CHEMICAL HERITAGE FOUNDATION

MARINUS LOS

Transcript of an Interview
Conducted by

James J. Bohning and Bernadette R. McNulty

at

American Cyanamid Company

on

17 January 1995

(With Subsequent Corrections and Additions)

ACKNOWLEDGMENT

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LOS, MARINUS

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MARINUS LOS

1933 Born in Ridderkerk, The Netherlands, on 18 September

Education

1955 B.Sc., Chemistry, Edinburgh University
1957 Ph.D., Organic Chemistry, Edinburgh University

Professional Experience

National Research Council of Canada
1958-1960 Research Fellow

American Cyanamid Company
1960-1971 Senior Research Chemist
1971-1984 Group Leader, Organic Synthesis
1984-1986 Senior Group Leader, Herbicide Discovery
1986-1988 Manager, Crop Protection Chemical Discovery
1988-1992 Associate Director, Crop Sciences
1992-1996 Research Director, Crop Sciences Discovery
1996 Retired

Edinburgh University
1969-1970 Senior Research Fellow, Department of Pharmacology

Honors

1954 Boots Drummond Prize in Biochemistry, Edinburgh University
1955 Blandfield Prize in Chemistry, Edinburgh University
1981 Cyanamid Scientific Achievement Award, American Cyanamid Company
1984 Cyanamid President's Award for Excellence in Agriculture, American Cyanamid Company
1990 Distinguished Inventor, Intellectual Property Owners, Inc.
1991 Thomas Alva Edison Patent Award, New Jersey Research & Development Council
1993 National Medal of Technology
1994 Achievement Award, Industrial Research Institute
1994 Perkin Medal, Society of Chemical Industry (American Section)
1995 Award for Creative Invention, American Chemical Society

ABSTRACT

The interview begins with Dr. Marinus Los' description of his family's origins in The Netherlands. When he was two years old, his family moved to England, where he received his early education during World War II. Encouraged by his older brother, Los studied chemistry at Edinburgh University, where he first became interested in biochemistry. He conducted his Ph.D. research on heterocyclic analogs of azulene under W. H. Stafford. Stafford encouraged Los to study at the National Research Council in Canada, where he conducted research in the structural chemistry of alkaloids and plants under Leo E. Marion. In 1960, Los became a research chemist at Lederle Laboratories, now a division of the American Cyanamid Company. Under Milon E. Bullock, he conducted early research on insect control via an insect molting hormone discovered by Dr. Peter Karlson. Los also worked on a synthetic steroid project involving anabolic steroids and artificial insemination of cows. Next, Los returned to Edinburgh University's Department of Pharmacology to organize a research program in prostaglandins. On returning to American Cyanamid, led at the time by George J. Sella, Jr., Los switched to research on herbicides. In his research on plant growth regulators (PGRs), Los's work on imidazolinones led to the herbicide Avenge. His discovery of the cyclohexyl derivative of phthalimides resulted in the development of other more concentrated, selective, nontoxic herbicides: Assert, Arsenal, and Pursuit. This work won him the National Medal of Technology. Los ends the interview by discussing his later career as first Senior Group Leader and then Research Director, focusing on his approach to the encouragement of teamwork at American Cyanamid.

INTERVIEWERS

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

Bernadette McNulty, Oral History Project Manager for the Chemical Heritage Foundation, holds a B.A. in communications and social work and an M.A. and Ph.D. in communications. She held several teaching and research-related appointments, including positions at Muhlenberg and Rowan Colleges and Temple University, before joining the Foundation's oral history program in 1994.

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INTERVIEWERS: James J. Bohning and Bernadette R. McNulty

LOCATION: American Cyanamid Corporation
Princeton, New Jersey

DATE: 17 January 1995

BOHNING: I know that you were born on September 18, 1933, in Ridderkerk, The Netherlands. Could you tell me something about your father and mother and your family background?

LOS: Yes. My father was a truck farmer in The Netherlands. He joined his father in the family business. He was the eldest son. As was wont there, it was taken for granted that he would go into the family business. He left school when he was about nine years old. My mother, she was the eldest of a rather large family—I think seven children altogether. Her mother died when she was fourteen, and she left school and brought the family up.

