THE BECKMAN CENTER FOR THE HISTORY OF CHEMISTRY

FRANK H. WESTHEIMER

Transcript of an Interview
Conducted by

Leon Gortler

at

Harvard University

on

4 and 5 January 1979

> Frank H. Westheimer, interview by Leon Gortler at Harvard University, 4 and 5 January 1979 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript # 0046).

Chemical Heritage Foundation
Oral History Program
315 Chestnut Street
Philadelphia, Pennsylvania 19106

FRANK HENRY WESTHEIMER

1912	Born in Baltimore, Maryland on 15 January

Education

1932	A.B., chemistry, Dartmouth College
1933	M.A., chemistry, Harvard University
1935	Ph.D., chemistry, Harvard University (Mentors: James B. Conant; Elmer P. Kohler)

Professional Experience

1935-1936	National Research Fellow, Columbia University (with Louis Hammett)
	University of Chicago
1936-1941	Instructor
1941-1946	Assistant Professor
1946-1948	Associate Professor
1948-1954	Professor
1953-1954	Visiting Professor, Harvard University
	Harvard University
1954-1960	Professor
1959-1962	Department Chairman
1960-1982	Loeb Professor of Chemistry
1982-1983	Senior Professor
1983-	Loeb Professor of Chemistry Emeritus
1944-1945	Research Supervisor, Explosives Research Laboratory, National Defense Research Committee
1964-1965	Chairman, National Academy of Science Committee to Survey Chemistry (Westheimer Report)
1967-1970	Member, President's Science Advisory Committee

Awards

1954	Elected Member, National Academy of Sciences
1970	Willard Gibbs Medal, Chicago Section, American Chemical Society
1970	James Flack Norris Award in Physical Organic Chemistry, Northeastern Section, American Chemical Society
1976	Theodore William Richards Medal, Northeastern Section, American Chemical Society
1980	Richard Kokes Award, National Academy of Sciences
1980	Charles Frederick Chandler Award
1981	Lewis C. Rosenstiel Award, Rosenstiel Basic Medical Sciences Research Center
1982	Robert A. Welch Award, The Robert A. Welch Foundation

1982	Arthur C. Cope Award, American Chemical Society
1982	William H. Nichols Medal, New York Section, American Chemical Society
1983	Christopher Ingold Medal, The Chemical Society of London
1988	Priestley Medal, American Chemical Society

ABSTRACT

In this interview, Frank Westheimer begins with his family, his childhood and early education in Baltimore, his undergraduate days at Dartmouth, his decision to go into chemistry, and his choice of Harvard for his graduate work. Next he covers his years as a graduate student at Harvard and talks about his research with James Conant and Elmer Kohler, the faculty at Harvard and the courses they taught, and his summer work with Alsoph Corwin at Johns Hopkins. He also talks at length about his early interest in biochemistry, his view of theoretical organic chemistry in the mid-1930s and the opportunities for research open to him, the development of theoretical organic chemistry in the early part of the twentieth century, and the publications of some of the early scientists. This is followed by a description of his year as a National Research Fellow at Columbia, his research, his colleagues, and more on the development of his interest in biochemical problems. Westheimer continues with the offer of a position at the University of Chicago from Morris Kharasch, and includes an extensive discussion of the university, his research, and his collaboration with John Kirkwood, Joe Mayer and Birgit Vennesland. In the next part of the interview he comments on his selection and training of students and discusses a number of former students who have been successful in research careers. The interview concludes with more discussion of physical organic chemistry, past, present and future; a review of his work on the hydrolysis of phosphate esters and pseudorotation; comments on the future of organic chemistry; and a review of the Westheimer Report, the analysis of American chemistry by the National Academy of Sciences.

INTERVIEWER

Leon Gortler is professor of chemistry at Brooklyn College of the City University of New York. He holds A.B. and M.S. degrees from the University of Chicago and a Ph.D. from Harvard University. He has long been interested in the history of chemistry, and helped establish the Beckman Center's oral history program. He has conducted over forty oral and videotaped interviews with major American scientists.

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INTERVIEWEE: Frank Westheimer

INTERVIEWER: Leon Gortler

LOCATION: Harvard University

DATE: 4 and 5 January 1979

GORTLER: If we could start with your childhood. It has no relevance to physical organic chemistry, but historians in general are rather interested in knowing where scientists got their beginnings, and so it would be useful if you could tell me about your father, Henry Westheimer, his education, his work, and perhaps some of the ways he influenced you and then tell me a little about your childhood in Baltimore.

WESTHEIMER: Okay. My father was born in St. Joseph, Missouri, and was one of a family of eight boys. My grandfather Ferdinand had been a German immigrant who came to the United States as a young boy in the early 1840s. I could find the exact year but I don't remember it. When he finally earned enough money, he bought a ticket to the end of the railroad, which was St. Joe, Missouri. It remained there for a few years, because of the Civil War, when railroad building stopped. The pony express left from St. Joe. My grandfather set up a whiskey business and his sons, including my father, were whiskey salesmen, all over the west.

After a bit the eight brothers decided that they were ready for expansion. My father came to Baltimore with one of his brothers to buy out a company, or buy into a company, to make Maryland rye whiskey, and the other brothers wanted to make Kentucky bourbon. But they didn't like the state of Kentucky, so they settled in Cincinnati, across the Ohio River, but their distillery was in Kentucky. Otherwise you couldn't call it Kentucky bourbon. It made quite a difference which side of the Ohio you were on.

My father was put out of business by the Volstead Act, and then went into the stock brokerage business. His education was mostly in the German-American high school in St. Joe, Missouri, though he had a year at a business college in New York. He was a damned good stockbroker. He was one of those who saw the 1929 crash coming, quite clearly. He was a person of very high standards and few illusions, and had a very good quantitative mind. Some measure of that was demonstrated when I was in college at Dartmouth. I came home my freshman year full of excitement because I was learning calculus. I could solve these marvelous maximum-minimum problems. I tried to explain to my father about it.

He said, "I can do maximum-minimum problems like that. No sweat." He sat down and did them by arithmetic. He did them the way a modern computer would do them. You know, just figuring out one set of numbers, then another, then another, then honing in and coming into the answer. Of course it took him five or ten times as long as it did to do it by calculus, but he could solve the problems perfectly well. The point is that when he had learned arithmetic, he had learned it thoroughly. He didn't know any calculus. But he <u>really</u> knew arithmetic. Although that of course is long past my childhood, it's a nice picture of the kind of mind that my father had.

GORTLER: The kind of mind that you were interacting with.

WESTHEIMER: Yes. The family was financially quite comfortable, in all the years I knew. Just after the Volstead Act, there was a moment of crisis, but I was only five years old and wasn't really aware of that crisis. The brokerage business prospered, and because of my father's foresight with respect to the 1929 crash, survived, so that I wasn't worried about money at all. And my parents, and particularly my father, were always quite, liberal is perhaps the wrong word, but liberal with me in the sense that my father would have been overjoyed if I had elected to go into the brokerage business, but he put no pressure on me whatsoever. Anything that I wanted to do was fine. He took enormous pride in any accomplishment of mine, and wherever the accomplishment led was splendid as far as he was concerned.

If there was family pressure, it was in two directions. First, whatever I did, I should work very hard at it. There was no pressure to go into the family business, but there sure was pressure to work. Second, there was pressure for the very highest standards of integrity. I don't know that it is appropriate to go into this history, but my father pointed out to me how fortunate I was to be Jewish, <u>because</u> there was prejudice against Jews. Any Jew who wished to make his way in the United States could do so, but had to work harder and maintain a higher standard of integrity than his non-Jewish neighbors. That was the philosophy with which I grew up.

GORTLER: It stood you in good stead, I think.

WESTHEIMER: Yes, indeed. Yes, indeed. It was his idea that mild anti-Semitism was an enormous advantage!

GORTLER: Your mother? Her influence, her role in the family?

WESTHEIMER: My mother was a third generation American, and grew up in an upper middle class Baltimore family. She was a beautiful woman, and, for her day, a very modern lady. Now, of course you have to know that her day was the height of the Victorian period, and it's true that when some gentleman who was calling on her actually kissed her, she thought she was ruined and that no one would ever marry her. But she graduated from Goucher in 1908. The number of women who graduated from college before World War I is small.

She was smart and well educated, but she didn't do very much with her life, really. A modern woman would have done much more. She was wife and mother, and she took some part in building the Child Study organization in Baltimore, but she was, in a sense, wasted. She had a much better mind and education than she used.

GORTLER: What kind of role did she play in your upbringing?

WESTHEIMER: I think the first thing to say about my upbringing is that I was, in effect, an only child. I had two brothers, but both died when I was very young. My older brother who died of tuberculosis when he was five and I was three was fabulously smart; he was reading fluently at the age of five, which was less common then than now.

I guess since he was ill, the family attention was focused on him and not on me. Then my mother was pregnant and had her third son, who died in infancy. My parents had bought and moved into a house in the suburbs, just as the Volstead Act was passed, and there was considerable family concern at the time. But everything turned out all right. My parents insisted that I be quite independent; despite the fact that I was then an only child, and they had lost two others, they gave me a great deal of freedom. I don't know if they went quite as far as Jeanne went. When our daughter Ruth was two and a half, Jeanne was pregnant with Ellen. She had had a miscarriage, and the obstetrician had put her to bed, so we put Ruth in the University of Chicago Nursery School. The first day I told Jeanne that I'd pick Ruth up at noon and bring her home, but Jeanne turned to me and said, "You'll do no such thing. That child will come home on the bus with the other children. We can't go on protecting her all her life."

GORTLER: My, that is wonderful.

WESTHEIMER: I don't know that my parents treated me quite that way but they wanted me to be independent. My mother read to me a great deal, but aside from that, I don't remember being clung to at all. Really, quite the contrary.

I went to a small private school, the Park school. I sat for the year of kindergarten under the grand piano, and wouldn't come out. The story is that I was trying to build a scale out of blocks, and every time I tried to build the top of the scale, it fell. It took me two years to find out that it wouldn't work and crawl out. I doubt that that story is entirely accurate. But it was true that I was a bit backward. They wouldn't promote me. They kept me a second year in kindergarten, and my mother was quite worried about me.

Somewhere around that time, I had my tonsils and adenoids removed, whereupon I suddenly developed. I think I am one of the people who was actually poisoned by diseased tonsils and adenoids. But maybe not. Maybe it was just time. I don't know. There's no way of going back and finding out. My tonsils and adenoids came out, and I skipped the third grade. The causal connection is not entirely clear. After that I was with the other kids in school.

It was an interesting school. It was a progressive school, in which I failed to learn to read properly. I still read very slowly. My children are dyslexic and it is quite possible that I am slightly dyslexic. I tend to reverse letters and reverse words, even today. My arithmetic is kind of sloppy. I never learned to spell. I've worn out several dictionaries. One of our favorite family stories is that when Jeanne and I were living in a two-story house, I called upstairs to her and said, "Darling, how do you spell professor?" I spell correctly now most of the time, but I still have trouble. I use the dictionary a great deal. I didn't learn to write properly. I didn't use the horrendous grammar that my graduate students do, but I didn't learn to write the English language until I was on the staff of the University of Chicago, where I had my English lessons. Do you want to listen to that too?

GORTLER: Sure.

WESTHEIMER: There was an old man at the University of Chicago named James Senior.

GORTLER: I remember Professor Senior. He used to walk around with a pipe sticking out of his mouth.

WESTHEIMER: Right. And his suit was a brown tweed with a button off the vest and the vest always misbuttoned, and the pipe was a corncob.

GORTLER: Yes. He probably had the same suit on when I was there.

WESTHEIMER: He was a stickler for proper English. On one occasion, when I walked out of my office, he was on his way across the hall to Morris Kharasch's office. He was a big man. I remember him waving a folder above his head and shouting at the top of his voice, "Morris, this is a wonderful thesis. Why don't you have it translated into English?"

Well, I submitted to him the first paper that I wrote at the University of Chicago. I submitted it with enormous pride, because I thought I could write. I thought it was a good paper. He handed it back to me with more red ink on it than black. I was angry with that stupid old man for tearing apart my beautiful English. I would have liked to kill him, but I thought first I'd read what he said. When I read what he said, I got twice as mad, because there was a mark on about every sentence. Then I read his remarks over again, and he was right every single time. I made grammatical errors. I had introduced redundancies. I had skipped essential parts of arguments. I had put sentences in the wrong order. I had committed every crime in the book!

When I submitted my second paper to him, it was somewhat better. By the time I left the University of Chicago, I had almost learned to write English. I've had a few English lessons since. By now, I'm rather pleased with what I can do.

But I didn't learn that at the Park school. The only thing I can remember really learning at the Park school was algebra. I learned simple algebra the way my father learned arithmetic. I can use it, and it has stood me in good stead.

GORTLER: Yes. We'll get to some of those papers later.

WESTHEIMER: I had a very good course in trigonometry. I was the only person in this small school who wanted to learn trigonometry. They couldn't have a class for one person, so, being a liberal school, they gave me an individualized course. The mathematics teacher gave me a textbook in trigonometry and said, "Here, take this. At the end of the year I will give you an examination culled from the College Board tests on trigonometry." So I learned two things--one, trigonometry, and the other, that you don't need anyone to teach you a subject. If you have a good book, and if you're willing to work, you can do it yourself.

I very much enjoyed mathematics and science. I had less of a working career than most kids. I did work summers in my father's brokerage office, as a board boy. In those days, one took the quotations from the ticker tape and wrote them up on a blackboard. It was a dull, routine job, but I enjoyed it. I had a couple of jobs doing bookkeeping for various firms in Baltimore. I got those jobs with my father's friends. But I think I did a lot less work than most kids my age, because there was absolutely no financial pressure to do it.

GORTLER: You've covered almost everything I wanted to ask. You said you read slowly, but were you an avid reader? Were there any particular books that appealed to you, aside from the math and science?

WESTHEIMER: Oh, I read a moderate amount, but they were the usual things that people read in those days. When I was a small child, I read through the entire series of the OZ books, which were coming out at that time, dozens of them. I read a very large amount of Dumas and Conrad, but, I would say that I read no more than other kids did. You know, those were the days before radio and TV. I read less than some. De Kruif's <u>Microbe Hunters</u> made an enormous impression on me (1). My family had a large and impressive library, stocked mostly with the classics of my parents' day--Dickens and Balzac, things of this sort, some of which I read.

I didn't understand reading the way modern kids do.

[END OF TAPE, SIDE 1]

WESTHEIMER: It didn't occur to me until much later than high school that authors might have a philosophy. They might be trying to tell something other than a story. I had an excellent memory in those days, and would remember the whole book. But the notion that the author might be trying to deliver a lesson didn't come through to me until much later.

GORTLER: I don't think that's uncommon. Even with today's sophisticated children, I don't think that they see that.

WESTHEIMER: Well, when my children were in high school they were much more sophisticated than I was, which gave them a great advantage.

GORTLER: They went to University of Chicago schools?

WESTHEIMER: Well, partly that, and partly that I knew by then what it was they had to learn. [laughter] My parents talked to me about schoolwork and so on, but there wasn't a strong interaction, except with my father with respect to mathematics.

Anyway, eventually it came time for me to go to college. By then I'd skipped another year of school. I was going to college at the age of sixteen, which was probably a mistake. I was socially very unsophisticated, and I would perhaps have been better off if I had gone to college later. I didn't know where to go to college. I didn't know anything about college, except that I had to go. There was never any question in my family about that; it was taken for granted. But where I was going to go to college was sort of up for grabs. I think my parents figured that I couldn't make it to Harvard or Yale, in part because then I would have to take College Board Examinations. Since I couldn't spell <u>at all</u>, I would never pass them.

Now, of course there was a way to solve that problem. I could have sat down and learned to spell. That solution never occurred to me or to anyone else in the family. Besides, the family favored my going to a college with a business school, because it was assumed then that I would probably end up going into my father's brokerage business. Dartmouth seemed a good place, because of the Tuck School. We talked about the University of Pennsylvania and the Wharton School, but not very seriously, and although Harvard Business School was considered marvelous, no one thought I should go to Harvard. My parents took me around to look at a couple of colleges. I was intimidated. I didn't know what I was doing in those interviews. I applied to several, including Johns Hopkins. It was a good school and we thought I could go there if I couldn't get in anywhere else.

I was accepted at Dartmouth, and went, without knowing what college was going to be like. Many years, perhaps two years after I had graduated, I went back for a visit. My eyes opened. I looked and said, "My God, it's beautiful." But I had been to Dartmouth without knowing that it is beautiful. It was, for me, college. That's what college was. I'd not really seen any other colleges. I didn't know of all the ugliness in the world. Dartmouth was beautiful, well, of course.

Because I was too young, I think, I got less out of college than I should have. I did all the classroom work, which came relatively easily to me, and I enjoyed it enormously, especially the mathematics, but also the elementary, the general chemistry. Paul Bartlett always made fun of me because I told him that I never took any notes until my senior year in college. I didn't know you were supposed to. Well, at Dartmouth you didn't need to. Most of the professors just lectured from the textbook. If you read the textbook, you knew what they were going to say before they said it. All they did was reinforce it a little, and there wasn't any point in taking notes. In better schools, or at Dartmouth today, that might not be the case.

At the end of my first semester at Dartmouth, the dean of freshmen called me in and congratulated me on my first term performance. I had very good grades. He said, "Well, you know, this is a splendid performance, but I don't want you to be disappointed when you are unable to do this well ever again. I have the records here of your intelligence tests. You did nicely. You're not going to have any trouble in college, and I don't want to say that there's a problem, but obviously you performed way over your capacity."

GORTLER: What a wonderful thing to say to a freshman student!

WESTHEIMER: "You shouldn't be disappointed if you can't live up to this." Well, it did make an impression on me, but it didn't bother me in any way, because I didn't have great respect for him or most of the faculty at the college. I always wondered why the kids in college seemed to want to know the faculty. I never wanted to know the faculty. I considered most of the faculty not very bright. It is within the realm of possibility, looking back on those days, that there was something to my vision. His statement didn't bother me. Incidentally, those were the lowest grades I ever got at Dartmouth.

GORTLER: I think it was just another one of the prodding statements, like your father had given you early on.

WESTHEIMER: I don't think I even took it as that.

GORTLER: It was a challenge to you?

WESTHEIMER: No, I think the challenge was there anyway, and I really don't believe the interview mattered much. But in retrospect it was amusing.

This is irrelevant, but I now understand that situation much better than I did then. At the University of Chicago, there was a famous psychologist, [Louis Leon] Thurstone. Thurstone decided to look not at intelligence tests in general, but what he called "profiles in intelligence." The psychologists haven't made much of it, although I don't understand why not. He made up an examination where each test was made up of only one kind of thing--spatial perception, number series, anagrams, various different items that he got from the Binet test. The test for spatial perception that he ended up with was a page of pictures of right and left hands in different positions, cut off at the wrist. All you had to do was write "right" or "left" under the appropriate picture. Some people would take that test and write down answers in thirty seconds and wonder what the problem was. Some people, at the end of thirty seconds, would be looking at their hands to figure out whether the first couple were left or right. It turned out to be a splendid test of spatial perception.

Anyway, he created these tests, gave them to University of Chicago students, and then correlated the answers. Whenever two tests correlated well, he threw out one of them so as to find the independent factors of intelligence. He ended up with a few, I think seven, but it might have been nine, of which spatial perception, number series and anagrams were three, but I don't remember what the others were. Maybe aural and visual closure. Then he found that for different people, you got enormously different profiles. The tests he chose showed a correlation factor of only two, which he called "general intelligence." The rest of the divergence among individuals was in profiles, and they're very uneven, very jagged. So people with the same Binet IQ can have enormously different profiles. Some people with moderately good Binet IQs show great highs and great lows on an intelligence profile, which probably is part of the explanation between the differences in performance, as contrasted to difference in IQ.

Of course, probably more important factors for success are energy and hard work. My great and good friend George Willard (Bill) Wheland, who was sick most of the years I knew him, was, I'm convinced, one of the brightest people who has ever lived on earth. But he had little energy. That really great mind was partially wasted. James Franck knew all the greats of his day. He once said to me in his lovely, thick German accent, which I cannot imitate, "You know, [Peter] Debye has the best mind of anyone I have ever met. If that man would only apply himself, he would amount to something." It's in that sense that I speak of George Willard Wheland. If he'd only applied himself, he would have amounted to something.

Anyway, I got through college well. I'd been taking chemistry courses, but I also took a couple of courses in economics so that I could go to the Tuck School, should I decide to do that. Of course, it was a perfectly valid part of my general education anyway, a good thing to do. But I enjoyed taking science and mathematics courses, and near the end of my junior year I told my parents that I wanted to go into chemistry rather than the brokerage business. They responded by taking the train from Baltimore to Dartmouth, to talk to my professors, and to find out whether, in their opinion, that was a realistic thing for me to do. The professors reassured them that indeed, I had some talent for chemistry, and one of them assured my father that if I applied myself and things went well, there was no reason why someday I couldn't earn a salary in chemistry as high as $5000 a year.

GORTLER: What was your father's response to that?

WESTHEIMER: Well, this was the middle of the Depression and $5000 a year wasn't so bad then, although it was not, even in those days, the top salary to which one might conceivably aspire.

GORTLER: What was your view of being a chemist when you made that decision? What did you think a chemist would do?

WESTHEIMER: I hadn't the foggiest notion. I didn't really know what chemists did. I didn't know whether I would be in industry or in academe. I knew that I didn't know much chemistry, and that if I was going to be a chemist, I had to learn a great deal more. I would say that my horizon, then, only went so far as knowing that. Someone I did like to talk to was a mathematics professor at Dartmouth named Bancroft Brown. He said that, if, at my age, I could see three years ahead, that was fine. I didn't have to see further. That satisfied me, and I was content to know simply that I would have to finish college and go to graduate school.

My parents--well, my father was of course terribly disappointed that I wasn't going to go into his business. But he was quite content, in a sense. If I was serious about chemistry, was going to work at it and had some talent for it, he was ready to provide the financial support to get me through college and graduate school.

The only graduate school I applied to was Harvard. I dared to do that because there was a pipeline from the Dartmouth chemistry department to James Conant, to whom previous Dartmouth graduates including Bill Wheland had gone.

GORTLER: In one of the biographical sketches of you that I read, they mentioned that some student had preceded you from Dartmouth to Harvard, and you followed that course. I guess it was Bill Wheland.

WESTHEIMER: That's right. I came to work with Conant. At Dartmouth I actually had read some of Conant's papers, but not many. I knew that Conant was interested in theoretical organic chemistry, and I knew that I was interested in theoretical organic chemistry, and I knew that the two "great" organic chemists in the United States were Conant and Roger Adams. I preferred Conant's papers to Adams's. But I really hadn't read much research chemistry, not anywhere near as much as many of the kids today have read. I'd never done any real research, and I did not have a clear idea of what graduate school was going to be like.

But I was accepted by Harvard, and came here, in the fall of 1932, which was just about the bottom of the Great Depression. Harvard tuition was $400. My parents were financially able and willing to pay that for me, and pay for my maintenance, which wasn't very much in dollars, but dollars weren't very easily available then. But my parents had weathered the Depression very well, largely because my father had foreseen the stock market crash, and that meant that he'd saved what money he had, and saved his firm.

I came here [Harvard] to work with Conant, took the qualifying examinations, and then was instructed that I should take the first-year graduate physical chemistry course here with [George B.] Kistiakowsky, and Chemistry 5, the intermediate-level organic chemistry course from E. P. Kohler. I wanted to say something about my intermediate-level organic chemistry course at Dartmouth too.

GORTLER: I'd like to go back to Dartmouth for just a few minutes. Do you remember anything about the chem courses there, what ideas were being promoted at that time--the atom, bonding, anything of that sort? Which books might have been particularly influential?

WESTHEIMER: I don't remember most of the chemistry books we used. In the senior review course, in general chemistry, we used Latimer and Hildebrand (2). We had some standard physical chemistry textbook; I don't remember what. For me, the most interesting part of the physical chemistry was reaction kinetics, with the possibility of applying calculus to chemistry, which, everything considered, is just what you'd expect.

Our elementary organic chemistry was a pure memory course. This was, by and large, before mechanisms of organic reactions were incorporated into teaching, or even had been determined. Although [Christopher] Ingold's work had begun, and there was some mechanistic chemistry, it hadn't penetrated to Dartmouth. So we had pure memory work.

I remember very well memorizing all the structures for the purines and pyrimidines in the box form that they were given then. I don't know if you remember those boxes, where the six-member ring was drawn as a rectangle. No one thought to draw it as a hexagon. I don't know if I could find an old text to show that to you, but that's the way it was done. And that's the way I memorized it, and although perhaps I had the originality to write them as hexagons, it was a very bold thing to do.

In our senior year, we had a classical organic chemist, who was to give the advanced course in organic chemistry. He was a martinet of sorts. I don't know how I would have come out that year, but, in fact, he got sick. He had been working with poison gas during World War I and it had affected his lungs. He became ill in 1931, a month or two after we had begun our course.

GORTLER: Do you remember who that was?

WESTHEIMER: His name was E. B. Hartshorn. I remember the name of the old man who gave the elementary course.

GORTLER: Who was that?

WESTHEIMER: A man named [Charles E.] Bolser.

But Hartshorn became ill and had to leave. He spent the entire year in a sanitarium.

[END OF TAPE, SIDE 2]

WESTHEIMER: The academic year was already partially over. I don't know that Dartmouth could have found anyone to take his place in the middle of the year, but they didn't. The result was that the half dozen of us who were taking the advanced organic course at Dartmouth gave ourselves our advanced course.

What we did was to get copies of Bernthsen and Sudborough (3). I don't think I own that book anymore. It was a Beilstein kind of book that presented the prep of this and the prep of that and the prep of other things in turn, a very old-fashioned book. We went through it chapter by chapter. For the preps, we took turns, and one of us would go through the various lab manuals in the library, pick out a preparation and assign it to the class, and he would be responsible for going through the prep first, seeing that it worked, before everyone else would do it.

