor of the Journal, which is, after all, the major financial obligation and activity of the Society. He's an ex-officio member of the committee. He has been all the time. But we've done very well. We've built up ample reserves with a good investment policy, and it continues.

BOHNING: I've essentially come to the end of my notes. We talked about your family and your retirement period last time. I wasn't quite sure if we had talked about your sons. I wanted to check that, because one of the things that I have found is that very few people whom I have interviewed have children who have followed in similar veins. That has been my experience. I don't know how common that is, but in your case, you have one son who has followed in your footsteps. Do you think you had any influence in that?

SMITH: The older one [Joseph Donald] always says he was brainwashed. He says that he never knew that there was anything exciting around except chemistry and biochemistry. He is a biochemist, and is presently professor and chairman of the department of chemistry at the Dartmouth branch of the University of Massachusetts, which is in North Dartmouth, Massachusetts. It is one of the branches of the state university. They don't have a Ph.D. program, but they have a master's program. He is primarily interested in lipid biochemistry, phospholipids, and membrane biochemistry. He has done work on microorganisms, and now he is doing work on cell cultures in mammalian systems, actually human cell cultures. He has had a succession of grants from the NSF. Earlier he had some from the NIH as well. So he is following his own career and his own interests. It's nice to meet him at Society meetings and to have related but not identical interests.

Our younger son [Jeffrey Bernard] has had a sort of checkered career. He started out with an interest in chemical physics, and did some undergraduate research at Harvard. He started out in medical school for a couple of years and didn't like it. So he dropped it and went to Caltech and took his Ph.D. in chemical physics. Then after four years in solid state physics, he decided to return to medical school. So he went back

and completed Harvard Medical School. He had to take an extra year to do it, having been out for eight years. Then he decided that what he wanted to do was pediatrics. He looked around the country and chose Children's Hospital in Philadelphia. He did three years of a regular residency and then two additional years in neonatology. He is now here at UCLA as an assistant professor in pediatrics, and becomes an associate beginning on July 1, 1994.

He has become a cell biologist, with some interest in biochemistry. He has come around the circle. [laughter] His major research interest up until about a year ago was in the development of cellular immunology in the newborn, and the lack of such immunological response in the premature baby, which is what the neonatologists are primarily interested in. But the amount of materials you can get out of neonates is very limited. He made some interesting discoveries in the cell properties of the neonate and the preemie. Now he is back culturing genes and determining sequences of regulatory genes.

Both of our sons have ended up in science. I think Jeff avoided biochemistry for a long time, knowing that his father and his brother were involved in it. But after a time, he got around to it. His first tutor when he was an undergraduate at Harvard was John Edsall. Then he did his honors thesis on the lithium atom spectrum with a man named [William P.] Reinhardt, who is now professor of physical chemistry or chemical physics in Colorado. As I said, he took his Ph.D. at Caltech and then spent two years back at Harvard with two different people—with [Roy G.] Gordon in chemistry and somebody else in physics. Then he worked at Carnegie-Mellon for two years with [James S.] Langer, who is now at Santa Barbara in solid state physics. He decided that physics is a lonesome job, and he was more interested in the human aspect of applied science.

BOHNING: It's an interesting place to end, in the sense of where his previous path had taken him.

If you don't have anything else at this point, I think that we can close.

SMITH: I'm about talked out after three and a half hours.

BOHNING: It's been that long, hasn't it? I appreciate your taking the time again today to complete the story that we started some time ago, which I apologize for, but I have enjoyed it again. Thank you very much.

[END OF TAPE, SIDE 7]

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