I was actually born in The Netherlands. I was the fourth child. But it was during that time, a few years after I was born, that the government decided to put a highway in from Amsterdam to Brussels. Unfortunately, this highway went right through what was my father's land. He was farming that land with his two brothers, and they just could not find any more land. That's how we ended up going to England when I was two years old. There was a fair Dutch community actually there. Quite a number of Dutch families had already migrated there.

My father was reasonably old at that time. They had a very difficult time in that they knew no English. Of course, the children knew no English either, so they were dumped into the schools and made the best of it. [laughter]

BOHNING: Was this Edinburgh?

LOS: No, no. This was in Yorkshire, near Hull, which is probably about the fifth port in England. It's a big city, but my father's business was about ten miles from Hull. The three brothers set up business, but it was rather tough. I think it made some difference to us too, because we always spoke Dutch at home. All the reading and all the newspapers that we got were Dutch, usually. There was even a Dutch minister, so our church was a Dutch church. Maybe our English language at that time suffered badly from that.

Anyway, we were sent to the local village school. In England, of course, they have a

very different educational system than what you're used to here. When it came to our being eleven years old, we took the Eleven-plus exam at the local school, which was just a little church school. I had an older brother, and he did very well. He went to what was then called the Grammar School. That was really a prep school for college. I mean, this was sort of an elite in England. Probably twenty percent of the students go to this type of school. When the time came along, I also made it to that school.

It was rather odd, because my parents really didn't understand—they didn't have the education, they didn't know which way to follow. So we sort of felt our way through. Fortunately my brother, who was four years older than I, paved the way to a certain extent. He became a doctor. I think I followed that path more or less instinctively. He talked about things; I saw his books; we were in the same high school together and so on. That was a significant influence on me.

I had another brother, and he went into the business. My father was very disappointed actually in many ways, because in the traditional sort of thing, we were expected to go into that business. I think it was a little difficult for him to see, really. He felt sort of out of it. I mean, he was terrific in what he was doing. He was a very bright man and a very good businessman, but this was sort of a new world for him—a foreign venture. It was really strange for him.

BOHNING: Did he learn to speak English then, in order to survive?

LOS: He did. But it was quite broken English, even at that. I mean, he was in his forties when he arrived in England. You know, it's not so easy at that age, especially with his background.

BOHNING: What about the war years?

LOS: The war years were rather tough. We had lived in England for quite a while, but we were foreigners—we were aliens. So we were under curfew during the war, as Dutch citizens. We were all still Dutch citizens.

My father had a bomb shelter built in the backyard, which was half underground, with walls this thick and so on. I actually slept in there every night for two years during the height of the war. There were several very close bombings that went on near us. I remember walking to school as a child, and I saw there had been a direct hit on a house just down the road from us. I can still see the body parts.

The thing is, there were certain things I still remember so vividly. I mean, I think the Germans didn't want to fly back to Germany with any bombs unused. They just used to drop everything wherever they were. I think that's how we got hit, more than anything. There was an airfield not too far away, and Wellington bombers flew from there to Germany. A

Wellington bomber didn't quite make it back and landed in our school playing field, and it had holes through it. We were allowed to get in it after a while. [laughter] I remember German bombers over the city of Hull. You could see them caught in the crossbeams of searchlights, and you could see the tracers going, but I never saw anything shot down.

I really have a lot of memories. They actually had prisoners of war working on my father's land at the time. They'd come in an army truck, and there'd be a guard come with them. They'd have Italian or German prisoners of war actually do work on the land, which was also something unusual.

BOHNING: When you were a child, did you interact with any of those prisoners?

LOS: We talked to them. I don't have a very clear recollection of that. But I remember being there one day, and it looked as if it was snowing in the middle of the summer. If I remember correctly, it was small pieces of aluminum foil. The planes would drop this to stop the radar. That was another thing I remember from that.

I have some quite vivid memories. The neighbors, those who didn't have bomb shelters, used to come in. I remember, the old lady next door, she'd bring her parakeet with her. [laughter] But I think what I remember most is the musty smell—I can still smell it—in that bomb shelter. [laughter] It was damp.

McNULTY: It was probably also crowded.