Well, there was no leadership. We didn't know what standards we were supposed to adhere to. The preps were an odd collection as far as the lab was concerned. But, like my high school course in trigonometry, it had the great advantage of demonstrating that you could do it yourself. It's a terrible lesson from the point of view of someone who has been a teacher all his life, because essentially it says that what I've been doing is totally unnecessary. But from the point of view of learning, the notion that you can do it yourself is extraordinarily important. So I think that it was a good course in advanced organic chemistry, however little factual material I learned.

GORTLER: What were the labs like, in terms of equipment and so on?

WESTHEIMER: Well, there wasn't any modern equipment. If Emil Fischer had walked into those labs, or the labs at Harvard, he would have been astounded by Pyrex glass. But that's the only thing we had that he didn't. Our distilling columns weren't much good, and I don't think they were much better than those that had been available in 1910. At Harvard we had the beginnings of electrochemical measurements of acidity. Fischer would not have had that. But the only UV was photographic, and I was enormously impressed--this was later--by the paper of [Louis P.] Hammett and [Leo A.] Flexser, who used photographic UV to determine the pK for the protonation of benzoic acid, and acetophenone (4). But there was no electronic UV.

GORTLER: Louis [Hammett] described that to me, and the work that they'd done. He said he had to have a certain kind of graduate student to do it because it was an enormous task.

WESTHEIMER: An enormous task, and way off at the frontier. We didn't have any photographic UV here at Harvard at the time. There were electrochemical measurements--this went back actually to Conant's training with [T. W.] Richards, which he then carried on with the EMF work on quinones, to which he initiated [Louis F.] Fieser, so all of Fieser's work on quinones was a continuation of his Ph.D. thesis with Conant.

Of course, there was no IR then. I don't know when IR was discovered, but there was certainly no IR instrumentation at all. NMR of course hadn't been discovered. Chromatography didn't exist.

GORTLER: That sort of answers one of my later questions, about why the study of acidity seemed to be so intriguing for a number of people--Hammett and Conant and so on. It was because the methods were available for doing it, it seems.

WESTHEIMER: Oh, I think acidity occupies a fundamental place in chemistry, especially in organic chemistry. When you think about mechanistic organic chemistry, one is repeatedly concerned with the ionization of extremely weak acids and bases. I believe it's a very fundamental problem.

GORTLER: I wonder whether they had that in mind, when the early work was done? I mean, to us in retrospect, it seems as though it's a natural. You know, Lapworth was dealing with the acidities of compounds, as well. Maybe the work in the 1920s was just an offshoot of that. Maybe they didn't realize that it would be so important later.

WESTHEIMER: I'll talk to you about that, because I think I understand some of what Conant was doing.

GORTLER: Okay. We'll come back to it.

We were talking about the labs at Dartmouth and at Harvard and the lab exercises. Did you do any research at all at Dartmouth?

WESTHEIMER: The professor of analytical chemistry gave me an analytical problem to try to work on. So I did a little bit, but very little, and it wasn't successful. Furthermore, I was smart enough then to have the same view which I hold today, namely, that it is a gross waste of time to do research when you're ill prepared. I consider most undergraduate research, not all of it but most of it, a waste of the student's time. It's very popular today, and my view is an idiosyncratic one, to put it as kindly as I can. It seems to me that, for most young people, a course in advanced mathematics is a much better expenditure of time and effort than doing undergraduate research. Now, if you're driven to do undergraduate research, if you feel you just have to, then you have to. And for some people, I guess, undergraduate research is a way to maintain their interest in science. I had no trouble maintaining my interest in science. I had an enormous amount to learn, and I knew it. I reached out in all sorts of directions and learned many different things. But I wasn't ready to do research, really.

Later, much later in my life, I found out that whatever it was that I had just learned was exactly what I needed for my research. Since it is absolutely impossible that my judgment was all that good, there is only one conclusion, which is that everyone needs everything for research. There isn't anything you can learn, in the area of science, that you can't apply to almost every problem. I just wanted to learn more.

GORTLER: You were a rare undergraduate, I'm afraid. So many just want to come in and do.

WESTHEIMER: Yes. I didn't want to do, then. I wanted to do, later.

GORTLER: It obviously paid off. Do you remember any particular students who were friends of yours then, who went on? Any particular people you were close to?

WESTHEIMER: There were relatively few people that I was close to at Dartmouth, certainly in the sciences. Not very many friends that I've held from then.

GORTLER: I'm interested in people outside the sciences as well, and which courses appealed to you outside the sciences.

WESTHEIMER: I will go back and pick up one of my college friends, whom I have seen.

I forget everyone's name. My wife says that I recognize her two times out of three but only if I see her in context.

GORTLER: At Dartmouth, were there any courses outside of the sciences that were particularly appealing? Philosophy? Literature?

WESTHEIMER: I took a collection of such courses. I guess I enjoyed the course in elementary economics as much as anything outside of the sciences. I found great difficulty with courses in both history and philosophy. For several years I signed up for such courses as extra courses, over and above my required ones, and then dropped them. I dropped them because I thoroughly disliked the course in philosophy that I tried to take, which seemed to me utterly disorganized and illogical, and I couldn't understand history and so quit.

Now, subsequently I've read quite a bit of history and love it. I believe I've learned some. The summer after my first year of graduate work I spent reading history books and went through two volumes of world history and two volumes of American history with enormous satisfaction.

What happened was the following. History as taught at Dartmouth in the 1930s and history as written in most of the textbooks that were then available, did not distinguish between well-established fact, conclusions from these facts, and pure prejudices of the textbook writer. I didn't know what was wrong. I just knew that I was terribly uneasy with the history. Only after I had done my first year of research in chemistry did it suddenly occur to me what was wrong with the teaching of history. Then I went back to the history books, and I could read them as if they were written in different colored inks. I could read a sentence and say, "Yes, that's the kind of thing for which one could have data. That could be true. Maybe it isn't true, but it could be true." The next sentence could be a conclusion that the author has drawn from the facts. I can examine that, decide whether I think it's right. And this next sentence is pure hypothesis. There's no way that anyone could know that or conclude that. That's just the author's personal speculation.

Once that was established for me, I could and did read a great deal of history. But at Dartmouth, it was hopeless.

Most of the things outside of the sciences at Dartmouth, I rejected. I took the English courses I was required to take. They didn't teach me to write. James Senior taught me to write. I took the standard course in psychology. One of the hour exams was given in an overheated room and I fell asleep. I only had twenty minutes to write the exam, which turned out to be plenty because the damn course had no content anyway.

So I was not utterly fascinated, outside of mathematics and science. I also was not fascinated by the biology course. I took the biology course because I thought maybe I would want to go into medicine. Well, the biology course was pure memorization. Perhaps the instructor, whom I disliked (whose name I know perfectly well, but I think I might as well not give you), wasn't so much to blame. The application of biochemistry to biology was a whole generation in the future, and there wasn't anything to do except memorize the stuff. But I really hated it. Besides that, I was not terribly skillful at dissection, and abhorred the sight of blood, which convinced me I shouldn't go into medicine.

GORTLER: You were talking about the courses at Harvard. I think you'd taken the preliminary examinations and you'd been asked to take certain courses.

WESTHEIMER: At that time at Harvard, you began research immediately. If you passed your qualifying exams reasonably well, you took a couple of courses, and started research.

GORTLER: Tell me about the courses.

WESTHEIMER: No, I want to tell you about something else.

GORTLER: Okay.

WESTHEIMER: Conant was chairman of the department. He came in and told me I'd passed my qualifiers, and I was to take these two courses, and that I should look to see whom I should do research with in organic chemistry, pointing out that I had a choice between Kohler and Fieser. I said, "Sir, I came to Harvard to work with you. When I wrote and applied, I applied to work with you. This is why I am here. I want to do the kind of work in"--I don't know if I said physical organic chemistry, because I don't know if the words were available then, but--"understanding organic reactions that you do. When you accepted me I thought you had accepted me to do that." He said, "Well, no. We just accepted you into Harvard, and my research group is full. I can't take any more people. You'll have to see Professor Kohler, see Professor Fieser, see if one of them will take you on in research. Good-bye."

I went away. Two weeks later Conant, who was an extremely good administrator, called me back into his office, and said, "I have no record that you've signed up for research. Have you seen Professor Fieser and Professor Kohler?" I said, "No, sir. I came to Harvard to work with you and I was waiting until you can take me on." He said, "I told you I can't take you on." I said, "Well, that's why I'm here. I'd rather wait." Three weeks later, he took me on.

GORTLER: So that's how it happened.

WESTHEIMER: That's how I became Conant's last graduate student, because in the spring of that year he became president of Harvard. He put me on a problem which never amounted to anything, and which I completed after he was no longer available.

GORTLER: That was the semicarbazone?

WESTHEIMER: That was the semicarbazone formation in sixty percent methyl cellosolve (5). You can see that he was concerned with solvent effects on acids and bases, and he set me up to determine the "pH" of that system, using a selenium electrode which had recently been advocated. It was a terrible electrode. It didn't work worth a damn, but that's what I was supposed to do. You can see how Conant was thinking, in terms of acids and bases and solvents. So that piece of work was--well, I completed it all by myself. It wasn't a great piece of research.

After Conant left, I had to decide what to do, and I seriously thought of working with Kistiakowsky in physical chemistry, and then decided, no, I didn't really want to be a physical chemist. I wanted to be an organic chemist. I did a piece of research with Kohler, which started out quite differently than it ended. He told me to do a condensation reaction. I don't think he had much in mind. It led in entirely different directions than he had expected or I had expected. That was quite interesting.

Kohler almost completely gave me my head in research. He assigned me a problem, and then, for practical purposes, didn't discuss it. He came around to see me once a week quite regularly, came around and looked at my bench, and said to me, "Mr. Westheimer, what did you do last week?" I would tell him. He would say, "What are these set-ups on your desk?" I would tell him, and he would say, "What are you planning for next week?" He would stand there for a while, nodding his head a little bit, and then he would say, "Hmph," and turn on his heel and walk away.

GORTLER: Did you ever find out what that meant?

WESTHEIMER: I never found out what that meant. I took it to mean that I was getting along all right, that I was doing some stupid things, but I would find out for myself what they were, and that was best. Now, whether that's what that "Hmph" meant or not, I shall never find out.

Toward the end of the first year, I came up with an explanation for the very complicated series of chemical reactions that I had uncovered (which explanation turned out to be almost right) and brought it in to Kohler. Again, I don't think he said anything much beyond "Hmph."

It turned out that some of the compounds I had made led to the formation of a furanol. Max Tishler took up that work and actually isolated the furanol, and I have a joint publication with Kohler and Tishler (6).

GORTLER: Who was Tishler working with?

WESTHEIMER: With Kohler. He got his Ph.D. with Kohler and then was Kohler's private assistant. In contrast to the situation at Dartmouth, where there was no one in the sciences with whom I was very close, Max and I have been good friends since the days before he got his Ph.D., when we were both graduate students. It wasn't merely that we collaborated on a paper. We didn't really collaborate on that paper. It was done in two pieces, quite far apart. But we were friends then and have been friends ever since, discussed science together, and everything else under the sun.

GORTLER: Any other students at that time you were talking to?

WESTHEIMER: Well, one of Conant's students was a scientific friend, Reginald Grice Kennelly, who was the son of Professor [Arthur Edwin] Kennelly, of the Kennelly layer. [Reginald Grice] Kennelly got his Ph.D. when I did, and became an industrial chemist, as I recall, at Monsanto, and died quite young. I don't remember when, but very young. I would bet he died in his thirties. I have no idea how.

I was scientifically friendly with and somewhat influenced by a postdoctoral student of Conant's named Bacon Chow. (He pronounced his name "Jo.") I was not particularly friendly with, but knew and in a way admired, Emma Dietz, who was one of Conant's postdoctorals. It's interesting that there was a female postdoctoral in the department at that time. It was probably not too common.

GORTLER: No, I'm sure it wasn't.

WESTHEIMER: There were quite a number of other interesting people here at the time. Melvin Newman was a postdoctoral with Fieser.

[END OF TAPE, SIDE 3]

WESTHEIMER: He and I were friends. George Wright was here at the time. We were friends, not intimate friends. I was much closer to Newman and Tishler. I knew many other people here, such as [Harold] Gershinowitz, who was working with Kistiakowsky, and I think, though this may be one of those things I'd better check to see that it is not a memory trick, that Richard Ogg was here at the time. Whenever it was I knew Ogg, he was quite fascinating, because he had all sorts of wild and usually erroneous ideas, but he bubbled with ideas. It was great fun.

There were quite a number of splendid people here at the time who were interesting and important. One of my lab mates was Merrit Quattlebaum. (I don't know what kind of a tree a "quattle" tree is.)

I came here from Dartmouth--you know, I was a young kid and very green. Sorry; there's a pun there but it was unintended. The first person I was introduced to here was Merrit Quattlebaum, and innocent as I was, I wasn't innocent enough to believe <u>that</u> name. I knew they were pulling my leg.

It turned out his name was Merrit Quattlebaum. He was doing porphyrin synthesis with Conant, on the next bench to mine. He helped me a great deal scientifically. He later set himself up in business in North Carolina, and I've seen him recently. He's been a great financial success and has a big, thriving personal business.

GORTLER: A chemical business?

WESTHEIMER: A chemical business, oh yes, indeed. And Bill McEwen was in the lab. This is a different Bill McEwen than the one who is now at the University of Massachusetts, who is a much younger man. I've no idea what happened to that Bill McEwen.

GORTLER: This is the one who did the acidity studies?

WESTHEIMER: The acidity studies. Now, Bill McEwen and I were acquainted. We were not really friends but having those acidity studies going on in the same lab as the one I was in, and having the porphyrin syntheses going on in the same lab I was in, were both very helpful. I got much more stimulation scientifically from Conant's lab than I did from Kohler's. On the other hand, my friendships and scientific discussions with Tishler and Newman were much better than the ones I had with the students in Conant's lab.

There was a graduate student of Fieser's who later went into medicine and then died of cancer, who made methylcholanthrene in Fieser's lab at the time, which was the most powerful carcinogen made in Fieser's lab, and one of the most powerful carcinogens then known--and I think still is among the "best," though I don't think it can compete with aflatoxin. That was an interesting piece of work to have under way at that time. The synthesis was interesting, experimentally. [Arnold] Seligman was his name.

One of the steps was a Grignard. Seligman had an aromatic bromide, tried to make the Grignard, and failed; it couldn't be made. He took the recovered bromide from the Grignard, recrystallized it, put it back in, and the Grignard worked, which was a nice demonstration that there must have been some minor impurity there, that probably was mopped up in the first attempt to make the Grignard, and then it went.

I don't know if that's so important, but it was a little vignette of the experimental part of chemistry that meant something to me.

You asked me where my interest in biochemistry came from. It comes I think in large part from the fact that there was biochemistry going on in Conant's laboratory, and I watched Quattlebaum do his porphyrin syntheses, and I'll say more about that later because I did porphyrin syntheses myself. A very important influence while I was there.

The discovery of vitamin K occurred. [Edward A.] Doisy's discovery of vitamin K structure and synthesis came out in the Journal of the American Chemical Society during my years as a graduate student, and made a great impression.

I'd like to tell a lot about Conant.

GORTLER: Yes. I'd like that.

WESTHEIMER: When Conant finally accepted me as a graduate student, I asked him for a good textbook in organic chemistry. He said, "Well, you know, there isn't a very good textbook. Do you read German?" I said, "I can read German but not very well." He said, "The best textbook is Karrer's Lehrbuch and if you don't read German very well, by all means, buy it" (7).

So I bought Karrer's Lehrbuch. This was before it had been translated, and I used that learning both chemistry and German. I also bought the first edition of Hückel's Theoretische Grundlagen der Organischen Chemie, which I read avidly, but I didn't like very much (8). I think I had the second edition when I was here at Harvard, and labored over Hückel's involved German with great pain.

GORTLER: You did footnote it in one article; I think it was the retroaldol article (9). I noticed that; I was going to ask you about it, so I'm glad you brought it up.

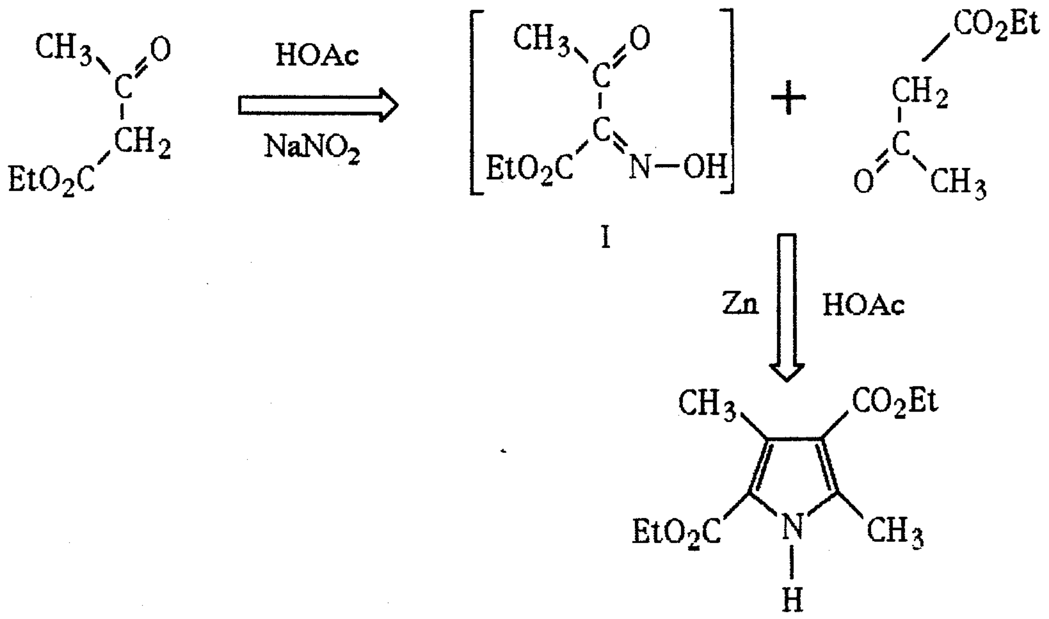
WESTHEIMER: It was the only textbook of physical organic chemistry in the world at the time, I think. Hückel didn't look upon physical organic chemistry at all the way I did. But it was the only one there was. I read it. I worked on it and sweated over it. My German was not terribly good then, and it isn't now. Karrer was easy. Karrer's was lovely, straightforward, simple sentences that I could read without any trouble.

Well, at the end of my first year, I was going to go home for the summer rather than spend the summer here at Harvard. I wanted to do chemistry, and Conant suggested that I spend the summer in Alsoph Corwin's laboratory, at Johns Hopkins. Corwin had been one of Conant's students engaged in porphyrin synthesis, and maintained a laboratory at Hopkins in which he did such work to the end of his career. I worked in Corwin's laboratory, on syntheses of pyrroles, dipyrrolmethanes and dipyrrolmethines. I don't think I ever got up any further, but I did a great deal of preparative synthetic chemistry, much of it on quite a large scale.

I needed that laboratory experience very badly. It was good for me even though I'd been doing research; it was good for me to do all these preps. They were extremely interesting mechanistically, because they involved the Knorr pyrrole synthesis. Do you know this synthesis?

GORTLER: No, I don't think so.

WESTHEIMER: One takes ethyl acetoacetate, acetic acid and sodium nitrite, which react to give the oxime (I). You add another mole of ethyl acetoacetate, zinc and acetic acid (acetic acid is the solvent for the reactions). That reduces the oxime to the amine. That condenses with the keto group. This, of course, is an activated methylene, which condenses and closes the ring system. Isomerization of the double bonds completes the synthesis.



Well, that synthesis can be modified hundreds of ways. It is the standard synthesis that was adopted and adapted by Hans Fischer in his widespread syntheses that led to his synthesis of hemin. It has nice mechanistic implications, as well as being good heterocyclic chemistry. I learned a lot by doing that work in that lab.

But I must also say that Alsoph Corwin was one of the important influences on my life. He's an eccentric, but he was always reading and talking about interesting things. I went back to Corwin's laboratory again the summer after I got my Ph.D., and he let me work in his laboratory. I was working on my own things then, but I had lots and lots and lots of conversations with Corwin. Corwin read very widely, and brought up many topics where he didn't always have the right ideas, but he stimulated discussions for which I'm enormously grateful.

The story about Conant that I want to tell--and this will get me almost into the things that I've listed--which was a very important part of my scientific career, is the following:

When I was a graduate student at Harvard, even though I did synthetic work with Kohler, and even though I did a lot of pyrrole and dipyrrolmethanes and methanes synthesis with Corwin, I was primarily interested in theoretical organic chemistry. I intended to be a theoretical organic chemist, and work on reaction mechanisms. (And I can talk a little bit about where the mechanistic ideas came from in those days.) When I got my Ph.D., I felt then more confident of my command of chemistry than I have at any time since. I knew a whole set of problems concerned with reaction mechanisms. I knew how to tackle them, what to do to get evidence that some hypothesis was correct or incorrect. And I could look around the literature, at the vast wasteland, and see that, except for Ingold's laboratory, which was doing quite different things--he was doing displacement reactions and I wanted to do condensation reactions--there wasn't anybody doing anything, especially in the United States. The people who were considered the great organic chemists were not doing anything that I considered of much interest, and certainly nothing that was competitive with anything that I wanted to do. So I felt that this whole vast field was mine! There was hardly anyone else out there.

Now, of course it's easy to see in retrospect how silly that was. What I had not realized was that there were then half a dozen, and soon to be dozens, of other people who knew exactly the same thing. They hadn't appeared yet. [Saul] Winstein hadn't surfaced; [Paul D.] Bartlett was just beginning. [John D.] Roberts hadn't begun. The large number of physical organic chemists that were going to build this whole new subject weren't there.

So I could look at Adams or [Carl] Marvel or [Marston T.] Bogert and know that he wasn't going to be a competitor. Hammett was doing extremely interesting things, but they weren't the kind of things that I wanted to do.

GORTLER: He wasn't even an organic chemist.

WESTHEIMER: He wasn't even an organic chemist. So, the whole world was mine. And I had won a National Research Council Fellowship. There weren't many of them, and I'd won one on this project that I'd submitted--of my own--on the kinetics and mechanism of the benzilic acid rearrangement. My project contrasted to many of the projects submitted today--you know, they're the research supervisor's.

Mine was a fine problem, although it had been my intention eventually, after I did just a little, to return to condensation reactions. But I didn't want to do that then, because I'd worked on semicarbazone formation with Conant, and I wanted to break away and not be associated with what I'd done with Conant. I thought the rearrangement was a perfectly good problem.

Well, after I got my Ph.D., Conant called me to the president's house. He hadn't seen me since he had deserted the ship in 1933. He sat me down and--

GORTLER: By the way, there was that feeling that he had deserted chemistry?

WESTHEIMER: Yes. Oh, yes.

GORTLER: Okay. I've heard that before.

WESTHEIMER: He sat me down. Well, I'd done work with him. I'd gotten my Ph.D. with Kohler. He was interested in what I was doing, and I said I had a National Research Council Fellowship. "Well," he said, "What are you going to do?" I outlined, with great pride, this problem. Conant sat there silent for a moment or two with me. Then he said, "Well, if you are successful [in solving that problem] that will be a footnote to a footnote in the history of chemistry." In contrast to the words of the dean of freshmen at Dartmouth, that remark struck home.

GORTLER: Did it then, or was it later?

WESTHEIMER: Right then! If there was ever an occasion when someone who had been looking down, looked up, it was in response to that remark.

Oh, I think I had not really been sufficiently ambitious. I had been concerned with things that I thought were fun and interesting. But it had never occurred to me, until that moment, really, that I would be able to have a real part in the history of chemistry.

And the notion that Conant essentially was saying, "Well, that problem is all right, but good God, you can do better," was very important to me. From then on, I tried to ask myself about problems, whether they were really worth the investment of time.

Then, I guess it's a very conceited thing to say, but I will say it anyway. It seems to me that many of the scientists I know who are much brighter than I, fail to ask themselves that question, and waste talents that I can only envy on problems that aren't worth it.

GORTLER: That's an important statement, with respect to how science develops, I think, and we can discuss that.

WESTHEIMER: That's one of the things I had on my list, that I wanted to say.

GORTLER: That's a terribly important statement. You were a John Harvard Fellow?

WESTHEIMER: Yes.

GORTLER: What was that? How were you appointed? What did it mean?

WESTHEIMER: It was an honor. What it meant was that my parents could afford to put me through the university.

GORTLER: It carried no stipend?

WESTHEIMER: It carried no stipend. In earlier days, I think the John Harvard Fellowships had carried whatever stipend the individual needed, but by the middle of the Depression it carried no stipend. My parents could afford to support me, and were willing to support me, and the John Harvard Fellowship carried no stipend. I'm very much in favor of that sort of thing. It would have seemed to me grossly unfair if my record at Harvard had shown no honors, because I wasn't financially poor enough to be entitled to them. Today, everyone who goes to graduate school essentially is supported on merit, regardless of finances. But in those days, if you could find the money, you weren't allowed any of the financial scholarships. I'm very pleased that Harvard gave me that one which carried no stipend.

Incidentally, I wanted to have the experience of teaching, and was barred from applying for a teaching fellowship because I didn't need the money. So I applied to Fieser for permission to teach in Chem 20, which was then Chem 2, for free. But he turned me down.

GORTLER: Before we get on to your real scientific career, I wanted to ask about the courses that you took, the courses that were offered here and the faculty members that were around at the time. Do you remember the courses?

WESTHEIMER: I remember very well the course in physical chemistry that I took from Kistiakowsky. It was quite a good course, although the quantum theory that was taught was Bohr theory. Although the Schrödinger equation had been published, George did not teach it. So the quantum chemistry was somewhat inadequate. On the other hand, I learned thermodynamics quite thoroughly, so that at the time of that final examination, I could sit down on my own and produce, I think, almost all the equations in Lewis and Randall (10). I can't do it today. But I really learned that material, inside and out.