LOS: Oh, pretty crowded too, yes.

BOHNING: Were any of the later V-1 or V-2 missiles directed toward that area?

LOS: No, they were not. That was fortunate. I think we were just out of range.

BOHNING: You said that you were following in the footsteps of your older brother, and that you were influenced by him. When was your first exposure to science?

LOS: It was in the high school. With it being the sort of English high school, the subjects tended to be more concentrated and fewer of them, so we got introduced to chemistry in particular, physics, and math, at a much earlier stage. At the age of sixteen, you had this definitive exam which was taken by all the people in the country—the same exam, set by the

Universities, either Cambridge or a group of northern Universities. These were not multiple questions or anything. These were definitive—you know, define this and how it applies, or what have you. They were essay-type.

Chemistry—you got quite a lot of chemistry, physics, math, and that sort of thing right from the start in the high school. That was the real introduction to that. It's important, because in the English system, if you wanted to go on, you had to decide—for instance, at the age of sixteen, after these exams—whether you wanted to be in the arts or in the sciences. Then, if you decide you're going to the sciences, you only do three subjects. I did chemistry, physics, and math. I did that for the next two years as the only three subjects, prior to college.

Now in chemistry, you do a lot of chemistry. You're introduced to organic chemistry. You have lab. I can remember, for instance, making nitrobenzene in high school, distilling it. You know, it's just a different system. It's not better; it's different. I think I would have liked a little broader education than I got, too, but it was not in this. Of course, this follows all the way through to college as well.

BOHNING: Was it your brother's influence that caused you to study chemistry?

LOS: Yes, that too. But I enjoyed it—I mean, I liked it too. It was interesting, because my brother wanted to go to medical school, and he knew this fairly early on. I can't remember why he didn't get in at his first attempt. Maybe it was just that he wasn't one of the top students, or what the reason was. So he stayed on a third year at the high school, which you could do. But what he actually did was take night classes at a local college. He actually did his first year of medical school in high school and night school. He went straight into his second year of medicine at the University of London. I saw quite a bit of the practical stuff as well, while I was still in this early stage. I think that had quite a bit of influence.

McNULTY: Did you have a high school chemistry teacher who influenced you?

LOS: Oh, yes, Mr. Chandler. Very enthusiastic man. He made it exciting. He sort of related it to life, to construction, or whatever the application might be.

It was funny. One of the things that really stand out with me concerning him was that at that time, the ballpoint pen had just come out. They were the rage in the stores, and the school kids all wanted them. Mr. Chandler had one. I remember he had a red one, and he used it for marking papers. But one of the problems with him was that he wasn't paid very much. To buy those refills was very expensive, right at the beginning. I remember staying with him after school. We tried to figure out how we could make a mixture that would actually work in a ballpoint pen, which was rather an ambitious research project. [laughter] I think it needed a lot more know-how than we could have ever put in—or certainly, I think, than he could have put in

even. We failed, but boy, did we have a lot of fun trying to change the texture, using some physics to try to fill these things and all these sorts of stuff. It was the sort of thing that would make you see the utility of the sciences.

BOHNING: Did he give special attention to many other people in the same way that he did with you?

LOS: No, just the ones who really showed their real interest, I think. There were just a few of us at different times.

BOHNING: You said your brother had gone to medical school. Had you given any thought to what you were going to do?

LOS: Yes. I had initially thought of perhaps going to medical school. In the last two years, the requirements to get in were probably the same. I was doing chemistry, physics, and biology. That would have been fine, but I'd sort of enjoyed, and I was better at, chemistry. I think that that combination, I really did enjoy it. Whether I was better at it because I enjoyed it or the other way around, I don't know. But I decided then that I would like to do chemistry.

I went to Edinburgh University. You have to state what major there, and I said chemistry. That was a four-year course. At the end of my third year—this is when you could actually get a bachelor's degree, after the third year; you did the fourth year to get an honors bachelor's degree—I went to see the professor of biochemistry at Edinburgh. This is where I really started chomping at the bit again a little, I think. I had done a biochemistry class in the third year. I thought, "I really like this interplay of chemistry and biology." In England and Scotland—now I'm in Scotland, Edinburgh—and at most of the universities, there's only one professor. Everybody else is a reader, or a senior lecturer, or a lecturer, or something. There are a few more professors now, but at that time there was just one professor per department.