The organic chemistry course was Kohler's Chem 5, and it was a marvelous course. It was the intermediate-level organic chemistry course with material that I and my friends had not taught each other at Dartmouth, and that I really needed desperately. For reasons not clear to me, I was not registered for the course. I audited it. Perhaps Conant told me that since I had had an intermediate-level organic chemistry course, I could audit Chem 5. But I knew better, and got Kohler's permission to take the hour exams and final along with the rest of the people in the course--which I did, auditing or no auditing--because otherwise I would never have known if I was doing it right or not.

[END OF TAPE, SIDE 4]

WESTHEIMER: I just started talking about Fieser's course on steroids.

Fieser gave in lectures what later became his book, The Chemistry of Natural Products Related to Phenanthrene (11). That was a very useful course in learning something about the dominant area of natural products of that time. The work of Heinrich Wieland and Adolph Windaus, and the early x-ray crystallography that was done on that system, that led to the solution of the structural problems of steroids, was quite important chemistry.

Parenthetically, I have maintained for years that steroid chemistry was a trap into which organic chemistry fell. When Emil Fischer dominated organic chemistry, the subjects were the sugars, the amino acids and proteins, and the purines and pyrimidines, though not the nucleic acids, but the purines and pyrimidines from the nucleic acids. Those were the topics that Fischer brought into organic chemistry, and constituted the core of organic chemistry, in his day. And of course he worked with enzymes, and the stereochemical demonstrations within the field of carbohydrates were often done in Fischer's laboratory enzymically.

When organic chemists became enamored of the steroids, the pendulum swung in that direction so far that they gave up studying and continuing with the things that Fischer had been doing. They left to a relatively small core of individuals, plus a new class of chemists called biochemists, the investigation of an area of organic chemistry which I regard as perhaps the most interesting.

If I have any proud boast, I claim to have a part in bringing organic chemists into biochemistry, in bringing them back to their patrimony. It's coming back to Emil Fischer. I've said for many years that what is good enough for Emil Fischer is good enough for me.

Nevertheless, I was fascinated by this steroid business, and it was a marvelous course that Fieser gave. But I wish the organic chemists had not gone what I regard as overboard in that direction and had maintained, to a greater extent, research into the subjects that had been the life's work of the individual whom most of us would regard as the greatest of organic chemists.

The following year I had Bartlett's course in physical organic chemistry. It was the first time he gave it. He came to Harvard as an instructor, a so-called faculty instructor, which meant a tenure track instructor. The course was precisely what I wanted and needed.

I went over to physics to try to take a course in electricity and magnetism, but I got into a course that was over my head. I couldn't manage it and quit, which is too bad. I didn't take a course in electricity and magnetism until I was on the staff of the University of Chicago, when I went over to the physics department and took the course that I should have had all along.

I don't think I had any other courses here at Harvard except the ones I've recited. There weren't many given here at the time.

GORTLER: Do you remember any course that was called "Physical Organic Chemistry?"

WESTHEIMER: Before Paul's? Paul gave a half year of physical organic chemistry.

GORTLER: Okay. Did Conant give it before him?

WESTHEIMER: I think he did, but I was not ready for it then and never had it.

And of course it was Conant whose enthusiasm for Hammett led me to read Hammett's work, whereupon I became very excited. I could tell you about the various papers I've read that really excited me.

It was Conant who got me to read Hammett, and of course the Hammett and [Alden J.] Deyrup papers, which seem so ridiculously simple today, were very difficult papers then (12). Hammett had a paper on acidity in general that was at the limit of my capacity, but I loved it (13). And the Hammett and Flexser paper, I thought was fabulous (4). So I was a wild Hammett enthusiast then, an opinion that I have had no reason to change at any time.

I don't know where I got onto [Arthur] Lapworth's papers. I don't know who told me to read those; maybe Conant. All my life I've regarded Lapworth as <u>the</u> great physical organic chemist, the individual who broke most sharply with tradition. Everybody stands on everybody else's shoulders. I mean, there is no such thing as total originality. But if I were looking for originality in the field of physical organic chemistry, I'd go back to Lapworth. I think his 1898 paper on cyanohydrin formation is wonderful, and his, I think, 1904 paper on the halogenation of acetone still seems to me, as it did when I read it as a student, the greatest paper in physical organic chemistry that has ever been written (14). I would like to present that argument, if you're willing to listen to it.

At that time, Lapworth used reaction kinetics to delineate mechanism. The reaction kinetics for the bromination of acetone were unusual because the reaction that involved bromine was zero order in bromine; those experiments led to a clear statement of mechanism. Furthermore that paper contains in it the single sentence that reads, "Neutral salts of strong bases and acids in general did not produce any marked influence on the speed of the reaction. It was noticed, too, that the velocity observed in diffused daylight was not appreciably different from that in darkness."

Those sentences were really food for thought, remarkable for 1904. In 1894, [Max] Bodenstein published the first of his famous papers on the reaction between hydrogen and iodine. In the series, he worked out the reaction kinetics, determined the activation energy, and proposed a mechanism for the reaction, a simple bimolecular exchange through a four-membered cyclic transition state (15).

My physical chemistry friends, especially [the late] Professor Kistiakowsky, regarded that as the origin, the first proper paper in reaction kinetics and mechanism, at least the first paper of any significance. It was dull by comparison with Lapworth's work. Bodenstein's reaction seemed to be a simple bimolecular one, whereas Lapworth's was a very interesting and intricate one. And Bodenstein, incidentally, had the bad luck to be wrong. The mechanism he formulated turned out to be incorrect, and the process is in fact a free radical reaction, where a rapid equilibrium controls the concentration of the iodine atoms, so that you get a transition state, which is I....H_2....I, coming apart to two molecules of HI, instead of this:

$$\begin{array}{ccc} \mathrm{H} & \cdots\cdots & \mathrm{H} \\ : & & : \\ \mathrm{I} & \cdots\cdots & \mathrm{I} \end{array}$$

Well, of course, he was unlucky. He was terribly unlucky. But it is interesting that less than a decade after Bodenstein, Lapworth applied reaction kinetics to mechanism in a highly significant way and got it right. And he wrote a paper in which he took for granted, that is he made no fuss about the fact, that in reaction kinetics in solution, you worry about photochemical reactions and about salt effects.

Those papers really made a tremendous impression on me.

GORTLER: They were probably almost as impressive as the fact that he was using bonding in a way that no one else was to use for another twenty-five years.

WESTHEIMER: My thinking about Lapworth is, he was a leader, and he got so far ahead of his followers that they couldn't see him. I believe he's been grossly underhonored in the world.

In the 1940s, when I was a professor at the University of Chicago, Sir Christopher Ingold visited our department. One morning, when I was breakfasting with Ingold at the Quadrangle Club, I casually mentioned Lapworth. I said something to the effect that I assumed that he [Ingold] valued those turn of the century papers as much as I did. Sir Christopher turned red and spluttered. No, indeed, he did not value Lapworth's papers. He had no debt whatsoever to Lapworth. I gathered that physical organic chemistry was Ingold's project, and that he and his coworkers had contributed everything of importance to its origins. Since Ingold had been only a young boy when Lapworth brominated acetone, it seemed to me that he could be relaxed and admit that at that time, someone else had made a discovery. But such was not the case.

The [Robert] Robinson 1917 paper on the synthesis of the tropinone alkaloids is the other paper that I thought was just marvelous (16). It was the kind of thing I would like to have imitated--the mechanistic approach to organic chemistry, to organic synthesis. Those were the big papers.

Then I was reading Ingold, though exactly what papers I read, when and where, I don't know. What I remember most clearly, and this puts it a couple of years later than graduate work, was my second year, I think, at the University of Chicago when Bill Wheland came on the staff.

GORTLER: Could it be that your interest in Lapworth was instigated by hearing Kohler talk about him in his lectures? Paul Bartlett mentioned that.

WESTHEIMER: It might very well be. It is also possible that Conant talked about him. And for all I would know, Kohler mentioned the Robinson work; I don't remember.

I know I was well acquainted with Ingold's papers by the time Wheland arrived at the University of Chicago in the fall of 1937. When he arrived and we met--

GORTLER: Had he been with [Linus] Pauling all this time?

WESTHEIMER: He had been with Pauling. He'd also been with Ingold for a brief period, maybe just a month or so, but he had been with Pauling most of this time. I knew <u>his</u> work of course, and had great admiration for it. But I hadn't done anything at that time that he should have known about.

When Wheland arrived at the University of Chicago, we met in the library of the chemistry department, and he quizzed me very, very thoroughly on Ingold's papers. Well, in fact, the reaction kinetics business was something I really understood, so I passed my test. If I hadn't passed my test, Bill and I never would have been friends.

GORTLER: But you were prepared.

WESTHEIMER: Well, I mean, it was fundamental to the physical organic chemistry of the time. But I don't know when I read them. I don't know how early I had read them.

Other things--and some of them related to biochemistry. [Wendell] Stanley crystallized the tobacco mosaic virus in 1935 (17). I went back and looked it up. When I met Jeanne for the first time, just after I got my Ph.D. in 1935, what I told her about was Stanley's tobacco mosaic virus. Now, that may not seem exactly romantic--

GORTLER: She married you anyway?

WESTHEIMER: She not only married me anyway, but it's her claim that she married me because of that conversation. The young men that she had been going out with were more frivolous, did not have a driving interest in their lives, and if she didn't understand much about the tobacco mosaic virus, she understood that I was very enthusiastic. So it's clear that somehow or other, I knew about the tobacco mosaic virus roughly as soon as Stanley published it. I have searched my mind to know how I knew it, because I am not as great a literature reader as many of my friends. I doubt that I picked that up on my own. Maybe I did. If you want a guess, my guess is that Alsoph Corwin mentioned it to me and then I went and read it, and Corwin seems a likely person. I don't know. But I was full of it at the time.

I don't know exactly when my fundamental interest in biochemistry arose. You asked about this, and I can say something about it, but I don't know how to date it. I had remembered, when I read your letter, just what it was. I knew perfectly. It was when I read [Ernest] Baldwin's Dynamic Aspects of Biochemistry (18). Well, it turns out that the first edition didn't appear until 1947, and so my previous recollection is just nonsense.

GORTLER: You know, it's interesting, you may have already started the work, but your papers just started to come out about then.

WESTHEIMER: No, but I'll go back, and you'll find that I'd been doing biochemistry much earlier. One of the best pieces of biochemistry I did never got published. It was done much earlier.

When I was at Columbia--and I want to talk about Columbia, because that was a wonderful group of people that had an enormous influence on me, a splendid group--there was a seminar program similar to the Bartlett Friday afternoon physical organic seminars, where students and postdoctorals spoke. I gave a seminar then on the pathway of alcoholic fermentation; so this was the fall of 1935 or the spring of 1936. The important papers, which were [O.] Meyerhof papers, had only come out that year or the year before (19). Meyerhof was the person who had discovered the retroaldol condensation of fructose-1,6-diphosphate. That was recent work, and of course that's the key, really to alcoholic fermentation, and to glycolysis in muscle. I gave my seminar at Columbia on that work, going back to the beginning of it as best I could, and giving Meyerhof's discovery, which was recent.

I no longer own, but I once owned [Arthur] Harden's book on alcoholic fermentation (20). The second edition came out in 1932. Now, whether I bought that when I was still at Harvard, or whether I bought that when I was at Columbia, or perhaps even later, I don't know. I think I must have had it when I was at Columbia and prepared that seminar.

Of course, Harden's book could not have in it the retroaldol on fructose-1,6-diphosphate because it hadn't been discovered. But it did have in it the phosphorylation of glucose and the various phosphate esters--the Harden-Young ester, the Neuberg ester and so on--that had been isolated and that looked like they were going to prove to be intermediates in the metabolic pathway of glycolysis and of fermentation.

It was the mechanistic aspect of Meyerhof's work that would catch me and did catch me, so I think that the fact that I gave that seminar in 1935 is fairly good evidence that I had those interests at the time.

While I was at Columbia, I had bought two textbooks of biochemistry; I remember the name of one of them and not the other. One of them was [Meyer] Bodansky's book (21). And I read them. I have not gone back to them since you've written me, but my recollection is that they were dreadful books, in that they were organized sort of as: What chemical compounds do you find in what body fluids? What can you get out of urine? What can you get out of blood? What do you find in muscle? And so on. The chemical notion that you have to transform one material into another somehow, in my recollection at least--it might be nice to go back to the books and see if I'm right--was a minor part of either Bodansky or the other book I had; whereas Harden's Alcoholic Fermentation, although it couldn't go very far, was concerned with: How do you get from here to there? which is the problem of chemistry. Well, that isn't totally true; chemistry has the problem of structures, and it has the problem of transformation.

So by the time I was at Columbia, I was off on a program of self-study in biochemistry, and gave a seminar, my guess is, on fermentation and glycolysis which was at the time up-to-date.

GORTLER: It's interesting that when you taught your course, which I took many years later, in the late 1950s I guess, in biochemistry, that's how you taught the course: How do you go from one place to another? I remember dealing with the Krebs cycle and everyone was having so much trouble, and not that I can repeat it to you now, but it seemed perfectly obvious because you were teaching us to go from one step to the next. Obviously you'd set out a certain plan at that time which you maintained for a long time to come. It certainly fits things together now in my own mind.

WESTHEIMER: I would not have thought of my organization of that course as growing out of what I had done before, but I suppose most of what one does grows out of earlier work.

The structures of DPN and TPN were determined in 1935. I don't think I knew about it at the time. I went back to see when they were discovered. When I was giving the sequence, one knew that there was an oxidation reduction coenzyme, but the structures--they had just been published, but I don't think I knew them. Of course, what one knew in 1935-1936 is very hard to say. I went back to look up the story on the crystallization of enzymes. I'm pretty sure that I knew when I was at Columbia that enzymes were proteins. That probably was even in a textbook like Bodansky's. The crystallization of urease by [James B.] Sumner was 1926. I imagine that by 1935 the textbooks had incorporated that fact. There was a lot of contention about it in 1926. I don't know if you know that story. That's a very interesting aspect of the history of chemistry. We'll talk about it at lunch.

[END OF TAPE, SIDE 5]

WESTHEIMER: Northrop crystallized pepsin in 1930, and trypsin in 1932, so that by the time I was at Columbia, the fact that enzymes were proteins was well established. I must have known that at that time, when I gave the seminar on fermentation.

Incidentally, just as some reflection on my own thinking at the time, I didn't know I was going to get a job at the University of Chicago, of course, and had to worry about what I was going to do next year. I had applied to the National Research Council for renewal of a fellowship which I might very well not have received, to work at Harvard with Edwin Cohn, who was then concerned with the basic physical chemistry of amino acids and proteins. In particular, and this bears on my later life, John Kirkwood was a collaborator with Cohn. He wasn't in Cohn's laboratory, but at MIT. He wrote papers on the activity coefficients of amino acids and proteins, and explained the enormous changes in solubility of proteins with added salts on the basis of the changes in the activity coefficients. That was on the one hand, an extension of the Debye-Hückel activity coefficient concepts to zwitterions, and on the other hand, could be regarded as an application of physical chemistry to biochemistry. It was that work in Cohn's laboratory that interested me, and that caused me to apply.

Cohn accepted me, subject to my getting the fellowship, which Lord knows if I ever would have received, but in the meantime, I had the opportunity to go to Chicago.

That's an interesting story too, although really irrelevant to the history.

GORTLER: That's a story I want to know.

WESTHEIMER: Well, anyway, I was at Columbia, working on the kinetics and mechanism of the benzilic acid rearrangement. At that time, Kharasch had published a paper on the "peroxide effect" in the Cannizzaro reaction (22). He had found that the Cannizzaro reaction of benzaldehyde was greatly accelerated by atmospheric oxygen, and could not be prevented but greatly diminished in rate by using strict anaerobic conditions.

Well, it turned out later that that was not a peroxide effect in the usual Kharasch sense. What happened was that oxygen caused the autooxidation of some benzaldehyde to form sodium benzoate. Sodium benzoate is a poor emulsifying agent but much better than none. It was a heterogeneous reaction he was studying and the emulsification increased the rate. That turned up much later, much later. At the time we didn't know anything about it. I was a great admirer of the work of Kharasch and Mayo, which had been published by then.

GORTLER: It was already out?

WESTHEIMER: It was already out. It had come out in 1933. It was out by the time I was finishing my graduate work at Harvard, and of course I knew that work and was greatly interested in it. Since I didn't understand the peroxide effect on the Cannizzaro reaction, and since I worried, and since I thought the benzilic acid rearrangement was something like the Cannizzaro, I tested the benzilic acid rearrangement, which I was carrying out in homogeneous solution, for the same kind of oxygen effect that Kharasch had observed in the Cannizzaro. Quite naturally, there wasn't any effect.

Well, Kharasch was looking for a staff member for the University of Chicago. He came to Columbia on his tour, and among other things, he asked Bogert whether there might not be a National Research Council Fellow there. Bogert said absolutely not. According to Kharasch, he essentially refused to let Kharasch see anyone but his [Bogert's] own students.

GORTLER: It wasn't out of ignorance that he said this?

WESTHEIMER: Well, it may have been out of ignorance. It may have been out of ignorance, I don't know, but he was concentrating on his own students, and this infuriated Kharasch so much that Kharasch asked the question elsewhere, and found out there was one, and came and found me, working away in the laboratory. He wanted to know what I was doing, and I explained this, and of course I explained to him how I had just done this test for the peroxide effect on the benzilic acid rearrangement and found none.

At that time, I was very much concerned that telling Kharasch that I couldn't find his effect was going to turn him off. But of course with the better perspective one gets with years, I realize that that probably is why I got my job. The fact that I had read his paper, thought it was important, and acted upon it, was, I am sure, the greatest possible recommendation for me as a really far-seeing, bright, alert young man. I'm convinced that that's how I got my start.

One of the foolish breaks, but a break. I'd applied for other absolutely terrible jobs, and been turned down out of hand by people who didn't consider me at all. I was considered at the time at Cornell, and went there and gave a seminar. My competitor was Bill Miller who does fluorine chemistry. They picked him instead of me. In retrospect, I think I have had a better career than he has had. Cornell didn't make a foolish choice in any way. Bill Miller obviously was working in an interesting and expanding field, organofluorine compounds, and he's done very well with it and made real contributions to the field. So I think he was a good man in a good field. I have no feeling that, if I'd been in their place, I wouldn't have made the same decision.

GORTLER: Hammett commented that a number of his graduate students in the 1930s were Jewish and he sometimes had a difficult time placing them. Most of them ended up doing well. Later he said there was definitely an anti-Semitic attitude in the area of chemistry, and it didn't really pass until after the war. Do you think this had any effect on your getting a job?

WESTHEIMER: Ah, that is entirely true. There's no question about that. At the University of Chicago, however, [Julius] Stieglitz was Jewish and Kharasch was Jewish. It may be that that department was less prejudiced. [Hermann] Schlesinger was not Jewish. I may have been very lucky in getting the Chicago job, but I have no feeling whatsoever that the decision at Cornell, which was the only other decent job I had a shot at, had anything to do with anti-Semitism. I think that was made strictly on the basis of people listening to the two seminars and deciding which was the better. As I said, I think if I'd listened to those seminars, I might have made the same decision they did. Although there was some anti-Semitism, I personally faced relatively little.

GORTLER: When you were at Columbia, did you spend much time talking to Hammett?

WESTHEIMER: I spoke to Hammett a fair amount. There was this group, whose names I wrote down, that formed a little nucleus of people who talked together a great deal, went out to lunch together almost every day, and not infrequently had dinner together. A couple of us may have had dinner together once a week or twice a week, and the whole group might have gone out to dinner together once every three weeks. We talked a great deal of science. In fact, I don't remember talking with these people about very much else except science.

This was in the middle of the Depression, and conversation could have been highly political. Some of these people were fairly political, but I was extraordinarily apolitical at the time. I wasn't anywhere near as concerned with the politics of the world as it seems to me in retrospect, I ought to have been, if the word "ought" has any meaning.

GORTLER: One of my questions later was going to be, did the social, political climate of that period have any impact on your science? Apparently it did not.

WESTHEIMER: No. But it was there.

Anyway, let me give the list, because this is a good list of people. First and foremost was Pete Treffers, whose real name is Henry. It's Henry Peter Treffers, but that was Pete Treffers, and I don't know where he is now. He was at Yale for a while. He became--

GORTLER: He became a biochemist, and went to Yale medical school. Hammett talked to me about him.

WESTHEIMER: He's a first-class scientist. And then Joe Steigman. Martin Paul.

GORTLER: I want to ask you about him later. I notice he did some work with you on the "Westheimer Report" (23).

WESTHEIMER: Yes. Martin and I were together three times--at Columbia, at the NDRC's [National Defense Research Committee] Explosives Research Lab in Bruceton, Pennsylvania, and again then when he was in charge of the chemistry section of the National Research Council.

GORTLER: That explains why he was consultant to that committee you were on.

WESTHEIMER: Right. Irving Roberts. Irv Roberts was the Roberts who postulated the bromonium ion intermediates in the addition of bromine to double bonds. That's a paper by [George E.] Kimball and Roberts (24), and I think many people today no longer quite know which Roberts it was. But that was Irv Roberts.

Then there was Joe Greenspan. Now, Treffers and Steigman and Paul and Roberts were students of Hammett. Greenspan was a student of [Victor K.] LaMer's.

Kimball was a physical chemist at Columbia. But Roberts wasn't working with Kimball; that is, he wasn't a graduate student of Kimball's.

Then at Columbia at the time, in addition to Hammett, there was quite a constellation of stars. V. K. LaMer was there, and contributed greatly to the field of reaction kinetics. And Greenspan, who was a very good kineticist, and a marvelous person with whom to discuss mechanistic problems. He was a sort of Talmudic scholar type, who would be glad to discuss questions which I've described as, "How many chemical angels can stand on the head of a chemical pin?" Although I'm rather scornful of that sort of thing, because I believe it can be so grossly overdone, there's nothing like discussion with a Talmudic scholar to sharpen your wits. Greenspan was very, very good at that.

There was a biochemist in the chemistry department there, J. M. "Pop" Nelson. I never learned very much about what Nelson did, but the fact that there was a biochemist in the chemistry department, and that people were interested in his work, certainly was not lost on me.

GORTLER: Hammett had a very high regard for him.

WESTHEIMER: Harold Urey was there at the time doing isotope separation by distillation and in particular, oxygen-18. Mildred Cohn apparently was there then. I don't remember having met her but I'll bet I did, because she was with Urey at the same time I was with Hammett. But I can't remember having known her at that time. That may have to do with my crummy memory for people.

That was a very exciting group of people at Columbia, and I had much more stimulation with respect to physical organic chemistry there than at any other time in my life. It might have been good with Conant here, if he'd stayed. When he left, the atmosphere changed away from physical organic chemistry. It began to revive when Paul Bartlett came back, but in 1934-1935 there wasn't a sizable group of people with whom to interact. The group at Columbia were all interested in physical organic chemistry and in reaction mechanisms. It was a splendid year.

GORTLER: That puts Hammett's work sort of in perspective as well, because there were these other people around him, and when I said, "Whom were you talking to?" he said, "No one." But I strongly suspect he was talking to these people, not about anything in particular, but in general, because that makes sense.

WESTHEIMER: I think he talked to all of us. When he says, "No one," he probably meant that he didn't have any colleagues to talk to. It was very hard to talk to LaMer, because I think that LaMer was as beloved at Columbia as one of my "friends" was at Harvard.

GORTLER: Hammett shared an office with him at one time, but apparently not any longer when you were there.

WESTHEIMER: No. I have a nice story to tell about Hammett, and me. I was trying to get my work started at Columbia. I was having a hell of a time. I couldn't get any supplies. I couldn't get anything done. I didn't have any money, and I didn't understand about money, and I wanted Columbia to put up a couple of hundred dollars for something or other, and I couldn't get anywhere.

I put up pretty much of a storm with Bogert, who was chairman of the department, and next thing I knew, Hammett came into my lab. He recited this business with Bogert, and said that he thought that I had been really very rude to this distinguished colleague who was chairman of the chemistry department. Hammett's always very mild. I knew enough to read between the words. I took off my lab coat (people wore them then), put on a jacket and said, "Professor Hammett, you're entirely right about it. I was absolutely out of line, and I am now on my way down to Professor Bogert's office to apologize." He said, "Oh no, don't do that!" [laughter] It suddenly dawned on me that it was his duty to come and chide me, but he probably thought I was absolutely right.

GORTLER: Do you remember an accident that you had when you were at Columbia? Do you remember burning your nose?

WESTHEIMER: Oh yes, of course.

GORTLER: Hammett told me that story off the record. I wondered if you could give me your version of it?

WESTHEIMER: Well, Jeanne will tell you that story.

GORTLER: He thought it was funny because apparently you had to go to the infirmary and he had to fill out an accident form or something like that. One of the questions on the form was, "Was the person to whom the accident occurred at fault?" He wrote back, "Absolutely, he was at fault."

WESTHEIMER: You know, I never knew that.

That was a very good year at Columbia. I was miserably unhappy socially. I had an apartment a few blocks away from the lab. I worked day and night, all year long. When I say miserably unhappy socially--well, I went to a lot of theater. It cost 85 cents in those days for standing room, and since practically no one sat in the theater because no one had bought any seats, after you'd stood up through the first scene of the first act, the ushers practically pushed you into the seats, so there'd be someone for the players to play to.

It was a hard slogging year. But scientifically it was great, absolutely great, to have all these people to talk to. And during the year I did all that reading in biochemistry. What set me off to do that, I'm not quite sure. I certainly knew about the existence of enzymes as proteins. I knew about Stanley's tobacco mosaic virus, essentially as soon as it was done. And I started my program of working out the mechanism of enzyme action because I decided that it must be acid-base catalysis by those groups on proteins. And so it is, you know, only what I did experimentally turned out not to work. The amino acids themselves turned out not to produce effects any larger than those you'd expect from their acid-base properties (25).

Well, many years later, Gardner Swain and Brown--the famous paper of Swain and Brown, do you know it (26)?

GORTLER: No, I don't.

WESTHEIMER: Swain and Brown looked at the mutarotation of tetramethylglucose, in benzene as solvent, using α-pyridone as catalyst, and found that α-pyridone was a catalyst--I'm going to say, ten thousand times more powerful than you would have expected, from a combination of an equally weak acid and an equally weak base, present in reasonable concentrations. Now, of course, the acid plus base reaction, with tetramethylglucose would be third order, whereas α-pyridone and tetramethylglucose is second order. You have to state at what concentration level you are operating. It was something like ten thousand times greater, at concentrations of something like 0.05 molar, which is a very high concentration, when you consider it, and the ratio would become even greater at lower concentrations.

Their experiment was really a very good demonstration. It was the sort of thing that I'd been looking for with amino acids, an acid and base group together. The difference between what Swain and Brown did and what I had done fifteen years earlier was that they had the brains not to work in water. Of course, it's water that ruins the kind of concerted catalysis that I'd been looking for. I don't think that I was so awfully stupid not to have realized that in 1935-1936, but I sure didn't. Swain and Brown, much later, did what I wanted to have done, but failed.

GORTLER: It took fifteen years for them to get that sophisticated?

WESTHEIMER: But anyhow, I was certainly interested in trying to do biochemical research then.

GORTLER: In that benzilic acid paper, there's a footnote where you cite Paul Bartlett, and the question I have is, were you communicating with Bartlett, or was he a referee (27)?

WESTHEIMER: He was not, to the best of my knowledge, a referee. A referee for that paper was Jack Aston at Penn State University, who picked up some sort of ambiguity or misdefinition or something in my chemical equations, and he had been one of Conant's students. He wrote a very nice and quite complimentary referee report, pointed out this error, and signed the referee report.

[END OF TAPE, SIDE 6]

WESTHEIMER: I was in touch with Paul. I communicated with him fairly regularly.

GORTLER: It makes sense now, because you already knew him before you went to Columbia, and I hadn't made the connection.

WESTHEIMER: Oh, yes. He had been a faculty instructor here for a year. I had taken his course. We had talked about semicarbazone formation quite a bit. Yes, we were reasonably well acquainted, well enough acquainted that when Jeanne and I were married in 1937, the Bartletts sent us a very nice wedding present, still preserved with great pleasure.

When I got to the University of Chicago, I started doing several things. One was that paper on the amino acids, which didn't work out so well (25). One was the business of amine catalysis of the dealdolization of diacetone alcohol (9), which together with the explanation (28) of this as going by way of a Schiff base, which I published in an obscure journal where it was never seen, I consider really respectable chemistry.

GORTLER: What is the obscure journal?

WESTHEIMER: The explanation was in the Annals of the New York Academy of Science. At the same time, that first year at the University of Chicago, I did two other things. I gave a course in physical organic chemistry which almost ended my career in chemistry, and I took a course in electricity and magnetism in the physics department, which I should have had as an undergraduate but was getting as a faculty member. But I needed it. I didn't know how badly I needed it. But I took it. I just felt that the way I'd wanted to learn biochemistry when I was at Columbia, I'd better learn some electricity and magnetism.

I gave the first course in physical organic chemistry that had been given at the University of Chicago. It was a new field. I had a group of very bright students in the course, and they kept asking me questions I couldn't answer. I kept writing Louis Hammett and saying, "Louis, I'm in trouble. I was asked the following question and I don't know the answer. Can you help me?" I would get back letters from Louis saying, "Gee, that's a good question, isn't it?" That didn't help me much either. There wasn't much physical organic chemistry known then, and these bright people were asking me questions I'd never thought of and couldn't answer. Well, you know, it's all right if you have a bright student in your class who asks you a question you can't answer. Maybe it's all right if you have two. But if you have six, then you have to face the possibility that the students aren't so bright after all, and there is another explanation for your inability to answer these questions.

It turned out that the University of Chicago had been pleased with my services, and had raised my salary from $1800 a year to $2100 a year. On the strength of that vote of confidence on the part of the university, and that salary, I picked up the long distance telephone, and phoned Jeanne and asked her to marry me.

GORTLER: Where was she at this time?

WESTHEIMER: Philadelphia. And I just didn't see how I could resign from the University of Chicago and have no job. I had an obligation to get married. I couldn't back down. I didn't know what to do, so I didn't do anything and stayed.

What had happened was this. There was a group of postdocs and graduate students from different years, all of whom came to this course because it was the first one in physical organic chemistry. The group included Ted Puck and Nathan Sugarman and Norman Davidson and Irv Klotz and Herb Brown. Looking back, it was rather an extraordinary group of people.

GORTLER: It wasn't just the undergraduates who were asking you?

WESTHEIMER: Oh, these were graduate students and postdoctorals. It was a graduate school course. It wasn't just any graduate student who was asking these questions that I couldn't answer. It was quite an extraordinary collection of stars.

GORTLER: What a fine baptism that was.

WESTHEIMER: It really was tough.

GORTLER: What kinds of things were you talking about? Do you remember?

WESTHEIMER: My guess is that I was talking about the work of Hammett and Deyrup on superacidity, and the work of Ingold certainly, on solvolysis. I don't remember. I don't have any notes from those days, and it's all faded from memory. I had a good friend then, who was a graduate student of Kharasch's, named Ernest May. He and I were about the same age. He was an old graduate student. I was a young instructor. He used to come into my office after each of my lectures, and slump down in the chair and look at me sadly and say, "You know, that was the worst lecture I ever heard."

"I thought the lecture you gave last Wednesday was going to be the worst one, but gee, this one was much worse than that."

Then he would tell me what I'd done wrong. It's marvelous to have someone do that. He was extraordinarily important in helping me.

GORTLER: His helping you with your lecturing and Senior helping you with your writing.

WESTHEIMER: Yes.

GORTLER: You really received a marvelous education.

WESTHEIMER: Well, the next year was another of those great things. Kirkwood came to the University of Chicago. He had been an assistant professor at Cornell. He was lured away to be an associate professor at Chicago and went back to Cornell the year after as a full professor. He was just at Chicago for one year.

GORTLER: Did you mention that he was also here [Harvard]?

WESTHEIMER: He had been at MIT and collaborated with E. J. Cohn [of Harvard Medical School]. I knew of his work, i.e., sort of what his work was, especially his work on the activity coefficients of proteins. When he came, I had been fussing with a paper of Ingold's (29). You know, I read almost all of Ingold's papers. This was a 1931 paper and it was on electrostatic theory. Ingold was trying to explain electrostatic effects on the basis of electrical saturation in the neighborhood of ions. I didn't understand that very well. It may have been that I took that course at Chicago on electricity and magnetism to try to get some understanding of that paper of Ingold's.

I wanted to explain electrostatic effects in organic chemistry. I didn't like Ingold's way of doing it at all. I didn't know how to do it. I knew the problem was there. I felt that the solution was in Kirkwood's papers, but I couldn't work it through. I was just frustrated.

So when Kirkwood came, it was a marvelous opportunity. I went to Kirkwood and I said, "I'm sure this is in your papers. I can't get it out. This is the Ingold paper."

He read the Ingold paper. I came back a day or two later and he said, "Sure, we can work that out on the basis of an extension of my earlier papers" (30).

The Bjerrum paper (31) and the Eucken paper (32) were both in the literature. I took those to Kirkwood, as well as the Ingold paper. I said to him, "The Bjerrum paper looks right to me. The Ingold paper doesn't look right to me, but there has to be something we can do." Do you know the Eucken paper?

GORTLER: No.

WESTHEIMER: Bjerrum had looked at charge-charge interaction, and had used the dielectric constant of the solvent in his calculations. Eucken had written the corresponding formula for dipole-charge interaction, for, say, chloracetic acid, but had used instead a dielectric constant of unity.

GORTLER: Right. I do know about that.

WESTHEIMER: I went in to Kirkwood and said, "Look, the Bjerrum treatment works for dibasic acids and the Eucken treatment works for dipole substituted acids, but you can't have both. It's inconsistent, and I don't think that what Ingold did is right, because if you're going to have electrical saturation, it should be more saturated for the charges than for the dipoles. In fact, it's the other way around. The solution is somewhere in your papers, I'm sure. But I don't understand."

He treated me sort of like an advanced postdoctoral fellow. "Yes, indeed," he said, "I'm sure this is going to come out. You take these two papers of mine and read them."

Well, you know, today I don't think anyone would have the courage to do this sort of thing, because everybody is in such a hurry, but I didn't know then that I should be in a hurry. There wasn't that spirit of hurry. And the University of Chicago had a very nice atmosphere. So I tried to read those papers, and I couldn't read them so I bought myself a book on the Legendre functions. Here it is, still on the shelf. Byerly, Fourier Series and Spherical Harmonics, copyright 1893. Following the tradition I'd begun in high school learning trigonometry, I learned this piece of mathematics. After I learned that, I found I could read Kirkwood's papers. I would guess that it was two months before I went back to Kirkwood and said, "Yes, indeed, I think I am now prepared to do this with you."

GORTLER: He must have thought you'd gotten lost.

WESTHEIMER: Oh, no, in Chicago in those days, we saw each other. He knew what I was doing. Maybe he thought I was slow. Then, we developed that electrostatic treatment together. When we derived the equation, I worked out the numbers with a hand-cranked Monroe, not even an electrical one.

GORTLER: That was one of the questions I had. Who was sitting there cranking out those numbers?

WESTHEIMER: You know, hour after hour, day after day, building those tables. Then, showing that the ideas made sense.

GORTLER: All the numbers you published were just a few distances, as I remember.

WESTHEIMER: Didn't we publish the tables?

GORTLER: Maybe later on.

WESTHEIMER: We published two papers, one where we solved the electrostatic equations for a sphere, and one for a prolate ellipsoid of revolution with charges at the foci (33). Now, if you had a prolate ellipsoid and didn't put the charges at the foci, the calculations required an infinite series of infinite series. We didn't try to put charges anywhere except at the foci because I could manage only so much calculation. With digital computers, all that calculation can be done today, and it has been done, quite recently. It's kind of interesting to me that there has been so little progress in that field until now. I think people are now going to do it better, by an extremely different method, but it's been forty years.

GORTLER: I'm thinking how nice it would have been if you had had a computer.

WESTHEIMER: Yes. Well, of course, the modern work was done with a computer. Here we are--Ehrenson (34). Now there's a little bit of personal shame in connection with this, that I guess I will recite to you, although I don't think it's relevant. In 1972, I got a paper to referee by J. T. Edward, P. G. Farrel and J. L. Job, which said that we, Kirkwood and I, had gotten some of our numbers wrong (35). Although I had done all the calculating, I did not go back to put it on a computer and check it, which I should have done. I just wrote to the editor of The Journal of Chemical Physics and said, "Gee whiz, if I've done it wrong and this man has done it with a computer, I'll trust him. I guess I've made a mistake and you'd better publish the new work."

Now it turned out that we hadn't made a mistake. What had happened was the following. We had carelessly published an equation where one of the terms had the wrong sign and we had published an erratum immediately thereafter correcting it (36). Ehrenson found the error himself. He didn't find the erratum. I called the erratum to his attention when I refereed his paper, and he was reasonably ungracious about it in his publication. But he had found the error. These other people had found neither the error nor used the erratum. They referenced the erratum but obviously hadn't read it.

GORTLER: I see. So they just did the calculation with the wrong sign?

WESTHEIMER: Yes, and the fact that that erroneous paper is in The Journal of Chemical Physics is essentially my fault.

The first real improvement on our approach was a paper by Sarmousakis some years after our work that developed the equations for the oblate ellipsoid of revolution which is not a common shape--well, you could use it for benzenoid compounds (37). Then the next improvement was Ehrenson's doing the calculation by computer, and allowing you to put charges or dipoles anywhere you like along the central axis, because the computer can sum an infinite series of infinite series, and I couldn't.

Questions then arise, as to the science involved in that work that Kirkwood and I did together. How good was the science, what did it contribute to organic chemistry, and why has it been so long before anyone has improved on our model which I don't think anyone has really done yet, but will soon?

Everyone I guess thinks very highly of his own work. I think very highly of that work. It seems to me, the first thing one wants to do is to establish a philosophical principle. I like Paul's. Paul [Bartlett] laid down the principle that one does quantitative experiments to establish qualitative principles. It seems to me that that is an extremely important idea. That is a kind of perspective on science that keeps one from getting lost in detail.

What the model that Kirkwood and I put forward did was to reconcile Bjerrum with Eucken and let one see why those two limiting approximations could both coexist in the same physical world. That seems to me to be a qualitative thing well worth doing, even if it required all that fancy mathematics.

GORTLER: By the way, Wheland does a marvelous job of explaining the importance of that work in one of his books on advanced organic chemistry. I looked at that a few days ago.

WESTHEIMER: Are you sure I didn't write that section?

GORTLER: You may have. I never thought of looking in the acknowledgments to see.

WESTHEIMER: [reading from Preface to Wheland's Advanced Organic Chemistry (38)] "Chapter 11 is based upon a memorandum which was prepared for me by Professor Frank H. Westheimer." Wheland's rewrite of a memorandum I wrote him. How much of that is then Wheland and how much is me--

GORTLER: You did a marvelous job of explaining the importance of that piece of work!

WESTHEIMER: But there are two things to say about it in retrospect. One is, the reason it's been so long in being substantially improved is that the physical chemistry of solutions is so difficult. And hydrogen-bonded liquids are especially difficult. So that it's taken a long time. It's just about now, I think, that people are getting ready to make big improvements.

The second thing was a matter of luck. And it is a matter of luck that Ingold's approach was wrong, because one should have had to take electrical saturation into account. I don't know if you know the history of electrical saturation, but Debye wrote a nice paper on it in which he showed how this would occur with increasing electric field, and he showed how the dielectric constant would fall sharply with diminishing distance from a charge because of electrical saturation (39).

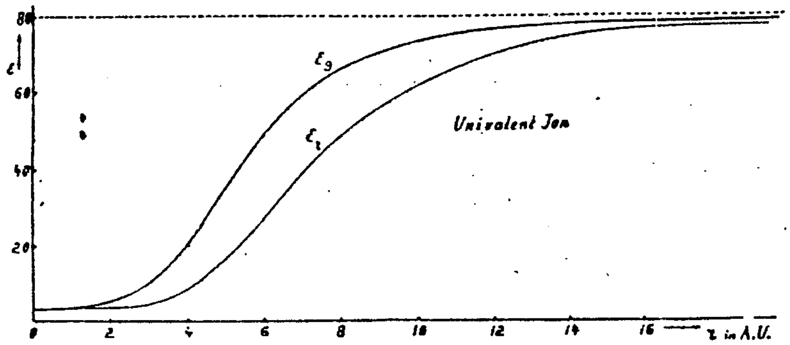


FIG. 30. Saturation effect near an ion.

And then a German, F. Malsch, did some experiments, in which he was able to get electrical fields enormously greater than those at which Debye had predicted breakdown (40). There wasn't any saturation up to electrical breakdown. It took a much greater electric field than Debye had indicated, to produce electrical saturation.

On the other hand, when Malsch used non-hydrogen-bonding liquids, like ethyl ether and ethyl acetate, the Debye curve was followed exactly.

Then Debye came along in another paper and said, "Oh well, yes, I missed hydrogen bonding," so he put hydrogen bonding in it, and of course if you use another parameter you can make the data fit, and he made them fit. And it turned out that you had to come in extremely close to an ionic charge to get the high fields that give you electrical saturation. And this is so close, about three angstroms, that you never get two things close enough together in water to have very much electrical saturation.

Now, of course, in detail that's got to be modified, as one gives up a continuum model for solvents and goes to real molecules with hydrogen bonds and so on. But if electrical saturation had occurred at the large distances that Debye originally predicted, then the kind of treatment that Ingold was trying would have been correct. And what Kirkwood and I were doing would have been wrong. But, in fact, electrical saturation isn't so important. It was known that it wasn't important in water but that knowledge wasn't very deeply implanted in people, and I must confess that I don't think I knew it at the time. Maybe Kirkwood did.

That was fun. And then very shortly after, I got Aaron Novick as a graduate student and we went off on that business I told you about at lunch. His thesis wasn't published until 1943, but that was because of the war (41). I don't know when he began, but, as I told you, we couldn't publish the first part of his thesis. We had to do something else. So he did the first chromic acid work. That was the second half of his thesis. The first half of his thesis was this thing where it began [reading from Novick's thesis], "Several years ago Bergmann advanced a hypothesis that the amino acids of protein are arranged in repeating patterns."

There's all this business on the iodination of tyrosine--I haven't reread this in a long time.

GORTLER: What was the name of the x-ray crystallographer again?

WESTHEIMER: Rose C. L. Mooney. It says here in the summary, "Professor R. C. L. Mooney, of the Sophie Newcomb College, New Orleans, Louisiana, who undertook the x-ray study, has not as yet found any evidence of the expected distances. This however does not necessarily disprove the Bergmann hypothesis, since there are a number of possible causes for failure of this method. These are discussed in the thesis."

[END OF TAPE, SIDE 7]

WESTHEIMER: You know, I'm reading this over now, after all these years, and it sounds awfully good to me. We worried, for example, that we had degraded the silk fibroin, and we measured its tensile strength from thirty-four kilograms per square millimeter to twenty-eight kilograms per square millimeter, and concluded that we had not substantially degraded it.

Well, that was great fun.

GORTLER: Let me ask a few specific questions about the University of Chicago, and then go on with your own work.

When you entered, who was the chairman?

WESTHEIMER: The de facto chairman was Hermann Schlesinger.

GORTLER: Who was running the department?

WESTHEIMER: He was running the department.

GORTLER: He was?

WESTHEIMER: He was, but he was called "secretary." There was no chairman of the chemistry department, because Robert Maynard Hutchins, who hated science and scientists, especially hated Schlesinger, and refused to allow him to be chairman. So he was "secretary."

Let me tell you a story. Maybe you can actually use it, because I'd love to see this story published somewhere. It's the greatest story I know about Hutchins and science. I've told it a million times, but maybe we can get it in print.

When I arrived at the University of Chicago, Hutchins gave a dinner for the new members of the staff, even including lowly people like me. I was then a research associate, not even an instructor. The dinner was in the cafeteria and, as I recall, each of us had to pay for his own dinner. But after that Hutchins spoke with us, and he congratulated us all on having been selected as staff members for the greatest university in the world--which the University of Chicago may very well have been.

Then he went on to say how fortunate the university was to have acquired the services of this brilliant group of young men and women, carefully selected for their specific abilities; how he wanted to welcome us all there, except perhaps the scientists; and that he did not believe that there was any intellectual content to science, and therefore could not see what a great university like Chicago was doing with departments concerned with science.

Then he paused and said, "Well, some of my friends have been trying to convince me that there is some intellectual content to physics. Although I remain unconvinced, I've decided to keep an open mind on the subject. But I'm quite sure that there is no better reason for a great university to have a department of chemistry than to have a school for barbers."

That was the man who would not let Schlesinger be chairman. But Schlesinger nevertheless was running the department.

I had been at Chicago about a week, set up my lab, and had gotten ready to go to work on this amino acid problem, which I was working on. I'd begun it at Columbia and I was working on it at Chicago (42).

GORTLER: Okay. For that work you borrowed a polarimeter from Dr. Marberg at the Sprague Institute. What was the Sprague Institute?

WESTHEIMER: I don't know; some place at the University of Chicago.

GORTLER: Okay. I just wanted to know whether it was important or not.

WESTHEIMER: No, it just meant that apparatus was not readily available.

Actually, in another part of the story, I went in to see Hermann Schlesinger and I said, "Professor Schlesinger, I would like to know how much money I may spend on chemicals and equipment."

He said--this was in the middle of the Depression--"Well, you can take the chemicals that are in the stockroom, and use the apparatus. You can scrounge around in the stockroom."

"Well, I may have to buy some things, and I have to know what I can spend."

He said, "No instructor in this department has ever asked that question before."

And, having no respect for anybody, I guess--but I loved that man--I said, "Well, I have to ask it anyhow."

He said, "Well, all right. You can have $200 a year."

Anyway, at the beginning Kharasch came into my lab when I was setting it up to do the work on this amino acid business. He came in and said, "I see you're setting up your lab, and you've done a nice job. It's neat. You've got solvents. Looks good. I'm busy today but I'll come in tomorrow and tell you what you're going to work on."

This was somewhat unexpected. So when he left my lab, I put my suit jacket on and went down to call on Schlesinger. I told him I was a great admirer of Kharasch's--which was the truth, the whole truth, and nothing but the truth--but that I had come to the University of Chicago with the impression that I was going to be allowed to do my own work. My own work might not be anywhere near as exciting as Kharasch's, but that's what I intended to do, and if that wasn't going to be the way it was, I guess I would leave right then.

Essentially, he said, "There, there, Sonny. Don't worry." He said, "You know, I'm sure Kharasch was only trying to be helpful. Maybe he thought you didn't have any ideas of your own. Don't worry."

That's the last I heard of it.

GORTLER: How long had Kharasch been there? He was already firmly established?

WESTHEIMER: Oh, he was firmly established. He had published a lot of papers, but he and [Frank] Mayo in particular had published that paper on the abnormal addition of hydrogen bromide to allyl bromide, which in my book is one of the landmarks in physical organic chemistry (43).

GORTLER: By the way, if you think of other landmarks as time goes on, I'm preparing a book on benchmark papers, and essentially I'm looking for people's favorite papers, so anything else that you think of.

WESTHEIMER: Well, I would supply a list, starting with Lapworth, and the Robinson 1917 paper.

GORTLER: Okay, I have those.

WESTHEIMER: But I think the Kharasch and Mayo paper easily qualifies. Kharasch was well established.

Kharasch was a very odd individual. He was the most generous man I knew. Or else, he was the meanest most generous man I knew. I don't know which. He was a very complicated person. We used to say this of him--I don't know if it was true--that if you came to ask him for a recommendation, and if he said a man was good, then you knew you didn't want him. If he said a man was terrible, really not very good, then you had to interview the man, because either he was no good at all, or else he was splendid, and Kharasch was really saying to himself, "But compared to me, he isn't much."

A very complicated person.

GORTLER: When I came to the university, he was an institution, and they referred to his laboratory as an institute. I don't know whether it was formally an institute or merely a name.

WESTHEIMER: Yes. It became formally an institute. Oh, he did marvelous work, absolutely fabulous work. He couldn't explain it very well, half of the time. He was an intuitive person. Very, very strange. He was a most careful experimentalist, and a lot of the techniques, operating a vacuum line and avoiding traces of oxygen, either came from his lab or were practiced in his lab long before they were common. The work in that lab was done very, very well.

Intellectually, he was inconsistent. You couldn't rely on what he said at all. He would tell me things and I'd say, "That's most interesting. Can you give me the reference? I want to read that."

He would say no, he couldn't quite remember the reference. It would turn out, it had never been done. It was something that he kind of thought maybe it should be that way. It should be--well, why not say it is. Sort of on the principle given in "The Mikado" when Pooh-Bah and Ko-Ko were explaining why they had said that Nanki-Poo, the heir, had been beheaded when he hadn't been. Do you remember that? They said to the emperor, more or less, "Well, your Majesty's word is law. You said he should be beheaded. Therefore he's just as good as beheaded. So why not say so?"

That was sort of the principle Kharasch operated on, and it was very difficult talking to him.

GORTLER: It's interesting, long ago I remember someone telling me something about his collaboration with Reinmuth, and when you said that he tried to come in and use you--somebody said he'd really used Reinmuth, and that Reinmuth had accumulated all the data for the Grignard book (44).

WESTHEIMER: Well, I don't know whether he was really trying to use me, or whether he was, as Schlesinger said, trying to be helpful. I don't know. All I know is that I wasn't having any.

GORTLER: Well, that was certainly a good move on your part. What about other people who were on the staff? You mentioned Schlesinger. He was certainly well known nationally by that time. Was Stieglitz still around?

WESTHEIMER: Stieglitz died very shortly after I came to the University. I would guess that he died in November or December of 1936. I started to attend his lectures, and heard him lecture only two or three times before he was taken ill. I don't quite remember how long after he was taken ill that he died. It wasn't a very long time, but it may have been a couple of months. So he disappeared from the scene. Perhaps the fact that I was used in teaching so early was because Stieglitz died. So I didn't know him.

Kharasch was on the staff, Schlesinger--there were a number of physical chemists there, none of whom, at that time, qualified as great.

Before World War II, the leading physical chemist in the department was William Harkins, who made important contributions to chemistry, and especially surface chemistry. His lectures to the undergraduates were miserable, because he never bothered to prepare them, and he had a highly inflated idea of the importance of his own researches, but he was nevertheless a significant scientist.

Thorfin Hogness, who had been a physical chemist at Berkeley, was then doing biochemical work with enzymes, which was at least interesting. I don't think he accomplished much, but, remarkably, it was an acceptable thing to do within the Chicago chemistry department.

Thomas Frazer Young was a thermodynamicist, concerned with the last decimal point, and had not thoroughly understood Bartlett's principle. That is, there was no qualitative idea he was trying to establish. Thomas Frazer Young didn't understand that. He thought there was something holy about the numbers. The great physical chemists, Urey, [Joseph] Mayer, [Willard F.] Libby, joined the department after World War II.

Schlesinger was doing interesting inorganic chemistry, and Anton Burg was working with Schlesinger on experiments on boron chemistry. That was good chemistry, pioneering chemistry in the boron field, that led later, during the war, to Schlesinger's invention of lithium aluminum hydride and sodium hydride.

GORTLER: Who was Brown working with? Was he working with Schlesinger at the time?

WESTHEIMER: Yes.

GORTLER: And then he just stayed on?

WESTHEIMER: No, he stayed on as a postdoc with Kharasch, but he did his Ph.D. thesis with Schlesinger. During the war, when I was away, he may have gone back to work with Schlesinger on that boron project. My guess is he did, but I wasn't there to see.

What distinguished the place for me was the group of junior staff that Kharasch had gathered, and the junior staff in organic chemistry were all people he, Kharasch, had hired. There were four of us--Frank Mayo, George Willard Wheland, Weldon Brown, and myself. I think that was an absolutely marvelous collection of people.

GORTLER: I'll say. The very next question I have is, the staff there seemed to be very heavily weighted with organic chemists who had a very physical bent, and no other place--here at Harvard there was one person. There, there were four or five, all at one time.

WESTHEIMER: Yes.