I went to see the professor. He was quite a famous man there, Professor Guy Marion, who was involved in the isolation and identification of the steroid hormones. It had a lot to do with controlling the body functions and what have you. He was very famous. He'd isolated and found out what they did, and all this sort of stuff. But what he told me was, "I've got enough people here who know biology but know no chemistry. I don't want any more people like that. Go away, go and do your chemistry degree, and then come back." I went away, but I never got back to him. [laughter] I ended up doing the degree in chemistry, and going on in chemistry too.

BOHNING: How did you decide on Edinburgh, since you were from Yorkshire?

LOS: From Yorkshire? The university had a good reputation. It had a particularly good medical school, and that was still sort of there. Also, one of my best friends at school went there, and I actually roomed with him. So there were a few factors involved. Of course, I applied to other places and was accepted at other places, but I finally chose to go to Edinburgh.

BOHNING: How did you finance it?

LOS: My father financed essentially all of it—except that I worked for him in the summer, which was part of the deal. That cured me of wanting to go into that business. [laughter] But he financed it, essentially.

BOHNING: What was the curriculum like in those first three years? I also would like to ask you about the fourth year for the honors, but right now I'd like to focus on the basic curriculum in chemistry.

LOS: In chemistry? It was a three-semester system. You'd have one semester on physical, one organic, and one analytical. I remember clearly that you'd have to do aromatic chemistry, for instance. You would have syntheses to do and you would have to develop syntheses of your own, and this sort of thing. Analytical, you had to go through the table and separations of this sort of thing. Physical—of course, I don't remember too much about what we did in the first year of physical. It must have been some classical type. I don't really remember too well.

BOHNING: You had all three of those in the first year.

LOS: In the first year. That would be true in the second year as well, and in the third year. Except that in the third year, now you would have research topics as well. It was fairly concentrated. I mean, we were having to do quantum mechanics—for instance, thermodynamics—in our third year, in the physical part. I remember that. We'd do a whole set of different topics in organic chemistry. We'd do natural product synthesis or structure determination, some things like that. It was really concentrated.

It was rather strange. I was keen on sports. Supposedly, the university was free on Wednesday afternoons to pursue your sport. But all the chemistry people, they all had to be in the lab. I mean, it was scheduled that way—there was just no way you could do it all. They scheduled it that way.

BOHNING: Your laboratory experience was pretty intense, then.

LOS: Yes, yes.

BOHNING: Also, it was the biochemistry that interested you, more than anything else.

LOS: It was, yes. The reasons for the structures and what they did, what responses you got from them, and that sort of thing—it really, really turned me on.

BOHNING: Were there any professors there, outside of the one you mentioned, who influenced you in any way or who were particularly good at what they did?

LOS: No, there's no real recollection of that. It's rather funny when I look back, actually. [laughter] You know, we used to go to college with a tie and a starched collar. It's rather strange when I've seen my youngsters go to high school or to college. I mean, I wore a suit to classes. There was usually a fair distance between teacher and student. It was not the camaraderie that I've seen over here, for instance. So you missed a lot of that. It wasn't until you got to be a graduate student that some of the barriers really fell. You had to be very careful to make an appointment with a professor, or to go and see him. I mean, you were very careful of how you behaved at that time. [laughter]

McNULTY: You won some awards at the university for chemistry and biochemistry. Was that during your undergraduate career?

LOS: Yes, my undergraduate. Yes, I happened to do very well in the biochemistry course as well. Actually, I didn't know I'd won it until the end of the year. It sort of came through the mail. I mean, nobody awarded me anything. [laughter] It was rather funny in that. It's written up in the department there that I'd won this. Not an awful lot was made of it. But I've got a nice diploma-type thing. The chemistry one, that was automatic almost, because I came in top of the class. That was given for the top honor student. I was lucky to get that.

BOHNING: Were there many students in your class?

LOS: No. My graduating class in honors chemistry, I think there were sixteen only. For the first time, this year we're going to have a reunion. There are fifteen of us still alive. I think they're all going to show up—which is going to be interesting—at Edinburgh this September.