GORTLER: How did that happen?

WESTHEIMER: That happened because there wasn't a democratic system at all. Although there was some voting and so on--I guess, I don't know; I was too far down on the staff to know--I think the decisions were Kharasch's. Kharasch found people and decided that those were the right ones. Kharasch himself was concerned with theoretical organic chemistry. He repeated--I guess half boastfully--Roger Adams's statement (I think it was Adams--either Adams or Marvel) that there were no organic chemists at the University of Chicago. But he went looking for people who were concerned with the theory of organic chemistry. That's how that group was assembled. It was really a splendid group, nice people with whom to interact. I especially enjoyed Bill Wheland, whose mind was built on precision lines, and didn't let anything shoddy slip by. A marvelous person with whom to talk, and I was also grateful to him for his statement, when I told him I was going to work on the mechanism of chromic acid oxidation, "I consider that the project least likely to succeed."

It seems to me that an important criterion for a project to work on is to have one that is not likely to succeed. If it's likely to succeed, someone else can do it. Or maybe it isn't worth doing in the first place.

GORTLER: You've put a lot of manpower in it but you've got a good deal out of it.

WESTHEIMER: Chromic acid oxidation?

GORTLER: Yes.

WESTHEIMER: I liked that project. Chromic acid was the most commonly used oxidant in organic chemistry. It still is. And it seemed to me then that there was an enormous effort being spent in America, in the world, on solvolyses, and ester hydrolysis and that no one was looking at oxidation-reduction.

There's a complete imbalance, in the importance of the reaction and the amount of effort that's being spent to unravel it.

Of course, I didn't have any idea, when I plunged into that project, how nearly Wheland was to being right. I had no idea how complicated it was. But it seemed like fun, and one thing led to another. Probably, you know, if I had considered it more carefully, I would have realized I couldn't do it. But it looked like a good project. Still does. And of course, a lot has been done with chromic acid oxidation recently. I don't know if you've followed it.

GORTLER: No, I haven't.

WESTHEIMER: Both by Ken Wiberg and in particular by Jan Rocek.

GORTLER: Yes, I talked to Jan and heard a little bit about his work last summer. But they are old hands at chromic acid oxidation. They've both been in it a long time.

WESTHEIMER: Both Wiberg and Rocek? Oh yes, yes. Though I think neither was in it when we began.

GORTLER: No, I don't think so. They couldn't have been, because first Wiberg wasn't even a graduate student until the late 1940s.

WESTHEIMER: Rocek was also much younger. You know the Rocek story, incidentally, of his escape and so on?

GORTLER: Yes, and I know pretty much your part in it.

WESTHEIMER: I didn't have any part in the escape.

GORTLER: Well, but getting him out of Denmark, coming up with your own money. Also, I think he's surprised to this day because of the fact that at some earlier point, I think, he'd obviously attacked some of your work in the literature.

WESTHEIMER: Yes.

GORTLER: To this day he's surprised you took him in, which I think is something to say for you.

WESTHEIMER: Well, it's just, one has to differentiate, it seems to me, very sharply between intellectual disagreements and personal attacks. I don't see why one can't disagree intellectually with, and even be corrected by, one's best friend.

This probably should be off record. Anyway, my wife says that the difference between men and women is that men discuss ideas without any personal bias entering in, and women can't do it. That's probably not true, but that's what she says.

GORTLER: What part of the story do you remember, since he's told it to me and I'd like to hear a little bit of your side of it.

WESTHEIMER: Do you want to hear that on this tape, or shall we just discuss that at dinner?

GORTLER: We can do that at dinner and then I'll make my own notes about it.

WESTHEIMER: I mean, I can put it on a tape. I remember the story in pretty much detail, back to parts that he probably doesn't remember very well, such as the time that he met with Wiberg and me at a conference in London, before he escaped. Have you heard about that?

GORTLER: No, I don't believe so.

WESTHEIMER: He quizzed us, up, down and sideways. In retrospect it's clear that he was considering escape then. At the time, it was very interesting. This was a conference on oxidation, and Wiberg and I flew to London and he flew to London. He was allowed out of Czechoslovakia--

GORTLER: Without his family?

WESTHEIMER: Without his family.

GORTLER: Did he give you some letters at the time? Did you take some letters for him, or was that someone else? I'm not sure.

WESTHEIMER: I don't remember. I don't think so, but if he said I did, I did. We met in some hotel in London, where all three of us were being stashed, and he started asking us questions about the United States. They were all accusatory questions that seemed straight out of Communist propaganda.

"Why is it that you don't have old age pensions in the United States?"

I said, "We do have old age pensions. They were instituted by Franklin Roosevelt in the early 1930s."

"Oh," he said. "No, I know better. You can't get away with that kind of propaganda with me. Why is it that you don't have any unemployment insurance in the United States?"

"Well, we do."

"No. I'll check up on it, but I'm sure you're just telling me that to try to make the United States look good. How much do your shoes cost?" And so on.

He didn't tell you that?

GORTLER: No, he didn't tell me that.

WESTHEIMER: Wiberg and I were quite impressed by the grilling. He probably thought the room had been bugged. If it had been, there would have been no way of telling that he wasn't the most devoted Communist.

GORTLER: You can tell me the rest of the story over dinner. If you don't mind, maybe I can record some of that.

The facilities at Chicago at the time--you told me what Schlesinger was prepared to offer you. The equipment situation was probably what, about the same as it was at Columbia, or Harvard?

WESTHEIMER: We didn't get our first IR machine--I don't know when they came in generally--until about 1951. I think that's probably when they came on the market. During World War II, I was in the Explosives Research Laboratory, and I got a Beckman DU in that lab. I think the Beckman DU came on the market during World War II. When I returned to Chicago after World War II, one of my requests was that I be given a Beckman DU, and the university bought it for me. You understand that Harvard today wouldn't buy me a Beckman DU, because they won't buy anything for the staff.

GORTLER: You have to go out and get your own grant.

WESTHEIMER: Yes, you must get your own grant. But at that time, the University of Chicago bought me a Beckman DU. Cost about $2000. Grants were not available. They didn't exist.

It was a very important instrument. It was the first real piece of instrumentation that I had in my laboratory. We had thermostats, and made the regulators ourselves.

[END OF TAPE, SIDE 8]

WESTHEIMER: We did kinetics by titration. We built our own dilatometers, to do reaction kinetics, which work fine. But you have to have very good thermostats. As I pointed out before, I did calculations on a handcranked Monroe, and after World War II, I had this Beckman DU, which was a great instrument, and very serviceable, and marvelous for things like chromic acid work.

GORTLER: At some point or other, you also managed to buy a mass spectrometer? It's mentioned in the Koshland work.

WESTHEIMER: Oh, no. I'll tell you what happened. That was after World War II, too, and splendid. At the end of World War II, Robert Maynard Hutchins made another famous pronouncement about science, which was, in effect, that if the university cannot avoid having science, it must at least have the best.

At that time, he brought to the university a really stellar collection of scientists, including Enrico Fermi, Joe and Maria Mayer, Bill Libby, and Edward Teller, who was never there, but oscillated about Chicago as his midpoint. He was officially on the staff, but he was like a pendulum which spends the minimum time at the bottom of the swing. He was minimally at Chicago.

Among the people that the university brought was Harold Urey. I don't know where he got the funds, but he had funds and he built his own mass spectrometers. He had excellent technicians, postdoctoral fellows and mass spectrometers. He had isotope ratio mass spectrometers (the Nier type) that he built (or his crew built), in order to determine the temperatures of the ancient oceans, by looking at the difference in the isotope ratios of carbon and oxygen in carbonate laid down at different temperatures.

Now, the isotopic fractionation factor isn't very great, and its temperature coefficient is even smaller, so he had to have extremely good instrumentation to measure it. So he had marvelous mass spectrometers. He would run experiments for us, from time to time. So his group not only ran Koshland's, they did the measurements for Myron Bender when he was a postdoctoral fellow in my lab. Before Myron came to the lab, I had arranged with Urey that he would, in fact, take care of Myron's mass spectrometry. So those instruments were there, postwar, from Harold Urey. Incidentally, let me say for the University of Chicago, especially postwar, that if one was looking for an atmosphere in which one raised one's sights, in which one tried to look for broadly important problems, that the University of Chicago was the best place, perhaps in the world, to find it. Without in any way wishing to depreciate the really great chemistry done in this department, there was a breadth of vision at Chicago, that wasn't anywhere else.

Here you had Harold Urey working on the temperatures of the ancient oceans, and after that, on the origin of the planets, and Bill Libby doing his work on radiocarbon dating. Although it was across the way, and I never understood any of it, Maria Mayer was working on the structure of the nucleus, and Konrad Bloch doing the original work that led to the path of carbon in the biosynthesis of steroids, and Morris Kharasch laying down the fundamentals of the chemistry of unstable free radicals.

It's a broader canvas. Mind you, Bob Woodward completely remade the way in which organic synthesis is done, and it's a great accomplishment, but it's a narrower kind of accomplishment than the great breadth of things that were going on in Chicago. One couldn't help but find Chicago very exciting and very stimulating. And conducive to an attempt to get at problems of considerable breadth, and perhaps a little bit--unusual isn't the word I'm looking for--but, a little off the beaten track. It was a marvelous atmosphere.

GORTLER: That's good to hear about my old alma mater. My first response, however, and we'll get to that later, I guess--"But yet, you left." That may be a different story.

WESTHEIMER: That's a different story. I left because I'm a coward. Some of our friends had been held up on the street at gunpoint. Some women I knew had been raped. Too many children I knew had been beaten up on the streets.

GORTLER: I must say that that was a story I heard way back when. Recently, when I talked to Hammett, he told me that he was trying to bring you to Columbia. I said, "Gee, if he was trying to get away from Chicago, he certainly wouldn't want to move into that atmosphere in New York." He said, "Well, it couldn't have been any better in Cambridge." Of course, at that time it certainly was.

WESTHEIMER: It certainly was, at that time. It isn't so marvelous now. There's an enormous increase in crime all over the country. Anyway, I now don't have two small children.

GORTLER: You lived in the community at Chicago.

WESTHEIMER: Yes, we lived in the university community. I guess we could have moved out of the university community to someplace safe, and then commuted. I loved the University of Chicago, and my reason for leaving was simply that that area became such a high crime area that I was frightened.

That didn't mean that I was so frightened that I was willing to run anywhere. But Harvard isn't <u>so</u> bad.

But let me say that no matter how good Harvard was, I would not have left, but for that pressure.

You want to know why I left? That's it. Not because I didn't love the place. I did.

GORTLER: It's nice to hear it from the horse's mouth. It's no longer a rumor. You told me about the physical organic course you were teaching. What else were you teaching at that time?

WESTHEIMER: At Chicago I taught a great many things. In particular, I took over the teaching of the elementary organic chemistry course, and taught that with enormous enthusiasm and pleasure.

GORTLER: Have you any recollection of what textbook you were using at that time?

WESTHEIMER: Yes. At least for some of it. I was using one of Fieser's books. And I was an enthusiast for Fieser's books. Many of the students were not. The reason I liked Fieser's books and preferred them to the other textbooks that were available, is that what they had in them was the truth. That is, Fieser gave <u>real</u> examples. Many of the other textbooks had "R groups," and recited reactions in general, including some that didn't work. Fieser might have given things that were contrary to the rules, and that had some gimmicks in them, and were special cases. But everything in Fieser's book referred to things that were real, that were true. It seemed to me that that was a fabulous advantage.

Later, he had a textbook that had one-line biographies of chemists at the bottoms of the pages, and I thought that was extremely important, especially because many of the one-line biographies referred to recent graduates, often recent Harvard graduates. I had never been very successful in telling students that they, too, were expected to invent new things and discover new things. When I said things like that, they would always laugh. It may have been a nervous laughter, I don't know, but they would always laugh. I would say, "We don't understand the following thing, but of course it's your generation that is going to find out what that is"--and they'd all laugh. It seemed to me that pointing out that someone whose name was mentioned in an elementary textbook had graduated only ten years earlier or five years earlier, was a way of telling the students, so they would believe it, that they too could contribute to chemistry.

For those two reasons, I liked Fieser's texts. Now, of course, from the point of view of theoretical organic chemistry, they were abysmal. But it didn't seem to me that that made any difference, because I could supply that.

GORTLER: He had those nice loops around the groups--the lasso mechanisms.

WESTHEIMER: Well, sure, exactly. But I was giving them the theoretical part. Fieser was giving them the straight facts, and these little biographies. I thought it was a good book and I liked it. The students didn't like it too much.

I enjoyed teaching that course. I even taught a course at Chicago, when someone got sick or something, in elementary physical chemistry. I gave a term of that.

GORTLER: You spent enough time talking and working with physical chemists.

WESTHEIMER: I wouldn't want to do it today, when you're supposed to teach straight quantum mechanics. I'm not a very good quantum mechanic.

GORTLER: Who was Herzl Cohen?

WESTHEIMER: Herzl Cohen changed his name to Hertsell Conway.

GORTLER: Then he <u>is</u> on your list of graduate students. I didn't find him listed as one of your graduate students as Cohen. Okay. That was the result of some of the anti-Semitism in the world at the time?

WESTHEIMER: Right.

GORTLER: How did you divide the research and the teaching? How much time did you have to spend at each? Was there ever a conflict between the teaching and research? Or did you find one was necessary for the other?

WESTHEIMER: I never felt pressed for time, then. I feel pressed for time now. It seems to me that I wasn't pressed for time then, for a number of reasons, some of them stupid. But anyway, I never felt a conflict between teaching and research. It seemed to me that it was great fun doing both. There was plenty of time to do both. I never felt that I was taking time from one for the other, either way.

Now, the reasons are probably all of the following, and maybe some others. First, if you don't know all the things that you should be doing, it doesn't hurt you so much when you don't do them. I had never read as much in the literature as many of my friends did. I have always been behind in the reading of current journals. What I've tended to do is rely considerably on the educational value of lunch, where my friends would tell me what it is I should have read, kidding me for not having read it --but you know, somebody points out what I should read and I go and read it.

It also has led me, I think, to read very much more broadly, a much greater variety of things. But to do that, you don't read everything. So whereas Frank Mayo tried to get me in the habit of going through Chemical Abstracts and readily reading everything to do with chemistry, I found I couldn't do it. I would be reading and reading and reading, and then I would stop and say to myself, "I have no idea what I've read."

It had all vanished. There wasn't any point in it. By and large, I found that I did better doing something like spending two months learning how to handle electrostatic equations, and not reading the journals very thoroughly.

So I guess I cheated, if you can call it that, on reading the journals, and read various things people called my attention to, or that I wanted especially to read. I was more likely to read intensively on a particular thing than to read the journals in general.

There weren't very many graduate students at the University of Chicago. Now, it's true that one could go into the lab and work in the lab but it would take a lot of time. If you have a few graduate students, and you worry intensively about their problems, it doesn't take as much time as it does when you have a big research group. And I'm not sure you get much less done. I'm not convinced that when I had a group of fifteen people, that I really had fifteen good research ideas. One of my dicta, which Dan Greenberg stole and published in Science without giving me any credit--he even wrote me a letter apologizing--is that a great scientist makes a discovery in his lifetime. A good scientist makes a discovery once a decade. Any damn fool can make a discovery every year.

You don't really need a large group of people to do revolutionary science. Frederick Sanger had two graduate students who worked successively, not concurrently, on the structure of insulin. He and two graduate students did that job and revolutionized a major part of chemistry. It didn't take a big crew of people. I've never believed that you had to have a big crew of people.

I keep having discussions--this is another subject, but on the question of philosophy of science really--I had these discussions with Bob Woodward all the time--

GORTLER: He was the first one I thought of, when you started talking about large groups working on projects.

WESTHEIMER: Bob will not--he doesn't like to accept my evaluations in chemistry. If we stick to synthetic organic chemistry, he is clearly the best there is in the world. If you say, "Well, yes, but if you're writing a history of science for the twentieth century, where will that work stand and where will Sanger's stand?"

GORTLER: You say this <u>to</u> him?

WESTHEIMER: Not in those words--but yes. Yes. This is where we get into a discussion of values. He doesn't want to look at values. I mean, if you ask him about Sanger's work, he says, "Well, that's obvious. Anyone can see that. It's obvious."

It is, in fact. Sanger's work is absolutely obvious. Anyone who knew any organic chemistry--hundreds and hundreds of my students who had taken my course in elementary organic chemistry at the University of Chicago, and certainly I, could easily have seen what Sanger saw. But we didn't and he did.

I had a discussion like this with Bob Woodward about H. G. Khorana, whose work I consider among the great accomplishments in synthetic organic chemistry. The synthesis of a gene certainly must take precedence over any other organic synthesis I know. It was prior to that time, when Khorana was making the trinucleotides and so on, from which the genetic code was finally firmed up. He was working out all the methodology to make nucleotides. I was praising this work to Bob, and Bob said that he thought it was routine, and that he knew at least twenty organic chemists who could have done the same work, more elegantly and much more quickly.

And I said to Bob, "My mother-in-law told me that she would have been Phi Beta Kappa, if only she'd gone to college." So, I don't think the large groups are needed. And I had a small group and it kept me busy. It was everything I could really handle.

It involved more thinking about what you were going to do, and the teaching didn't get in the way at all. In fact, the chromic acid project arose directly from teaching elementary organic chemistry, getting up at the blackboard, reciting these facts about chromic acid oxidations, and having the inside of my mind turning over and saying "My God, my God, what are you saying? How does this work? What's going on?"

So in that sense, the teaching of elementary organic chemistry was a direct prod to research.

I'll go a step further, and say that it seems to me, to a considerable extent, the research projects that arise out of elementary teaching are going to be the best ones because it's the most fundamental aspects that you teach in the elementary courses. If there's something that you don't understand about the elementary course, one ought to do something.

GORTLER: That makes a lot of sense.

WESTHEIMER: I think I ought to say a word or two about the project with Joe Mayer, which I think was a nice project. That really, I think, was the beginning of molecular mechanics, which has blossomed a great deal.

GORTLER: I would like you to do that. I wanted to ask you about Joe Mayer, too. He came along with Urey from Columbia?

WESTHEIMER: Yes. Well, he was part of the group, along with Maria Mayer, that came to Chicago after World War II, in the marvelous acquisition by Hutchins.

GORTLER: You know, part of that acquisition was because Urey was angry at Columbia. He had been chairman, and the rest of the staff just didn't want him to be chairman anymore, or enough people weren't happy so they wouldn't re-elect him chairman. I don't know if you know anything about that or not.

WESTHEIMER: No. I didn't know anything about that. Harold Urey is--well, an eccentric, but a hero of mine. I'm taking up so much time doing this, I don't know if it's worthwhile, but let me tell you one of my stories about Harold Urey, which is just personal. It doesn't bear on science, really. It just tells you about Harold Urey. It's part of my feeling about him.

A few years ago at La Jolla, he was taken to the hospital for an operation. I don't know, an abdominal operation of some sort, quite a serious one. And he was put in a semi-private room, the day before, the way they always do to prepare people for operations. His roommate was Nathan Kaplan. I don't know if you know Nate Kaplan. He's a biochemist. He had had a heart attack and had been in the hospital for weeks.

So Harold Urey got in the hospital bed, and opened his brief case and put on his glasses, took out a paper and started to write.

After a while Nate Kaplan said, "Harold, put that stuff down." Nate said, "You know, I've been in this hospital three weeks, and am bored to tears. I haven't had anybody to talk to. We're old friends. Put that stuff down and let's talk for a little while."

So Harold took off his glasses and he looked over at Nate. He said, "Nate, I'm well over eighty years old. I'm going into surgery tomorrow for an important abdominal operation, and there's a reasonable chance I won't survive. And I intend to finish this paper." He put his glasses on and went back to work.

GORTLER: I think one of the problems with history of science, and history of chemistry, up to now, is that most of the people have gone through the journals and said, "This happened at this point, this happened at this point," and nobody wrote about the fact that scientists are people, that they interact with one another, they do have ideas and feelings and so on.

WESTHEIMER: Well, when I do my history of science, it's going to be a collection of stories, anecdotal stories about scientists.

Anyway, I came back to Chicago after World War II, and the university was very good to me. They promoted me to associate professor, on the basis of hopes as much as accomplishment. I'd done some fairly good things that weren't published, that got published later, that had been classified.

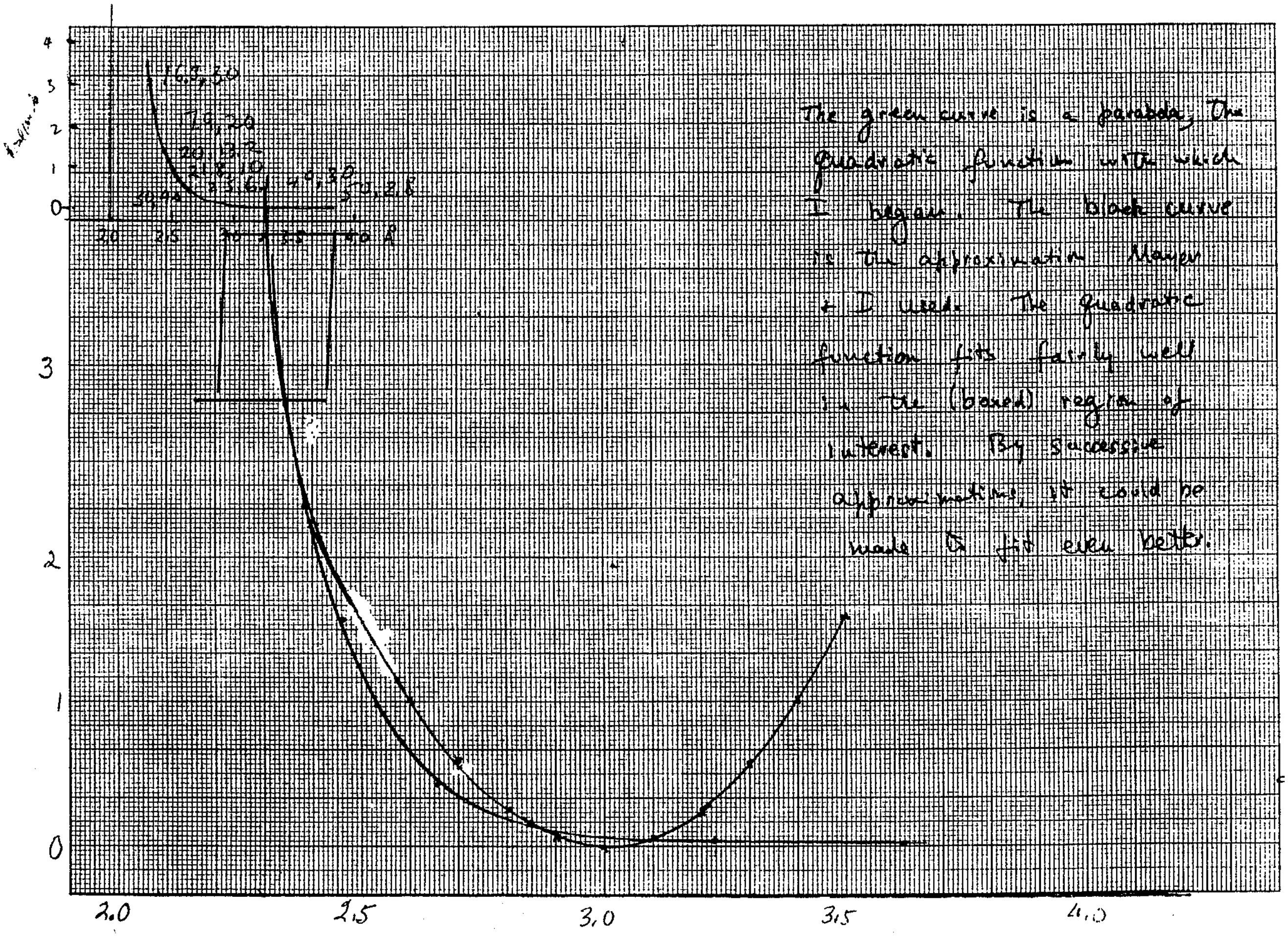
[END OF TAPE, SIDE 9]

WESTHEIMER: So, my problem was to think what research I could do, that would make the largest contribution to science that was available to me with my resources. I don't know how I had the general idea of looking at the racemization of optically active biphenyls, and figuring out how the activation energy was constituted. I started to do that, and as I started to do it, I came to understand, probably by a process very similar to my father's doing his maximization and minimization by arithmetic, --that you had to bend and stretch, and push past the van der

Waals repulsion. And it eventually occurred to me that if you were going to minimize the energy of activation, then Hooke's Law, a quadratic function of the energies, meant that if you did a little on a lot of coordinates, you were going to have a lower energy than if you did anything much to any one.

When I set the problem up, I realized that I had a multi-dimensional problem, and I didn't know how to handle it mathematically. What was I to do about the van der Waals function? I decided, what I would do about the van der Waals function was cheat; that is, approximate and consider that also as a quadratic function, which it isn't. It's much steeper than that. But if one considered it as a quadratic function, one could by successive approximations, eventually approximate the van der Waal's potential by a quadratic function in more or less the right region, and then it wouldn't be so bad. Do you follow what I'm saying?

That is, if you have a curve that is really very steep, you can find a parabola that won't miss it so much at any given point, but you can't have a parabola that will follow it all the way:



The green curve is a parabola, the quadratic function with which I began. The black curve is the approximation Mayer & I used. The quadratic function fits fairly well in the (boxed) region of interest. By successive approximations, it could be made to fit even better.

So, by successive approximations, one could find the right place for the functions. You would then have a set of quadratic functions, and could do the minimization by calculus. What you end up with is a set of N linear equations and N unknowns where the number N may be fairly large.

That gave you an N by N determinant, but it would be unmanageably large. But aside from that, I had solved the problem.

I knew that Joe Mayer had been working with the very first digital computer, the one the army had had during World War II. I don't know how I knew that but I did know it. So when he arrived, I went to him and said, "Joe, I have a chemical problem, and what I need to do is solve a large N by N determinant, and I can't solve it, and presumably you can solve that on the ENIAC (or whatever the hell it was).

Well, of course, today, that's a standard computer problem. Then, I bet, it would have been a major job. But of course Mayer wasn't that stupid and he wasn't having any of that, and he said, "Before we discuss solving an N by N determinant, explain what the problem is."

So I explained about optically active biphenyls. Joe Mayer might have known about them, because he had sat in on Bill Doering's lectures in organic chemistry, when Mayer and Doering were both on the staff of Columbia. But, in fact, he had never heard about optically active biphenyls and he wouldn't believe me, and I had to go and get models and show him. I gave him a lecture, I guess, for about an hour, with models, on optically active biphenyls. Then he looked at my mathematics, and in, perhaps, fifteen minutes, showed me how to solve the mathematical problem. Without an N by N determinant. And then the thing was off and flying (45).

That one was very much more mine than the Kirkwood one. In the Kirkwood work, I really didn't see how to solve the problem. This one, I would have solved myself anyway, in a sloppy sort of fashion.

GORTLER: Your willingness to tackle the problems, in both instances, I think is important, and your willingness to go and seek help from and collaborate with the physical chemists, is important.

WESTHEIMER: Well, they were good physical chemists and very nice people to collaborate with. <u>Very</u> nice people to collaborate with.

GORTLER: You did a lot of collaboration with colleagues.

WESTHEIMER: Yes. Chicago was a place that encouraged that.

GORTLER: How did the paper with Kharasch get started (46)?

WESTHEIMER: Oh, that's pure cheating.

GORTLER: Somebody wanted to know that, obviously. It was in 1941, before we entered the war, but we already must have been working on war projects.

WESTHEIMER: Yes, indeed. That came out of an NDRC project. The NDRC had been set up prior to World War II, in part due to Conant's great efforts, and his worries about Nazi military strength.

That project, looking at the mechanism of nitration, was assigned to Kharasch. In fact, he had nothing to do with it. All he did was put his name on it, which he and I had some very sharp discussions about at that time.

GORTLER: But you did the work and the money came through his grant.

WESTHEIMER: Yes. That was not Kharasch's type of research.

GORTLER: Yes, I didn't think so.

WESTHEIMER: But this business of triphenylmethane indicators--

GORTLER: That was very sophisticated thinking, by the way, I think. Did you realize you were working with a new acidity function?

WESTHEIMER: Yes, but was stupid enough not to name it.

GORTLER: You could have named it "the Westheimer function."

WESTHEIMER: I could have named it something. Yes, I knew I had a new acidity function, and that it was the appropriate one for nitration reactions. I missed understanding the Raman spectral data that were in the literature, because I was afraid to go to physical chemists to talk to them about the spectral data, stupidly, because the project was classified.

GORTLER: I see. I was going to say, you'd never been afraid to go talk to them before.

WESTHEIMER: No. But I was under this pledge of secrecy, and I didn't think I could go to someone and talk to him about nitric acid, which, of course I could have and should have. The Raman spectral data were in the literature and were later interpreted by Ingold. At the time, I didn't understand them, although I knew they were there. I knew I ought to understand them. But I think I knew what I was doing then. And that, of course, was direct inheritance from Hammett, having been in Hammett's laboratory and intimately acquainted with him.

GORTLER: It's interesting. Hammett told me that it wasn't until much later that he realized that there was more than one acidity function. In fact, it had been almost pure chance that he had chosen a series of compounds that were all related, so that in fact he got a decent series. He refused to believe in other acidity functions until much later. It may have been even during the preparation of his second book. I'll have to go back and look at those notes.

WESTHEIMER: Oh, no. That couldn't be so. I talked to him about the triphenylmethane indicators at the time and I'm sure--Hammett was director of the Explosives Research Lab in Bruceton.

GORTLER: Yes, tell me a little bit about that.

WESTHEIMER: I went there in 1943 as research supervisor in charge of organic chemistry, and Hammett, I don't remember specifically talking to him about this nitration project, and I can't therefore swear that I talked to him about it. But it's inconceivable to me, that if we were in an explosives research laboratory together for two years, and I saw him every second day, that I never discussed that with him. I even have a vague recollection of--no, that was different--that was the oxy-nitration process, I remember talking to him about.

GORTLER: I'm not certain that he wasn't aware of the work. I just don't know if he realized the import of having chosen the right series of compounds, for a while anyway. He thought it was sort of a unique function, and it took him a long while to accept the idea that there could be other series.

WESTHEIMER: Well, I don't think it was as hard for him to accept the triphenylcarbinol series, as it was for him to accept that in simple protonations, that didn't involve an extra molecule of water, that there is more than one function.

GORTLER: Yes, I know what you mean. When you went to Bruceton, you cut off everything at University of Chicago. You weren't doing work there as well?

WESTHEIMER: No, cut it off completely, and did nothing but the explosives work.

GORTLER: And you became an explosives expert.

WESTHEIMER: Well, it was an extremely interesting set of experiences, in many ways, with lots of stories that in retrospect are quite fascinating. But I was absolutely cut off from the University of Chicago. No connection. Did one job at a time.

GORTLER: I think I'd like to hear about that war work sometime.

WESTHEIMER: The other themes that I've carried for a long time, one was the decarboxylation business, and the other was the direct and stereospecific transfer of hydrogen, which was done in collaboration with Birgit Vennesland.

GORTLER: That was one of the things I was going to ask about. Before I get to that, let me get back to the Novick paper for a second. You pretty much told me what prompted your interest in the oxidation mechanism, and apparently some other people had looked at oxidation before, and it appeared from the first paragraph of that paper that one of your incentives for doing the work was to do it right. It seemed to me that you looked at the other papers and noted that it had been done poorly. That appealed to me, for some reason, and we'll go back and look at the first paragraph of that work.

WESTHEIMER: All right, I don't remember that.

GORTLER: What I wanted to ask, a question I raised earlier--this paper can be characterized as classical kinetic analysis.

WESTHEIMER: Yes.

GORTLER: What I put down in parentheses here is, "In the Hammett-Bartlett-Westheimer tradition." If you want to be part of a tradition, now. Where did the methodology develop? Where did you learn it? Did it just develop over time? Was it in the Conant laboratories? Did you get it out of the literature?

WESTHEIMER: All right. I want to say something about that, because it seems to me that the paper, from the kinetic point of view, that I'm most proud of is the one with [Warren] Watanabe (47). I'll talk about that in a second.

Where did this methodology come from? When I was at Dartmouth College, the one thing in physical chemistry that I could grab onto and enjoy was reaction kinetics. I understood those reaction kinetic equations, and I understood algebraic manipulation and all that is just very easy and automatic.

In that Novick paper, the nice thing was the business of introducing the acid chromate-dichromate equilibrium, and that just comes out of feeling at home with algebraic equations.

The business of looking out for acidity effects and salt effects and so on really goes back I think to the 1904 paper of Lapworth's. Lapworth knew about salt effects in 1904, and then I read the Brønsted-Bjerrum papers, and LaMer was concerned with salt effects, and I saw that work at Columbia. I would say I grew up with it. I grew up with it the way someone who was fortunate enough to grow up in China grows up speaking Chinese.

GORTLER: That's interesting. After a while, if you talk to enough people, things start to coalesce. It turns out that lots of people were reading Brønsted's papers or Lapworth's papers, and it's not so surprising then that they began to do a certain kind of work. So it's important to the development of physical organic chemistry. That's why I ask. That was a good answer [for me].

WESTHEIMER: I would like to say a word about the Watanabe paper. In that paper with Watanabe, we tried to analyze the possible pathways for the chromic acid oxidation, through all of the various mechanisms, including free radicals. We laid down some ground rules that said, we will assume that there is only one kind of pentavalent chromium and only one kind of hexavalent chromium and so on. Of course, automatically that's wrong, because you know there are two kinds of hexavalent chromium, the acid chromate ion and the dichromate ion, and there might be two kinds of pentavalent chromium similarly. I guess we didn't make that assumption for hexavalent but we did for pentavalent. Only one kind. And assumed only one kind of tetravalent chromium.

Within that limitation, we were then able to write down every pathway that could lead from isopropyl alcohol to acetone. Of the pathways, there were only two that fit all the data--the right one, and the one we chose.

What we did, however, was, write down all of them, and eliminate down to only two, and then we said, "We don't know which of these two is right, but we'll take the simpler of them, till we know better.

Well, the simpler one turned out to be wrong, and Wiberg was principally the person who proved that the simpler one was wrong. But the methodology has a thoroughness about it that I rather like.

GORTLER: Okay. I think that work, then, is in the same tradition.

Let's talk for a couple of minutes about the Steinberger paper (48) because that was the beginning of the decarboxylation work. That was one of the first enzyme models that you were serious about, and you carried it for a long, long time.

WESTHEIMER: Until we got to the enzyme.

GORTLER: That's right.

WESTHEIMER: Yes. The enzyme, of course, was kind enough to follow through with the same mechanism that we had been worrying with in the dealdolization, the Schiff base mechanism (9).

GORTLER: Okay. That explains why you called to my attention the formation of the--

WESTHEIMER: Yes. That's right.

GORTLER: Okay.

WESTHEIMER: It all circles back. Actually, we had done a paper on decarboxylation earlier. There was a paper with William Jones (49). Of course there are about a million William Joneses. It must be about the most common name in the Western world.

GORTLER: Yes. I'm in communication with one at the University of Florida. I strongly suspect that's not the same William Jones.

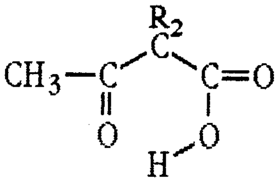
WESTHEIMER: No, it's not. This man went up to Canada; I lost track of him. But William Jones and I did a study on the decarboxylation of dimethylacetoacetic acid. That was the same compound on which Kai Pederson had done his perfectly gorgeous demonstration of decarboxylation via the enol. I'm sure you're acquainted with that work of Kai Pederson's.

GORTLER: I believe so.

WESTHEIMER: What he showed was that for dimethylacetoacetic acid the rate of decarboxylation and the rate of bromination were identical, whereas, methyl isopropyl ketone did not brominate at anything like that rate. Therefore you were not decarboxylating and then brominating, but producing the intermediate for bromination by decarboxylation.

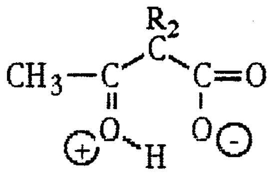
It's a classic paper. It's a marvelous paper. 1934 J. Phys. Chem., I think (50). What Jones and I did was to do the decarboxylation in various solvents, of differing dielectric constant. We reasoned that, if the reaction went through the zwitterion, then, even though the transition state would partially lose that charge separation, there would still be considerable charge separation in the transition state. The rate would go down sharply, as the solvent was changed from water to methanol or dioxane-water or whatever the hell we used, I've forgotten.

In fact, the reaction rate was not affected by changing solvent, so we concluded that the reaction proceeded from a hydrogen bonded molecule (I), not from the zwitterion (II):



I

as opposed to



II

II, of course, need not necessarily be in this configuration.

GORTLER: Which would have been solvent dependent.

WESTHEIMER: Which should have been solvent dependent.

So we had been in the decarboxylation business. Well, everything builds on everything else. The fact that I'd been in the decarboxylation business was probably why I was aware of the metal-ion promoted decarboxylation of oxaloacetate. If you read the papers on the the metal-ion decarboxylation of oxaloacetate then you were pushed to reading the papers on the enzymic decarboxylation, where the enzyme is metal-ion dependent.

Steinberger and I formulated a metal-ion mechanism. Then, I wanted to follow Pederson's example, of putting two methyl groups on the methylene group, so that there could be no enolization of the starting material. The biochemists at the time were writing nonsense, with metal enolates of the starting material.

GORTLER: Yes, you mentioned that in the paper, and I wondered why. If there was an enolization in advance, decarboxylation would not take place.

WESTHEIMER: It's all wrong. You know, if you go back far enough, even chemists but certainly biochemists didn't have any feeling for mechanism. They knew there were metal enolates and that metals promoted the decarboxylation. As you say, if you thought about it, it couldn't go by way of metal enolates of the starting material, and what one required, in order to know that, was, education as a physical organic chemist on the one hand, and you had to read the papers that the biochemists wrote, on the other.

In Chicago, you had to cross Ellis Avenue, mentally. [The chemistry department was on one side of Ellis Avenue and the department of biochemistry was on the other.]

The long tradition, in organic chemistry, of ignoring biochemistry made it so that very few organic chemists ever read a paper in the Journal of Biological Chemistry. They considered it dirty and they shouldn't do it. I really think that's true. I think that there was a revulsion, on the part of organic chemists, with respect to biochemistry, and they didn't want to look. But then, of course, there are the people who don't want to look for the other reason, namely, that if you look too broadly, your own work may not be so significant.

GORTLER: With respect to this, I notice that a number of your early papers were published in the Journal of Chemical Physics. Why did you do that? You were working with physical chemists.

WESTHEIMER: No, wait. The work with Kirkwood belonged in the Journal of Chemical Physics. The work with Mayer seemed to me definitely to belong in Chemical Physics.

[END OF TAPE, SIDE 10]

WESTHEIMER: The paper with [Aaron] Novick and the paper with Watanabe on the chromic acid oxidations were published in the Journal of Chemical Physics, but I think they would have been more appropriately published in The Journal of the American Chemical Society. I will have to check the answer I'm about to give you on that. I'm not sure.

After the paper with Kirkwood (33), I was, believe it or not, very briefly appointed as one of the associate editors of the Journal of Chemical Physics. Since I was an associate editor at that time, I may have felt that I ought to submit something to them. But I'm not sure. I'll have to check the dates [associate editor: 1942-1944; the paper with Novick was published in 1943, that with Watanabe in 1949].

Anyway, having begun on decarboxylation, which is a result of reading and admiring Pederson, Steinberger and I started that project. We sort of imitated Pederson, with respect to putting the two methyl groups on the molecule. The condensation reactions we used were based on Charles Hauser's condensations. The business of putting on tertiary butyl groups and taking them off with HBr to get the unsymmetrical ester, I forget whose work we were following. That sort of thing was in the literature.

Steinberger is a first-class scientist. He's an interesting man who worked nine to five, five days a week. The hours I worked seemed to him outrageous and unreasonable. That's all he would do. But he worked extremely hard during that time, and he worked using his mind.

GORTLER: As a footnote, what kind of hours were you putting in at that time?

WESTHEIMER: Oh, four nights a week, regularly.

GORTLER: Weekends occasionally?

WESTHEIMER: Saturday all day, but not at night.

GORTLER: Okay. Fine.

WESTHEIMER: I took Sundays off, always. Took my children to the zoo, usually. But I worked many, many evenings.

But Rudy [Steinberger] came in with the claim that the product of the decarboxylation is a reasonably stable enol, and wrote it down perfectly casually, out of ignorance. He didn't know it was impossible.

I told him, of course, that a stable enol was impossible. He said, "Look at the spectra."

So I looked at the UV spectra and decided, it may have been impossible, but it was true.

So then we had all those pretty ferric complexes, and there were a lot more in a thesis by Bill Grigsby that we never published, but should certainly have been published. It had a great deal more of that decarboxylation work in it.

Recently, Ernie Rose, at the Cancer Institute in Philadelphia, has shown that he can carry out an enzymic hydrolysis of phosphoenolpyruvate, and that the enolpyruvate itself has transitory existence, and is perfectly easy to detect.

Steinberger and I should of course have continued that work, and picked up the enol of pyruvate. We failed to do it because I succumbed to one of Joe Mayer's dicta. Joe Mayer says that the reason young chemists are so much more successful than old ones is, that the old ones know so many things that don't work. And I already knew too much. I was familiar with Reynold Fuson's work, in which he had very early on isolated the enols of acetylmesitylene.

If you take 2,4,6-trimethylacetophenone (acetylmesitylene) and treat it with a Grignard, it enolizes, and you get the metal enolate. If that is then acidified, you get the enol, and Fuson isolated and crystallized that enol, at least I think it's that one.

I knew then that you could have transitory enols if they were sterically hindered, and therefore, I understood full well, after Steinberger proved to me that he really had an enol, that it was because of the steric hindrance of the methyl groups.

Ernie Rose proved that isn't so at all. It's just the nature of the compound, that it doesn't ketonize very rapidly. Maybe the equilibrium isn't even all that unfavorable.

So, by knowing too much, I missed that. But that's where that came from. That carried over, of course, to the work with decarboxylase later here [at Harvard].

The Vennesland work is an interesting story (51). That began because I read a paper of Ted Geissman's (52). Now, the paper of Ted Geissman's is in a journal I don't usually read, so somebody must have called it to my attention. I looked back at it, and it's in the <u>Quarterly Review of Biology</u> in 1949. That paper "explains" enzymic oxidation-reduction. The way it occurs, according to Geissman, is that the protein chain (hydrogen bonded) is essentially an electron conduit, by resonance, and you carry out an oxidation at one end of this chain, removing an electron, and it flows in from the other end, down the protein.

You know, from a physical organic chemistry viewpoint, that makes absolutely no sense at all. It's an outrage.

I was sufficiently outraged that I decided I had to DO something, and I was going to demonstrate that hydrogen transfer occurred directly.

Well, at this precise moment, Harvey Fisher, who was a graduate student (either in chemistry or probably in biochemistry) came over, and said, "Do you have any problems that you could assign for research? I'd like to do research with you."

I said, "Yes, how would you like to do this project?"

He said, "Oh, that's great."

I said, "The only trouble is that I never worked with DPN or DPNH [DPN = NAD: Diphosphopyridine nucleotide or Nicotinamide adenine dinucleotide]. To tell you the truth, I've never had an enzyme in my hands. I think it's a good project, but we'd better get a biochemist."

Harvey said, "Oh, I'm a biochemist," which, incidentally, he is.

And, I guess not being very flattering, I said, "No, I mean a real biochemist."

So I went around to the biochemistry department to pedal this project. I don't know, I can't remember any more if I tried anyone before I tried Birgit [Vennesland]. But she had been working with DPN, and it may be that when I went over to the biochemistry department people said, "Well, you know, the person you really want is Birgit."

So I told her about this idea, and she thought it was a fine project, and we started a collaboration. She and Harvey Fisher. Harvey Fisher, under her supervision, purified the enzyme and chromatographed some of the crude DPN that one could buy in those days. I went in the lab myself, to make dideuteroethanol, and we set up the most horrendous method of analysis you can imagine. It was the best available in those days, and it was the way you did it.

We set up a combustion train, in the chemistry labs--it was awful. You took the compound that you wanted to analyze for deuterium, mixed it with copper oxide, and combusted it to CO_2 and water, collected the water, and distilled it over zinc, which had to be held at about 400 °C, or whatever the temperature was, just a few degrees below the melting point of zinc. If you melted the zinc, the reaction failed, because you didn't have enough surface area. If you didn't get the temperature to the incipient melting point of zinc, the reaction failed because water only reacts with the film of liquid zinc. To make the analysis work, you get particles, with a little liquid zinc on the surface, and this reacts, and then converts the water to hydrogen. You used a Toepler pump to push the hydrogen into a tube, took it down to one of Harold Urey's best spectrometers, and measured the hydrogen-deuterium ratio.

So that project began because Ted Geissman wrote an outrageous paper, which someone, I have no idea who it was, called to my attention.

GORTLER: Is that the uncomplimentary story that you're concerned about?

WESTHEIMER: Yes. But you know, in a way, it's interesting to see the driving power of bad science--but, that's how all that got started.

GORTLER: It takes a certain kind of mind to recognize bad science. It doesn't drive absolutely everyone.

WESTHEIMER: What it took--somebody else recognized that, you know. Somebody called that paper to my attention, because I don't read the Quarterly Review of Biology. Now, whether someone came to me and said, "Look, Geissman has worked out how oxidation reductions go," or whether he came to me and said, "Isn't this ridiculous?"--I don't remember who it was, or how it--I can't answer that question.

But somebody else saw that paper first, then brought it to my attention.

GORTLER: There's one instance in a longer paper in which the ethanol was obtained from acetaldehyde (53).

WESTHEIMER: Are you talking about the stereochemical inversion?

GORTLER: No. You took acetaldehyde and treated it with DPND, and the ethanol that you obtained only had half a deuterium per each molecule. That bothered you at the time. I think my conclusion would have been that it was just absolutely random, because you know it was reducing from both sides. But that wasn't your conclusion at all, and you went through, and everything else afterwards fit, the stereochemical business. I wondered if you'd ever resolved that? Whether that was just a matter of this long train failing or something of that sort. Although I think you had duplicate experiments that showed that it was only half a deuterium per molecule.

WESTHEIMER: You're sure? I'll have to go back to the papers. Are you sure this wasn't the chemically reduced DPND? Where we only ought to get approximately half, because the chemically reduced--sort of half--

GORTLER: Yes, because that would have been from either side.

WESTHEIMER: That would have been from either side. Not necessarily in equal quantities, because those two compounds are diastereomeric and not enantiomeric.

GORTLER: You reduced it using dideuteroethanol.

WESTHEIMER: Oh, if we reduced it enzymically, using dideuteroethanol.

GORTLER: You were distressed by the fact. You mentioned it and said you just didn't understand it, but then you went ahead and used that DPND on pyruvate and it seemed to transfer completely, almost, 0.88 or something like that.

WESTHEIMER: I don't remember this. I'll have to go back. My guess is that it was simply experimental trouble.

GORTLER: Yes. But everything else fit, and, it seemed to me, that longer paper is one of those classics of logic. Anyone could have thought of it. But you did.

WESTHEIMER: That was an early paper. But of course, the critical paper, in the course of establishing what we now would call enantiotopic and diastereotopic atoms, was a paper of Ogston (54). Do you know the Ogston work?

GORTLER: No, I don't.

WESTHEIMER: That's important in the history of science. It's another one of those great papers. It's a little note in Nature, I think, and it may be one page long. The biochemists had had a severe problem that had turned up in the study of the Krebs cycle. One of Kharasch's former students, Sid Weinhaus, had been involved in this. In the Krebs cycle, one produces citric acid which is a symmetrical molecule. But the CO_2 that comes off in a subsequent step, comes off exclusively from one of the two apparently identical carboxyl groups of the citric acid. This naturally caused a great deal of distress. The first argument that was made was that perhaps the citric acid never leaves the enzyme. It is formed from oxaloacetate and pyruvate. If it just stays on the enzyme, then the two ends of the citric acid are in different positions on the enzyme, so that the molecule could lose CO_2 from one carbonyl group and not the other. Then people came along and took the citric acid off the enzyme, put it back on, and the citric acid remembered which of the two ends had come from pyruvate and which from oxaloacetate.

This would have caused even more distress if chemists had known about it. Although only biochemists knew about it, even they were distressed.

And Ogston, in Britain, saw that if you put the citric acid onto the enzyme with three points of attachment, the two enantiotopic $-CH_2CO_2H$ groups were in fact distinguishable. He didn't use the word enantiotopic, of course, and it isn't necessary to have a three-point attachment. It's only necessary to make a one-point attachment to an asymmetric center, but Ogston saw the problem in terms of the three-point attachment. It was something that was discussed very widely at the University of Chicago. It was of great interest to Weldon Brown. It was of great interest to Bill Wheland, who was very much concerned with stereochemistry. It was of great interest to me. We discussed it and were very excited about Ogston's work.

Our work was, I think, the first good work on enantiotopic deuterium compounds, and it is, I believe, at the base of a great deal of work that's been done since, and I'm very proud of it. But the intellectual father of that was Ogston.

GORTLER: One last question. This has to do with the Nicolaides paper, using k_H/k_D (55). You commented that that was an early use of the k_H/k_D on mechanism. There had been work done in the early 1930s and the only reason I know about that is because I looked at your review paper.

WESTHEIMER: Yes, indeed. There was perfectly splendid work on k_H/k_D on enolization.

GORTLER: Right.

WESTHEIMER: I guess one could say that that work confirmed the mechanism of enolization, which had previously been postulated, and actually goes back to Lapworth.

But it seemed to me, maybe I'm mistaken, that the business of deliberately using a kinetic isotope effect in developing a mechanism, hadn't been done. The other papers, were by people who were trying to find out about the deuterium isotope effect and what deuterium would do, and I don't think that the notion that you could use it as a tool for mechanism appears in those early papers. It appears very clearly in the [Lars] Melander paper, on the nitration of benzene (56). That paper and the Nicolaides paper were more or less simultaneous. And in a way, they are a pair, because Melander found that in the nitration of benzene, there was no tritium isotope effect from which he concluded that the addition of NO_2^+ occurred during the rate limiting step. The elimination of the proton from the carbon atoms to which NO_2^+ was attached was a fast subsequent step. It didn't make any difference to the rate whether it was hydrogen or tritium.

So, there were the two contrasting cases, his where there was no isotope effect, and you could show therefore that the hydrogen was not removed in the rate limiting step, and ours, where there was a big effect, and you could show that it was.

Those are the first two cases, to my knowledge, where people had deliberately designed experiments to utilize the deuterium isotope effect, even though, as you say, the effect was well established. I think that's true. I don't know.

GORTLER: It can be checked.

There was another paper, the second Vennesland paper, where you made the optically active deuteroethanol (53). The preceding paper in the Journal was Streitwieser's paper on the optically active deuterobutanol (57). Since you acknowledged one another, you were obviously in communication.

WESTHEIMER: Yes, Jack Roberts was the link. I told Jack about our work. He, of course, knew about Streitwieser's work. We therefore got in touch, and published simultaneously, by agreement. As I recall, there was only a very slight delay, on either side, and I don't even remember clearly which way it was, although I think that we had to wait a month on publication for Streitwieser to be entirely ready. Maybe, I don't remember, maybe he had to wait a month for us. I think it was the other way around. But they were essentially ready simultaneously. It would have been a shame if they hadn't been published side by side.

GORTLER: Was he at MIT at the time? [He did the work at MIT while he was a postdoctoral fellow with Jack Roberts.]

WESTHEIMER: He was at MIT at the time. So was Roberts.

[END OF TAPE, SIDE 11]

GORTLER: Are there some things that you want to tell me about?

WESTHEIMER: Not really. I did once attend a set of lectures on biochemistry. That was fairly late in my career. They were given by Frank Putnam. Frank Putnam is now chairman of biochemistry at Indiana. He was at the University of Chicago from 1947 to 1952, and some time during those years, I went in and sat in on his lectures on biochemistry. But I don't know exactly when.

One of my good friends among physical organic chemists all these years has been Frank Long. He was at Chicago as a postdoctoral fellow with Harkins when I first arrived, or shortly after I first arrived as a research associate. I knew him vaguely then. We became quite good friends when we were both at Bruceton, during World War II. I liked his physical organic chemistry. I don't think he has made the great contributions that for example Winstein made, but I liked his work.

I think by and large, I've said everything I intended to say, and will sit back now and try to answer whatever questions you care to pose.

GORTLER: How did you select your graduate students? Did you choose them or did you let them choose you?

WESTHEIMER: Certainly, at Chicago where the demand greatly exceeded the supply, the graduate students chose me. What I did do at Chicago on several occasions was to stop people working when they had finished their master's degree on the grounds that I was not at all confident of their ability to get a Ph.D. In general, they went ahead and got Ph.D.s with other people and some have done very well since, so apparently my judgment was overly severe.

At Harvard, where the number of graduate students was much larger, it was more of a bargaining process, and at first, I turned down graduate students when I felt I had a large enough group. But sometimes even then someone would argue me into taking them on. I was in a bad position to resist, remembering how I'd argued Conant into taking me on.

Sometimes I would deliberately try to discourage a student from working with me, on the grounds that I didn't think he would do well with me.

But usually, it was more the student's option than mine, even here.

GORTLER: How did you usually choose postdocs?

WESTHEIMER: Usually, although not always, these were people who applied to me. Sometimes I asked or wrote around, but usually they were people who applied. Pre-affirmative action, I just tried to select the one I thought was best, without bothering to get all the documentation that one must now have, to make an appointment, at least at Harvard.

I have in general not merely favored but strongly favored Americans over foreign postdocs. I don't know that this is the way to get the maximum research done, and I'm not sure that I can make a full justification for having made that preference, but I did. I've had relatively few foreign postdocs.

GORTLER: Once in your group, do you have some sort of general methodology with respect to graduate students and their work? How closely do you oversee their work?

WESTHEIMER: I have a very--rigid is too strong of a word, but I had a plan that I administered for many many years, although in recent years I've slipped. Early on, certainly at the University of Chicago, and early on here, I tried very hard to see graduate students quite regularly, several times a week, at the beginning of their work. And then tried gradually to withdraw, and tried to see to it that after a year or two, I didn't go to them at all. I waited for them to come to see me.

A little bit, I guess, on the principle of Kohler's. I tried to get people started, and then would walk away slowly. Sometimes one couldn't walk away. Sometimes students were very eager to have you walk away much earlier. I tried to make that a principle, but I must confess that in the last two years, I haven't adhered to it, and have left people very much more on their own, even at the beginning, probably more than I should have.

It depends on the student, too. It really does.

GORTLER: Can you make any comparison between the general students thirty or forty years ago and the graduate students today? Do you think they've changed significantly in their attitudes?

WESTHEIMER: The students at Harvard certainly used to work a good deal harder (I think they still work harder) than those at the University of Chicago. Furthermore, the average quality of the graduate students I've had at Harvard was better than the average quality of the graduate students I had at Chicago. Brighter, as well as harder working.

Until very recently, however, the best individual graduate student who has worked with me was at the University of Chicago, and in fact is Dan Koshland. There is now a graduate student sort of working with me, working ninety-four percent on his own, three percent with Woodward and three percent with me, in my lab and our group. I think I've finally seen someone brighter than Dan. That remains, of course, for the future.

GORTLER: Could you identify him now?

WESTHEIMER: Oh sure. It's a young man named Stephen Benner. That's a prediction. I claim that he's going to be a star.

GORTLER: Are there any other students over the years that we have not already talked about, that you might mention?

WESTHEIMER: Well, I have had a fairly large number of students who have done at least well. I think the large majority of them, have been in bioorganic chemistry, and I have been really very proud that at the Gordon Conference on Enzymology, there were a dozen or fifteen of my former collaborators who have been accepted and attended.

So that's sort of a measure of the success of this nature.

Of the people I've worked with, besides Koshland, Bob Abeles, a postdoc, was and is a superlative biochemist. Myron Bender.

Then I have had some postdocs who were fairly well along when they came here, and I don't know how much credit I can claim. I think it goes the other way. But Burt Zerner and Irwin Fridovich, who is a full professor of biochemistry at Duke, are outstanding individuals. Tom Morton, an assistant professor from Brown, who is in my laboratory now, I think he's going to turn out to be quite good.

Then there's a whole list of people who are in academic life and carrying on bioorganic chemistry of one sort or another. I'd do better looking down the list (of grad students and postdocs) than remembering off the top of my head, but I can give you quite a large number, starting with Gordon Hamilton, Paul Haake, and David Sigman.

GORTLER: Tom [E. T.] Kaiser certainly has quite a reputation.

WESTHEIMER: Yes. Tom Kaiser of course. Perry Frey who was a postdoc here and is now professor at Ohio State, is really splendid. Harvey Fisher of course has continued in bioorganic chemistry. Dave Mauzerall from University of Chicago days is on the staff at Rockefeller, and has done good work, I don't think great, but quite good work.

Aaron Novick, of whom we've spoken before, has turned biologist, so I haven't really followed his work carefully, but I think he has done really quite well.

I'm a wild enthusiast for Barry Cooperman, who's at the University of Pennsylvania. I think he's going to turn out to be splendid. Peter Guthrie, who is at Western Ontario, is a real scholar. George Kenyon was a graduate student with me, and is now at the University of California Medical School in San Francisco, and is doing very pretty biochemistry.

I'm going to look because I'm likely to forget.

Well, there are a number of other people here who were certainly interesting, and have done interesting work or are doing interesting work. Charles McKenna may turn out to be a star. I don't know if he will or not. I mentioned Marion O'Leary, I'm sure, already. I don't see how I can make much claim on either [Jan] Rocek or [David] Samuel, except to say how pleased I was to have them in these labs.

[Edward] Thornton at the University of Pennsylvania is doing all right, but he's back in physical organic chemistry and no bioorganic chemistry.

GORTLER: Oh, no, on the contrary. He's now working on the nervous system.

WESTHEIMER: I see. I didn't know that but I'm pleased to hear it. I thought I'd sort of lost him to physical organic chemistry.

Roberta Coleman is at the University of Delaware. I haven't followed her work very well, and Ed Dennis is at La Jolla. John Gerlt who's at Yale and who's just begun, I think will do well. David Gorenstein and Ronald Kluger are both physical organic chemists with biochemical overtones. Charlie Lerman's a very good teacher, but I don't know that he's ever going to turn out to be a great research man. A number of these people went into industry. Charlie Perrin is a pure physical organic chemist. I don't want to say I lost him. I should have mentioned Stan Seltzer who is at Brookhaven still and doing very well and Vinay Chowdhry, who is at Du Pont. Irving Sigal, who's now taking his postdoctoral at Caltech, is another one who, I predict, is going to be a star, although he will not be a supernova, and Benner might be.

But, you know, there's a good bunch of people there who constitute a sizable fraction of the group doing bioorganic chemistry in the United States. They constitute something like ten or twelve percent of the people who show up at the Gordon

Conference on Enzymology. That's really very gratifying. It goes without saying that I know very well the difficulty of attributing very much of that to what I've taught them.

What happens, of course, is that if someone gets started in a relatively new field, the people who are interested in that field gravitate to that laboratory, and then if they're good people, they do well afterwards. The question of how much influence any individual has on any other is open to question. There's a good deal of argument about whether, for example, Harvard was any better a university than Podunk. It turns out that bright people choose to come to Harvard. If for some unknown reason they got forced to go to Podunk, they might turn out just as well. Or they might not. I don't know.

I think, in the early days of physical organic chemistry, Paul Bartlett attracted a stream of spectacular people, who came because if you were looking for a laboratory in physical organic chemistry in the United States, in the middle 1930s, you didn't really have a wide choice.

GORTLER: Since you've brought that up, what was the choice? Assuming that you were going to run a conference on physical organic chemistry in 1935, who would you invite?

WESTHEIMER: Well, in 1935 we had lost Conant. So one couldn't have him. One would have started certainly with Hammett. One would have invited [Howard] Lucas who was easily visible at that time. One should have invited Kharasch, who was visible by then. One would certainly invite [Linus] Pauling. I think one would have invited Wheland by 1935. You certainly would not have invited me, and you would not have invited Winstein. If you reached outside of the United States, one would certainly have invited [Christopher] Ingold and one would have invited [E.D.] Hughes from the same laboratory. One might or might not have invited Robert Robinson. One would have invited H. Meerwein, R. Criegee, probably a very young man at the time but easily visible. You probably could do a better job of listing these people than I.

GORTLER: Of course, Lapworth was still alive.

WESTHEIMER: [Arthur] Lapworth was, yes. He died in 1938. One might have invited Lapworth.

GORTLER: What about Frank Whitmore?

WESTHEIMER: That's a splendid suggestion. Yes, indeed. I think one should have invited Whitmore.

I was wondering whether one would have invited Kai Pederson. I think his independent work, his important papers were the decarboxylation papers, the ones he did independently of Brønsted. I don't think they came out that early. If my recollection is correct, the major paper was 1938, and whether anything had come out by 1935, I'd have to check back to see.

GORTLER: I haven't checked on W. G. Young's dates. Did Young make much of a--

WESTHEIMER: Splash by then? Well, of course, he was one of Lucas' students. I think one would have invited Young too, but one certainly would have invited Lucas.

GORTLER: Can you think of anyone else from the West Coast?

WESTHEIMER: Well, I was trying to think when Melvin Calvin's name became prominent, and my guess is, not that early.

GORTLER: No. He didn't get to Berkeley until the late 1930s. By 1940?

WESTHEIMER: Well, certainly by then.

GORTLER: You would have been on the list.

WESTHEIMER: I think I would have been on the list. Saul Winstein would I think have been on the list. When were Winstein's papers with Lucas?

GORTLER: Probably the late 1930s. He was around here some time in the early 1940s.

WESTHEIMER: I think one would have had Winstein on the list by then. I'm not sure. Probably [Bill] Young would have been on the list. Pederson would have been on the list, anyway on my list, by then. Whether one would have invited any other of Ingold's collaborators or not, I don't know. Christopher Wilson, perhaps. But it may be that that's too early for Chris Wilson. He may have surfaced more or less with Winstein, and I don't know that one would have included him. I don't know when Price started doing his work in physical organic.

[END OF TAPE, SIDE 12]

GORTLER: You just mentioned the mechanism conference in 1946 [Conference on Organic Reaction Mechanisms, Notre Dame, Indiana, 1946].

WESTHEIMER: When did [Donald] Cram do his first work? He got his Ph.D. here with Fieser, went out to UCLA, and his first two papers immediately put him on the map. One would have invited Cram immediately after those papers.

GORTLER: I think the important thing for me is to find the list of people for that first mechanisms conference.

WESTHEIMER: Yes. Yes.

GORTLER: Do you have any idea of who might have records?

WESTHEIMER: Well, the conference was arranged by Paul [Bartlett] and by Charlie Price.

GORTLER: Charlie Price doesn't have the records, and I just asked Paul for them. He doesn't have them either.

WESTHEIMER: I see. I really don't know. I'm quite sure that I don't have a list of the people at that conference.

GORTLER: Just about when do you think physical organic chemists started calling themselves physical organic chemists?

WESTHEIMER: Certainly by the time Hammett's book appeared on physical organic chemistry (58). I think that crystallized the field. I suspect it was called physical organic chemistry before that, but certainly by 1940 when that book came out.

GORTLER: Do you think it was about that time that they sort of started to recognize themselves as a community?

WESTHEIMER: Oh no, the recognition of the community was earlier than that. There was no question that there was a community, even when it was Bartlett, Hammett, Wheland and Pauling. I knew I belonged to that community, and that there was that community, when I was a postdoc with Hammett.

GORTLER: Okay. That's the important thing.

WESTHEIMER: There was a feeling that it existed, whether or not we called ourselves physical organic chemists, I wouldn't know.

I'm looking down the list of members of the National Academy, and it is surprising how few physical organic chemists of any considerable age are in the list. [Andrew] Streitwieser, Jr. and [Kenneth] Wiberg are a good deal younger.

GORTLER: Yes. They didn't enter graduate school until after the Second World War.

WESTHEIMER: Another thing one could do is to look down the reference list [the footnotes] in Hammett's book. I open immediately to Roberts and Kimball, Bartlett and Tarbell.

I think Bartlett and Tarbell was eighty-nine percent Bartlett and eleven percent Tarbell.

Henry Eyring's name is here. I don't know if you'd call Henry Eyring a physical organic chemist or not. Certainly he made an enormous contribution.

Charlie Price goes all the way back. He was in graduate school when I was. He's a bit older than I. I don't know when he surfaced. One really should have included [Erich] Hückel in any list of physical organic chemists of the day. I don't know when he promulgated his 4n + 2 rule. There were two Hückels.

GORTLER: That's right. Walter was the one who wrote the book (59).

WESTHEIMER: There's Erich and Walter and I get them mixed up. My recollection is that one of the Hückels [Walter] did very nice work on stereochemistry, and one of the Hückels [Erich] was a physical chemist who promulgated the 4n + 2 rule.

GORTLER: Yes.

WESTHEIMER: I haven't hit any names here that I feel have been omitted from the 1940 conference. There are some, there are a lot of names here other than those we cited. One might have invited Charles Hauser, because he really understood more about condensation reactions and what drives them than anyone else. Then, I probably omitted somebody, but I don't see, just turning the pages and looking down this list, many people whom one would describe as physical organic chemists of any prominence.

Now, by the time you got up to 1946, and that conference, that Bartlett and Price held, there may have been more free radical chemists that one would have included. I think one would have invited Mayo, and maybe would have invited him by 1940. I don't know when [Cheves] Walling got into the free radical business.

GORTLER: Well, he worked for Kharasch in the late 1930s, then went into industry.

WESTHEIMER: I don't know when he published independently. So I don't know whether one would have known to invite Walling or not.

GORTLER: I'll be talking to Walling soon and I'll ask him when he would have been invited.

WESTHEIMER: I wonder who was at that conference. I don't know whether one would have invited Weldon Brown or not. The most prominent work he did certainly was the exploitation of lithium aluminum hydride. That was postwar, so he wouldn't have been there, I don't think. That conference was immediately postwar, before Weldon Brown had a chance to do that work.

Gardner Swain, I think, would have probably been at the 1946 conference. I'm sure he would have been. There was a physical organic chemist briefly at the University of Illinois. He died in an airplane crash [fall, 1950].

GORTLER: Elliot Alexander?

WESTHEIMER: Elliot Alexander, yes. I think he had begun to publish by then, though I'm not entirely sure. I think this is way before [Nathan] Kornblum did his work on the diazotization reaction. After he did that work, one would certainly invite him to any conference on physical organic chemistry one was giving. I don't know how old [Jack] Roberts is, but I don't think he had published in 1946.

GORTLER: He wrote about the mechanism conference though, so I think he was there. Yes, I was just reading something about it.

WESTHEIMER: Okay. Jack Roberts is certainly a physical organic chemist to be reckoned with. The only question one is asking is how old he is. I think, as we said, Streitwieser and Wiberg were too young to have shown up at that time.

GORTLER: That's very helpful.

WESTHEIMER: I don't know. That's probably about it. There are undoubtedly some missing. One always misses people, sometimes very prominent people.

GORTLER: Do you remember when the conference was? Maybe that will help me in searching out references.

WESTHEIMER: Yes. The conference was at Notre Dame, and Charlie Price, one of the organizers, was at Notre Dame at the time. The University might have records. It's a very interesting question, who was at that conference.

GORTLER: We've sort of brushed on this question a couple of times. We've talked about the fact that there was a lag of almost twenty-five years, between Lapworth and the new beginning of physical organic chemistry.

WESTHEIMER: Yes. A man named Dawson in England is the only feeble thread that I know of. He was doing reaction kinetics on halogenation reactions, a la Lapworth, and perhaps dressed up a little bit from knowledge of Brønsted and Lowry.

GORTLER: One of the possibilities for explaining the birth of physical organic chemistry is the fact that Lewis' bonding theory came out, and was, by the mid-1920s, being accepted by most everyone. Do you remember whether they were teaching it when you were an undergraduate?

WESTHEIMER: Well, oh I had the two-electron bond and the Lewis octet as an undergraduate. I remember sitting around with my friends, in our own class in advanced organic chemistry, and wondering what was wrong with the idea of describing benzene as just having three electrons in each of those bonds instead of two in one and four in the next? So we were clearly talking about that sort of thing at Dartmouth in 1931-1932.

I don't know why the lag and why the rebirth. One of my aphorisms is that nothing fails like success. I believe that organic chemistry, in a sense, went wrong because the German technique for carrying out organic structure determinations and synthesis was so successful. The great work on steroids and alkaloids went forward so well with this process in German labs of getting very skilled laboratory people who worked terribly hard, and tried innumerable ways of doing things, based upon a thorough knowledge of the literature of what people had done before. With that equipment, they were able to do things so well that, I believe, there was almost a scornful attitude toward Lapworth and the other people who attempted to do theory, as people who were just wasting their time, describing, well, the angels on the head of a pin business. That it wasn't really of any significance, because the significant things were the business of making new drugs, discovering the structure of alkaloids, and of the coloring matters in plants and so on, and you did this by this method of hard work and vast empirical knowledge.

It seems to me that it took a long, long time to build the theory of organic chemistry to the point where it became useful, took over organic chemistry and become incorporated into it, in the way you've already discussed at lunch, so that it doesn't exist really as a separate discipline anymore.

It seems to me what Woodward did was to show that if you applied theory, you could run rings around the people who did synthesis by the old-fashioned German way.

But whenever anything is very successful, it seems to me, it is continued longer than it should be. That's what I mean by nothing fails like success. That, I think, is the reason why the Lapworth initiative was not picked up.

If I can recite a story on this subject that is peripheral, in a way. One of the historians of science, one of the very good ones whom you must know is Cyril Smith. He's an historian of metallurgy as well as a metallurgist. He and a German scholar got together to translate a, I think it was a 15th century, maybe 16th century book on metallurgy, which Cyril couldn't do alone because his knowledge of very old German is inadequate, and the German scholar couldn't do alone because he knew nothing about metallurgy.

Well, I read part of that book. It was fascinating. And if you allow for the fact that you have to translate their terms into modern chemical terms, their metallurgy wasn't bad. I said to Cyril, "These 15th century, whenever it was, metallurgists really did very well. Another way of saying that is, you boys haven't learned much in the last five hundred years, have you?"

Cyril said, "Well, in a subject like metallurgy that is so vital to the human race, there was an enormous amount of empirical work, so much empirical work that it has taken centuries for theory to catch up."

And I think the same thing happened, to a lesser degree, in organic chemistry. The drugs and natural products were so important that an enormous semi-empirical effort went into them, and it took a long time for theory to catch up. During the period when theory was hopelessly in arrears, people didn't bother with it. Just as during those centuries when the theory of metallurgy was hopelessly in arrears, no one bothered with it. For quite a while there wasn't any chance of doing anything in the theory of metallurgy that could be applied, relative to this great body of empirical knowledge.

So, that's my explanation of this lapse. What I find more remarkable than the fact that physical organic chemistry did not develop was that a few people, like Meerwein and Lapworth, did see this opportunity, and did do marvelous things. That seems to me the remarkable thing, and the lapse was caused by the great success of doing things in a semi-empirical way.

GORTLER: Maybe we've already covered this, but about a year ago I had a conversation with Phil Skell and he said, "Physical organic chemistry is dead, and those people who practice it now are merely adding additional digits to already well known numbers." Would you have any comment on that? Do you really think that physical organic chemistry is organic chemistry today?

WESTHEIMER: In a way, I think it is. However, I don't think physical organic chemistry is dead. I think a phase of it has been destroyed by its own success. But there are other things that are coming along, and that will constitute new revolutions and a new birth of physical organic chemistry.

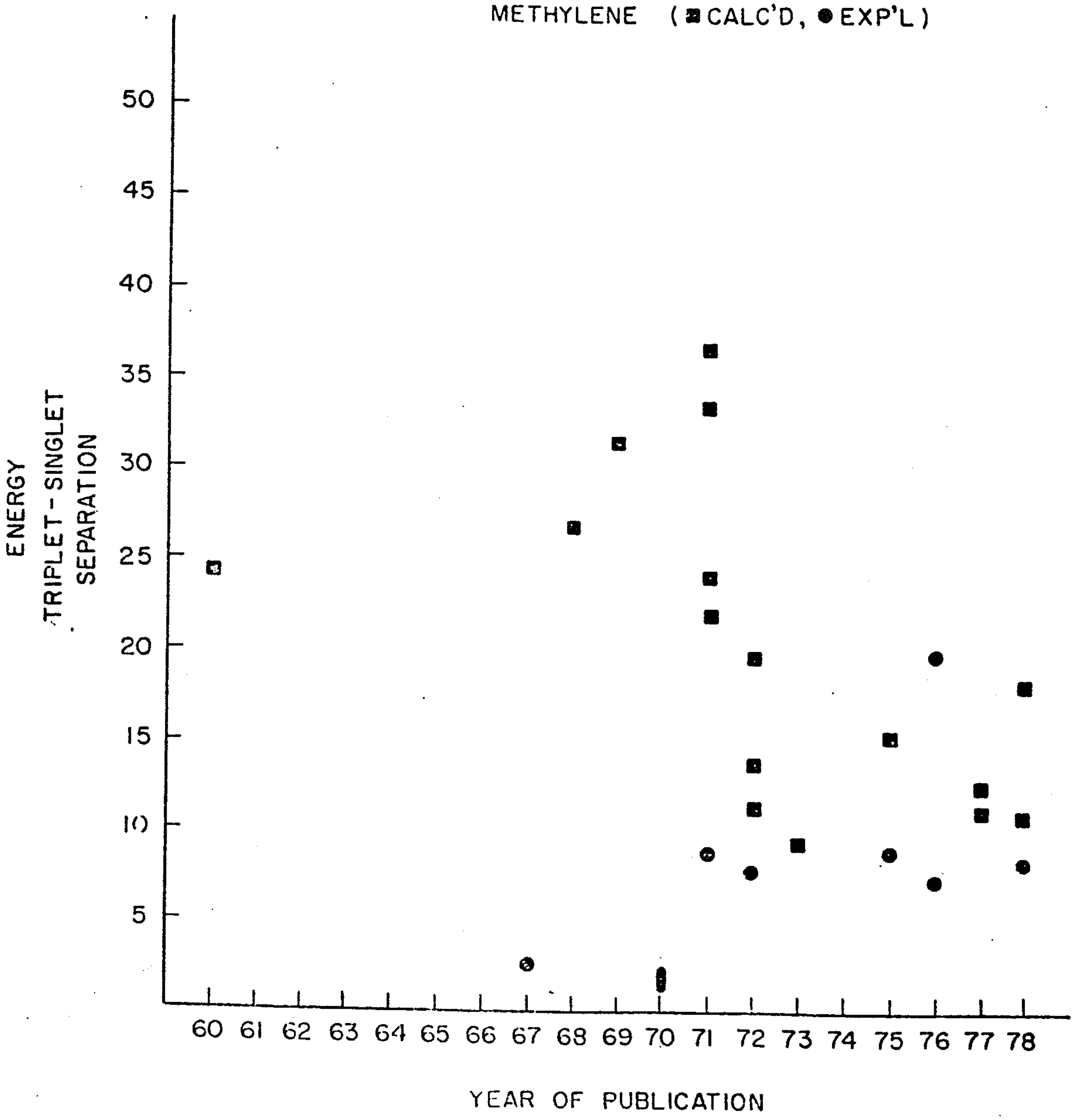
Now, when I say that, I would like to go back and restate it. It is my belief and hope that that statement is true. I don't know if that statement is true. It's just a prediction.

The things that are coming along, it seems to me, are the following:

First and foremost, about a third of every Journal of the American Chemical Society is crammed with articles on quantum mechanical "computations." In my view, almost all of that is garbage. I gave a paper at the Leermakers Symposium this past May, I think it was [Wesleyan University, Middletown, Connecticut, May 1978]. I plotted the experimental and calculated gap in energy between singlet and triplet states of methylene as a function of the year of publication. It's a case where the quantum mechanical calculations have not zeroed in within ten kilocalories.

I can show you the graph [see page 95]. It might be interesting too.

Methylene has only three atoms in it. Two of them are hydrogen. Regardless of what the quantum mechanical calculators tell us, if they can't do methylene, it is quite clear that they cannot do pyridoxal phosphate.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TRIPLET - SINGLET
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YEAR OF PUBLICATION

I talked to Bill Lipscomb about this, who is a quantum mechanical calculator, and said that I thought that most of the work that is now being published in The Journal of the American Chemical Society on these calculations would have to be redone in the future. He said no, that all of it would have to be redone.

GORTLER: Before you leave that Leermakers conference, Ed Thornton said that you had somewhat of a heated discussion with Henry Eyring. Was it over just this point?

WESTHEIMER: No, it was not that. I had looked at the history of physical organic chemistry, and did not include, among the great contributions of physical organic chemists, the Eyring absolute rate theory. This caused Eyring enormous distress. That was a mistake of mine. I certainly should have included that. I hadn't looked upon that as physical organic chemistry, but rather as something chemists use, but with the benefit of hindsight, I simply was wrong. I should have included it. That is what Henry Eyring got terribly upset about.

Now, he also was upset because I criticized Bodenstein and pointed out how much superior Lapworth's work was to Bodenstein's. It is a tenet of physical chemists that Bodenstein began reaction kinetics, and in that instance, Eyring and I strongly disagreed. I don't back off a half an inch from what I said. He started with Bodenstein, but then it became quite clear that my omission of the absolute rate theory was really what had done him in and gotten him so upset. He was right about that.

GORTLER: We were talking about the future of physical organic chemistry.

WESTHEIMER: Yes. It seems to me that what has happened is this. The ability to calculate by quantum mechanics is, at the moment, inadequate. Large numbers of people are using various computer programs to grind out results that should not be published.

I think that eventually the real mathematical physical chemists will work their way through to much better computational methods, and that the quantum mechanical calculations will come into their own and be an important aspect of physical organic chemistry. For example, physical chemists are just beginning to be able to handle individual solvent molecules, on several levels, including the quantum mechanical level of computation. The major problem of physical organic chemistry which, it seems to me, remains to be solved is the question of solvent effects, which are often enormous.

[END OF TAPE, SIDE 13]

WESTHEIMER: We still don't understand solvent effects in any quantitative way. Eventually, a piece of physical organic chemistry is going to surface where one can calculate solvent effects properly, and incidentally go back and do over again the stuff that Kirkwood and I did, at a proper level, where one incorporates at least the first shell of solvent molecules specifically as individual molecules that have specific orientations and activation energies for turning. It will be a much more complicated picture.

But there are people who are at work on that now. The people who are at work on that now intend to do the whole thing on a quantum mechanical level, and it may turn out that what one will do is, rework what Kirkwood and I did, with three shells instead of two--a molecule, a first shell of solvent molecules, and a continuum. Even though my physical chemical friends tell me they're going to do the whole thing all out in quantum mechanics. I don't know that that is going to be true.

But there's a big piece of physical organic chemistry there.

On the subject of enzymes, I've already said that I don't think one understands enzymes until one can make a catalyst, designed to do a particular job, and show that it in fact does it.

A number of people such as [Martin] Karplus here, are trying to apply molecular mechanics to proteins. [Harold] Scheraga is trying a different kind of stunt. Proteins constitute an enormous, difficult challenge. Maybe eventually that can be worked through.

In recent accomplishments in physical organic chemistry, certainly the most prominent by a wide margin, are the Woodward-Hoffmann rules. They constitute a real generalization in physical organic chemistry, and by no means a dotting of i's and crossing of t's. An accomplishment in physical organic chemistry that I cannot perhaps see in perspective because I'm too close to it was the work we did on showing that pseudorotation accompanies the hydrolysis of some phosphate esters. I don't know if you know that mechanism.

GORTLER: I'd like you to talk about the phosphate work. Perhaps you could tell me how it began and then you can say something about the pseudorotation result.

WESTHEIMER: The phosphate work actually began all the way back at the University of Chicago. The first paper was done there, with Walter Butcher (60). We eventually came up with the idea of monomeric metaphosphate as an intermediate in the hydrolysis of phosphate esters, more or less simultaneously with the same concept from C. A. Bunton, in Ingold's laboratory, at the University of London.

I can't quite say how the work began. It certainly was the result of considering intermediary metabolism, and looking at all those phosphates, and thinking of all the physical organic chemistry that had gone into hydrolysis of carboxylic acid esters and amides. Here were these phosphates, which are much more complicated, because phosphoric acid is a tribasic acid with very different relationships with the hydrolysis of the first, second and third ester groups. The hydrolyses are dominated by the negative charges which you get when you hydrolyze and therefore ionize one or more of the groups.

Certainly one of the stimuli to my interest in this field was the perfectly marvelous set of lectures which Alex Todd gave at the University of Chicago, related to his own syntheses of the nucleotides.

I can't remember what year those lectures were at Chicago. One could, I'm sure, find out. I would guess that they were 1948 or 1949, something like that.

Although they were concerned with synthesis and not mechanism, they stimulated or crystallized or enhanced, my interest in doing something with the physical organic chemistry of the phosphate esters.

But of course, once one has formulated a statement in roughly the form I've just given it, namely, that these compounds dominated intermediary metabolism, and yet very little physical organic chemistry had been done on the system, one has a compelling reason to keep on pushing forward with that set of systems.

Now, the pseudorotation business was really quite interesting from a psychological point of view. The idea of pseudorotation in phosphorous compounds came out of Steve Berry's considerations of the NMR spectrum of PF_5 (61). PF_5 shows a doublet in its ^{19}F NMR spectrum, with the signal split by the odd spin of the phosphorous atom. But a doublet implies that all five fluorine atoms are equivalent, but there is, of course, no way in which you can have any three-dimensional figure with five points on it where all of them are equivalent. If you have any sort of regular structure, it must either be a trigonal bipyramid or a square pyramid, so at best four and probably only three fluorines can be equivalent. IR spectroscopy and electron diffraction had led to the very firm conclusion that PF_5 was a trigonal bipyramid.

So, under those circumstances, there ought to have been two different fluorine signals, with each of the signals split by the other fluorine atoms as well as by the phosphorous.

Steve Berry had suggested the pseudorotation mechanism to make all five fluorine atoms effectively equivalent. Pseudorotation begins with one of the normal vibrations of the trigonal bipyramid, and just continues through a square pyramid and on to another trigonal bipyramid.

We of course knew about that work. Ed Dennis had, as a matter of fact, given one of the physical organic seminars on the work that Schmutzler and Muetterties had done at Du Pont, expanding on Berry's work (62).

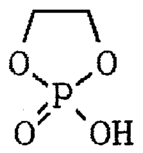
We had been looking at the rate of hydrolysis of ethylene phosphate and of methyl ethylene phosphate, the corresponding triester, in these labs, stimulated by a knowledge of the action of the enzyme ribonuclease, which forms and then hydrolyzes a cyclic phosphate. That cyclic phosphate, related to the action of ribonuclease, had been synthesized in Todd's laboratory by Dan Brown, and the fact that it hydrolyzed rapidly had previously been established.

When we studied ethylene phosphate and methyl ethylene phosphate, we wanted to know whether it was the five membered ring, or whether in the enzymic case it had something to do with the pyrimidine base, or (whether it was something else) that caused this rapid reaction. We'd come to the conclusion, which has later been verified properly, that a large part of the rapid reaction stems from steric strain. We then went off in an almost mindless extension of this, to look at the rates for hydrolysis of the corresponding phosphonate esters.

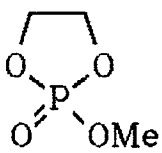
But then, when Paul Haake discovered rapid oxygen-18 exchange into ethylene phosphate during its hydrolysis (63), we were faced with a terrible dilemma with respect to our strain theory. One can easily understand strain accelerating the breaking of the ring; but how is strain able to accelerate a reaction of exchange in which the ring didn't break?

We also looked at methyl ethylene phosphate, and found that that underwent hydrolysis in part, to ethylene phosphate, where the methyl group came off but the ring didn't break.

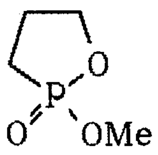
Then we examined the five member ring, which is a phosphinate and has only carbon to phosphorous bonding in the ring. Since the external methyl group comes off very rapidly from methyl ethylene phosphate because of the strain, we expected it to do so here too, but it didn't.



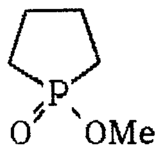
Ethylene phosphate



Methyl ethylene phosphate



Methyl trimethylene phosphonate



Methyl tetramethylene phosphinate

I went into a panic. I decided that there was no real explanation for that contrast in behavior and that the only explanation must be that Paul Haake's work was wrong. Careful as he had been, his work must be wrong. There could have been no exchange. We had fooled ourselves. We hadn't used oxygen-18 water with a very high oxygen-18 content. Looking back over it, the work hadn't been done as well as it could be. And it must be wrong.

It was harder to explain how we'd made a mistake with the methyl ethylene phosphate work, but I worked out a way in which that could be wrong. I just decided we must have made mistakes. We had published all this work. It was all garbage. We had fouled the literature with nonsense. I mentally wrote out my retraction.

But before I wrote the retraction, I thought it might be a good idea to check. So we went back and checked, in the most elaborate fashion. I took everybody in the laboratory and made them work on this problem. Wachiro Tagaki, who was doing work on acetoacetate decarboxylase, went back and did Haake's experiment over again. We did it and we did it right.

To begin with, we used water with a great deal of ^{18}O in it, so the effects from exchange would be much larger. One of the ways in which we could have fouled up was by having some hydrolysis product, that carried ^{18}O with it, as an impurity in our recrystallized ethylene phosphate. So this time, after we isolated the ethylene phosphate, we added the possible impurity, without ^{18}O in it, and then recrystallized the barium ethylene phosphate back to purity. Now, even if there was any impurity in the barium ethylene phosphate, we would have diluted out the ^{18}O. And we also converted the ethylene phosphate into a salt that was soluble in an organic solvent and recrystallized it from that organic solvent. We worked all this out.

Of course the ^{18}O was in the product of exchange and it was in there in exactly the amount that you would expect from Haake's work, so there was no question that Haake's work had been absolutely right from the beginning. And at the same time we checked the methyl ethylene phosphate by an entirely different method, involving NMR spectroscopy, and that checked out. It was absolutely right.

So, the psychologically interesting thing is that up to the time this work was checked, I had no idea what explanation could possibly be found for this apparent discrepancy we had. Literally the day I heaved a sigh of relief and knew that we had got it right the first time, I knew the explanation (64).

It's clear that I must have known all along, but been unwilling to let myself off the hook, so to speak, by explaining the results, until I was <u>sure</u> that they were right.

Then we checked out our explanation by making the prediction for the methyl phosphonate. I can give you a reprint that has this written out in it.

There have been a very large number of pieces of research since, where either the products or the stereochemistry of reactions at phosphorous depend on this analysis, and the field has grown a great deal.

There was also some NMR spectroscopy connected with this project that was very interesting. In fact, many people didn't believe our explanation until the NMR spectroscopy came out. The NMR spectroscopy began in the following way. Do you want to listen to all this, or are we going too far afield?

GORTLER: Aside from the fact that it opened up the field and a good deal of research has resulted from it, what other impacts do you think it had?

WESTHEIMER: Well, I can tell you about one of the impacts it has <u>not</u> had. Naturally, I had hoped that some of the enzymic reactions at phosphorous, involved in intermediary metabolism, would involve pseudorotation. It turns out that they do not, and that is fairly well established now. There has been a great deal of good to brilliant stereochemistry at phosphorous, begun first by Fritz Eckstein and David Usher. Usher is a first class scientist.

Eckstein and Usher did the first work on stereochemistry in this area. There's been a great deal done since, including some marvelous work recently by Jeremy Knowles, some brilliant work by "Moe" Cleveland, (that's William Wallace Cleveland at the University of Wisconsin), and some nice work by Mildred Cohn, and they have all examined different enzymic processes. I just wrote a review that included their work. Perry Frey did some too. There are eight or nine examples of enzymic reactions at phosphorous, and every single one of them proceeds with stereochemical inversion at phosphorous.

A single pseudorotation maintains the stereochemistry, that is, there is retention and not inversion so that the inversions amount practically to proof that there is no pseudorotation. So the enzymic processes presumably evolved in such a way as to avoid the pseudorotation process.

So one of the places to which this does not apply is in the biochemical examples which are, to me at least, of primary interest.

On the other hand, if you never had this work, you'd never know to ask the question. So that there is at least that little bit of consolation.

Now, this same sort of thing is showing up all through inorganic chemistry. I am too ignorant of the field of inorganic chemistry to know to what extent our work had any impact or is having any impact in the field of inorganic chemistry.

GORTLER: Are there any other areas where you think physical organic chemistry will go, or chemistry in general?

WESTHEIMER: Sure. I think that there is a field of organic synthesis that is growing rapidly and beautifully at the moment. This is the field of mixed chemical-enzymic synthesis. The prize example of that at the moment is, of course, Khorana's synthesis of a gene, where he made big pieces of nucleic acid and then made double helices, and linked the two pieces together by an enzymic process.

But if you look at the work that [Duilio] Arigoni does, and the work that [Alan] Battersby does, and the work that [Sir John] Cornforth does, you find the use of enzymic steps, mixed with chemical steps. George Whitesides at MIT is trying to incorporate Ephraim Katchalski's idea of immobilized enzymes, to make enzymic columns over which you can pour things, and take the products out at the bottom of the column. I think he's got one example, and he will get more.

So I envision eventually an organic chemical laboratory that, in addition to the present equipment, has a set of columns, marked "esterase" and "acetylating column" and so forth, where you pour your reagents over the top of a column, and take the product out of the bottom. And I envision cases, lots of cases, where people will have mixed syntheses, doing one reaction in sulfuric acid at 80 °C, and the next reaction in aqueous solution at pH 7.5 at room temperature, using an enzyme or perhaps an immobilized enzyme, so as to be able to get it out at the end of the reaction, and to preserve the enzyme as you can when it's immobilized on a column, and use it again.

Steve Benner, whose name I've mentioned before, has made some nitrilase, an enzyme that hydrolyzes nitriles, and he is trying to persuade Woodward that this is the right way to hydrolyze nitriles, rather than the ways that Woodward has used before.

The hydrolysis of nitriles doesn't go very readily, and usually takes fairly drastic conditions. If you do it by the hydrogen peroxide method, producing amide, followed by nitrous acid to destroy the amide, you can run into other problems.

So, I think nitrilase is going to turn out to be a useful reagent in the organic chemical laboratory. I envision enzymology as entering into organic synthesis. The organic chemists who feel somehow that it's cheating and that they shouldn't use enzymes will be replaced by those who are anxious to make something, and are willing to seize on any reagent in sight that will let them do it.

I really believe that that's going to be a big field of organic synthesis. I mean, there are half a dozen practitioners today.

GORTLER: There's more and more of this marriage between organic chemists and biology. That's the direction we're going.

WESTHEIMER: And of course, when you think about it, all the fermentation industries involve that. When John Gerlt and I wanted to determine the heat of hydrolysis of phosphate esters, to look at this question of strain, we could hydrolyze ethylene phosphate rapidly in a calorimeter but dimethyl phosphate doesn't hydrolyze worth a damn. The half-time for that hydrolysis is a couple of days, in 2 N sodium hydroxide at 110 °C. Not good conditions for calorimetry.

So we decided that the only way to measure the heat of hydrolysis was to get the rate up. The only way to get the rate up was to find a catalyst. The only sensible catalyst was an enzyme.

So we went looking for an enzyme to hydrolyze diesters of phosphoric acid. Well, there are special ones, of course, that hydrolyze nucleotide diesters, but we wanted a general enzyme and we didn't have one.

But Dick Wolfenden had reported in the literature that he could grow aerobacter on a diet containing dimethyl phosphates as the only source of phosphorous, and that fact carried the strong implication that there was an enzyme there that would hydrolyze the phosphates.

[END OF TAPE, SIDE 14]

WESTHEIMER: Gerlt got some aerobacter, grew them up, broke them open, isolated the enzyme, crystallized it, and found that it would hydrolyze phosphates rapidly enough, and then in collaboration with Julian Sturtevant, who has marvelous calorimetric equipment at Yale, measured the heats of hydrolysis of cyclic and acyclic phosphates and compared them.

Well, it's another case where one reaches into biochemistry to get an enzyme to do something that you don't know how to do any other way. One just, it seems to me, mixes chemistry and enzymology, with no apologies on either side. After all, enzymology is really chemistry.

I think this sort of thing is going to grow, as more and more chemists learn something about enzymology. One of the reasons I think this department is such a great department is that we had Konrad Bloch, who has been giving a splendid course in biochemistry, and at least a modest number of the graduate students and postdoctoral fellows in chemistry audit that course, and so are aware of problems and methods with which people are not acquainted in conventional chemistry departments.

GORTLER: This question is out of context, but you did consult a little bit at one time or another with Hercules and U.S. Rubber. When did you start?

WESTHEIMER: Well, the consultation with Hercules was an outgrowth of the explosives work, and I was consulting with respect to solid rocket propellants. I don't know really the extent to which such solid propellants were ever used for anything, but they may have been used for some of the satellites.

GORTLER: Did that last very long?

WESTHEIMER: It lasted a few years. Then I consulted for U.S. Rubber for a while, and that was also a few years, but I don't think I was a great consultant. When I was appointed as a member of President Lyndon Johnson's Science Advisory Committee, I withdrew, because I didn't wish to have any industrial connection while I was on that committee.

I thought it would be nice if U.S. Rubber simply gave me a leave of absence, but they would have none of that. And, in fact, I didn't get along with them very well anyway. The director of research at U.S. Rubber believed firmly in planned obsolescence, and I did not. We used to have some fairly vigorous conversations on the subject.

GORTLER: None of the consulting work carried over into your academic research?

WESTHEIMER: No, it never did. No, it was quite different.

GORTLER: No discussion with you would be complete without at least talking a little bit about the so-called Westheimer Report--"Chemistry, Opportunities and Needs," published in 1965. That was sponsored by the National Academy of Sciences. Who funded that?

WESTHEIMER: It was funded very largely by the American Chemical Society, with a supplement from the National Science Foundation. I was quite eager that we should have no government funds in it, but I wasn't successful in managing that. It seemed to me that if you were addressing a report largely to government funding agencies, that you were much cleaner if you didn't have any government money. Some people felt that the government money was laundered, in that it was not given directly to us, but given to the Committee on Science and Public Policy of the Academy, who in turn gave it to us. I don't think that that laundering did much good. I believe that we, in fact, used government funds.

GORTLER: You couldn't justify it in terms of the fact that the report was really for the good of the government as well?

WESTHEIMER: Yes, indeed. But what you had to say about that set of reports from the National Academy of Sciences is that they were, in effect, lawyers' briefs for the various sciences. Now, one hopes that they were honest briefs, but there's no doubt that they were briefs, and that's different from an evaluative report.

I would have been happier if we hadn't had any government money.

A group got together and decided to do this. I think I was invited to that meeting. I'm not sure, but whether I was invited or not, I did not attend. Frank Long was primarily responsible for suggesting me as chairman. Perhaps one got to be chairman by not being at the meeting.

I put a tremendous effort into that, including the fact that I had a sabbatical that I devoted pretty much full time to that job. The committee was, with the exception of one member, extremely enthusiastic and extremely hard working. Or I could even say, the committee was extremely enthusiastic and, with the exception of one member, extremely hard working. One member goofed off completely. But everybody else actually worked and worked hard. Harrison Shull especially. He was doing our computer work.

We, I think, did a number of quite innovative things there, such as looking into the literature of chemistry to find out what instruments were used, looking into the literature to see the background for inventions, to show that fundamental research had been extremely important in the practical applications of chemistry, both in chemical products and drugs. I think we did quite a number of innovative things.

There were something like one hundred and twenty people who worked on the various committees, and they turned in big reports which then were condensed by me or by Martin Paul and me, and rewritten. The condensed version became various sections of the final report. Martin Paul and I, it turned out, wrote quite similar English. So I don't think one can tell which parts of that report were massaged by Martin, and which by me. Quantitatively I guess I did about two thirds of it, he did one third. We both worked very hard. I think we did a good job.

Looking back, I wish we hadn't been quite as optimistic. On the other hand, the report is less optimistic than it would have been, I think, under a chairman other than myself. My native pessimism helped to produce a report which was merely optimistic instead of wildly optimistic which was to our benefit.

GORTLER: What about the politics of it? You've already implied it was a lawyers' brief, that you were going hat in hand to ask for money and knew you were going to do that.

WESTHEIMER: Yes.

GORTLER: Were there any strong disagreements on the committee, as to the best way of doing it, or whether you could have made your case stronger?

WESTHEIMER: The committee was a very strong committee, and contributed an enormous amount. The committee's first decision was that we ought to point out to the scientific community and the government that chemistry had become an instrumented science. It was no longer what I'd said was true when I went to graduate school, namely, Emil Fischer's laboratory plus pyrex, but had become a heavily instrumented science and needed those instruments. That was to be a primary message, if not <u>the</u> primary message. That was a committee decision. So we wrote that chapter first, and it went to the National Science Foundation as a chapter before the Report was written. It was, I think, directly responsible for the introduction of a line item in the NSF budget for instruments in chemistry.

Next, I wrote the introductory chapter, and submitted it to the committee. The committee didn't even tell me to revise it. They threw it out absolutely and rejected it. I was quite upset. Nevertheless, with Frank Long patting me on the shoulder and saying, "There, there," I went back and rewrote it absolutely from the start, in an entirely different fashion and produced something that the committee said had some chance of being massaged into the initial chapter.

That initial chapter was rewritten seven times, which says something about the impact of the committee. It also, I think, says that the chairman was willing to work very hard.

Most of the report was thoroughly rewritten, but not rewritten that often. The disagreements with the committee were not severe, although not everybody agreed about everything. There were several members of the committee who wanted to make a harder sell for chemistry, but I think I was writing for the consensus of the group. If there was a deviation, it was in the direction of some people wishing a harder sell than we gave it.

It was a working committee, and we worked. We met fairly frequently and did a tremendous amount of work in between.

GORTLER: The product demonstrates that. I mean it was really obvious. I was talking about this retrospective that I've seen fairly recently concerning the reports and the authors suggested that, in fact, the process may have been almost as important as the product. The process that was developed for preparing an overview of science. Yours may have been the first report completed.

WESTHEIMER: No, it was not the first report, but it was one on which, at least the biology report and perhaps several of the later ones were modeled.

The astronomy report was the first one. And the physics report, although it came out slightly after ours, was in process at the same time, and so was produced independently.

There was also one on the geological sciences that pre-dated ours.

What we did, that I think was good, was this. We tried to base all our arguments, not on, "What does the science of chemistry need?" but "What can the science of chemistry do for America?" and "What does America need?" The one great mistake that I made with respect to that report was at the news conference, when I didn't have the courage to come out and say that. That involved criticizing the other reports, and I was under pressure not to criticize the other reports, and succumbed to that pressure. I believe that was a mistake. I believe one could have managed that by saying that in the development of these reports, in the Academy, there had been an evolution of thought, so that one now was looking at the report from a somewhat broader perspective than just that of the individual science.

But really the thing that marked our report, and made it different and I think made it a model, was that we looked to the contributions chemistry was making to America, whereas the astronomers were looking at what contributions America could make to astronomy. The titles from our chapters were taken over by Handler when he did the biology report, almost one by one with paraphrasing. That made it clear that we were right.

The thing I didn't do, that would have given chemistry a lot of good publicity, at the expense of having my head chopped off by Fred Seitz, was to point out what it was about our report that was superior.

GORTLER: I've essentially come to the end of what I wanted to talk about. It's been very, very helpful, I think it will be helpful for other people as well. The last question which I ask everyone is, can you suggest anyone else I might interview?

WESTHEIMER: Well, probably. I'll have to think a minute. It's a shame that Ingold is dead and Winstein is dead and Wheland is dead, and I don't think it's worthwhile talking to Pauling any more.

GORTLER: There are people who have hours and hours of interviews with him.

WESTHEIMER: You're going to talk to Cheves Walling, you said. Are you going to talk to Frank Mayo? I think it's important to talk to someone who comes out of Kharasch's laboratory, but doing Walling may be sufficient. No, I believe you should talk to Mayo. You brought up the interesting question of Whitmore. I think that he made a very important contribution to carbonium ion chemistry, and is grossly under-appreciated. I don't know whom one would talk to, from that laboratory, in that tradition, who would give you any picture of Whitmore. I remember very well when he lectured at the University of Chicago, and I was bitterly disappointed. He didn't understand his own contribution anywhere near as well as lots of other people did. He hadn't kept up, and he didn't really realize how much had grown out of his ideas.

If you want to talk to someone on the impact of quantum mechanical thinking, that is, both the resonance theory and molecular orbital theory, it has to be someone who knows the field very well, and has it in fairly good perspective. Perhaps Roald Hoffmann. I'm not sure. I assume you're talking to Roberts.

GORTLER: I will be. I hope so. I've contacted him.

WESTHEIMER: I find D. J. Cram's work of very considerable interest. I don't think it's of as much interest as he does. But I'm especially interested in the work where he uses dimethylsulfoxide (DMSO) as solvent, and got enormous solvent effects which I think are important to physical organic chemistry.

I wonder who else in the quantum mechanical area? R. S. Mulliken is still available to talk to. If you can understand anything he says, you're doing better than I. I find him extraordinarily difficult to understand.

Wiberg and Streitwieser I think are in a way too recent, for this study.

GORTLER: When I start to work on the next twenty years.

WESTHEIMER: Yes, when you start working on the next twenty years, you will necessarily talk to them.

I wonder if there are any foreigners? A quantum mechanical person of considerable ability, and detachment, is [Edgar] Heilbronner, who is now in Zürich.

GORTLER: How long ago did Coulson start his work? He's still alive.

WESTHEIMER: H. C. Longuet-Higgins? Coulson and Longuet-Higgins are both very good theorists. Yes, I think either Coulson or Longuet-Higgins would probably be splendid in that area. That is an important area, and certainly, putting aside the present computations, which as I said I think are grossly overdone, the impact on thinking of molecular orbital theory and of resonance theory is enormous. If you can't get it from Pauling--because I don't think he'll talk about anything today except how Vitamin C cures cancer--and you can't talk to Wheland, without a Ouija board, you'll have to find somebody. You really do have to find somebody in that area.

GORTLER: That's an area I've totally neglected. I think you're right. Thank you so much.

[END OF TAPE, SIDE 15]

[The following was added by Professor Westheimer after the interview.]

WESTHEIMER: In this interview, I told something about some of my successes, but little about failures. I did mention my failure with respect to the Raman spectra of the NO_2^+ ion, but would like to add a much more significant story.

In 1956, I was working with L. L. Ingraham on the mechanism of action of thiamin--a problem that Ron Breslow was working on at the same time (and which he solved). I felt sure that the problem involved the ionization of a proton from the coenzyme, and looked for that ionization by measuring hydrogen-deuterium exchange. But I had decided where in the molecule I should find it. On one occasion, Ingraham told me that, in an odd experiment, he had found deuterium in the thiazole portion of the molecule, where I had not expected it. I put his statement aside, and had him continue to work on the part of the molecule that I thought was important. That action of mine violated the first rule of research--that one must go where the data take you. Before I had time to recover (and I'm not sure I ever would have), Breslow had succeeded.

Of course, in the most fundamental sense, my mistake was not relevant. Breslow solved the problem promptly so the discovery was made, and science benefited. It would not have benefited any more if I had come up with the solution simultaneously. But if one is interested in my career as a scientist, then this stupid failure is part of the story.

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