BOHNING: Wonderful. It's going to be forty years.

LOS: Forty years, yes, actually. I haven't seen any of them in forty years.

BOHNING: My goodness, that will be interesting. To change the subject a little, you had two papers (1). I'm assuming that you must have done some research during that honors year.

LOS: That's correct.

BOHNING: With [Gerald O.] Aspinall?

LOS: Aspinall. I got a letter, actually. It's funny you should mention that.

[END OF TAPE, SIDE 1]

BOHNING: That's marvelous. Would it be possible to get a copy of this letter?

LOS: Oh yes, I'll make a copy of it.

BOHNING: After all these years, he saw your work.

LOS: He saw my work. I have not spoken to him since then. I'm going to give him a call. [laughter]

BOHNING: That's marvelous. When you were doing this work with him, did he just assign you this particular topic?

LOS: No, he had a postdoc working with him on a very specific topic, and this was a sort of small part of it. It was a young lady from America, actually, who was postdocing with him.

BOHNING: Mary [E.] Carter.

LOS: Mary Carter, that's her name. That's right. I don't know what happened to Mary Carter, but I can still see her face. She and Dr. Aspinall sort of gave me directions and described the project, and so on.

It was really my first introduction to real research, that. I think it was a really good experience, because most of the other class experiments that we did usually worked. [laughter] If we got a seventy percent yield or eighty percent yield, that was good or better, but in this research, a lot of things didn't work. Trying to fish things out in small quantities, for instance, in this sort of thing, and using chromatography—which I had done a little of, but here for real. It was a good experience, and I enjoyed it.

BOHNING: In 1955, probably the only procedure you had for separation was chromatography.

LOS: Correct. It wasn't that old, either. I mean, people used to give lectures on the common adsorbent-plus-solvent system they would use, and why that solvent system. It was a big issue. It was in the very early days of chromatography.

BOHNING: I was intrigued by the fact that your first entrance into independent research had to do with plants.

LOS: Yes, carbohydrate chemistry. [laughter]

BOHNING: You studied that for most of your life.

LOS: Of course, Edinburgh was probably very well known for carbohydrate chemistry. That was its forte at that time. Professor Edmond L. Hirst was there, and he was very well known for that in that school. Aspinall, of course, was in that too. It was probably the strongest part of Edinburgh University's organic chemistry department.

BOHNING: Did this connection with biology continue to keep your attention focused, as you went on to graduate work?

LOS: No, I don't think so. In graduate work, I think chemistry actually took over. There I was doing primarily heterocyclic chemistry. That was sort of an area that I needed to learn and to develop some new chemistry in, and this sort of thing. That sort of occupied me, and I found it fascinating anyway. I don't think biology really played a major part there.

BOHNING: All right. Was it a given that you would stay on at Edinburgh for your Ph.D. work, or had you thought about going elsewhere?

LOS: I had thought about it, but it was more common in the UK at that time to stay at the same university. I wish I hadn't, but that's the way it turned out. I chose—and I really did choose as my supervisor—a young man who had really excellent credentials. But he was young; he didn't have a reputation. He was a Cambridge man, really enthusiastic, and young—much closer to my age, which actually turned out to be very good. Unfortunately, he never lived long enough to develop a reputation, either. I think that one or two years after I left there, he died of a heart attack walking to college.

BOHNING: [W. H.] Stafford.

LOS: Stafford, yes. Actually, while I was in my postdoc position two years later, I wrote up one of the papers from Canada. He'd already died at that stage. I think he would have been a well-recognized name, had he lived.

One of the things I fretted about at the time was that Derek [H. R.] Barton was at Glasgow at that time. That was one of the moves that I <u>should</u> have made, if for no other reason than that one should—I tell this to everyone—pick the <u>best</u> place, the <u>best</u> person you could possibly go to, in the field you want to work in. It will pay off in many ways, substantially. I didn't do that, so I was lucky a little farther down the road, too.

But he did direct me, though. I mean, I must say that Dr. Stafford directed me to the postdoc position, which I think was a correct thing that I did.

BOHNING: Your Ph.D. work actually had two different parts to it. One was that you were preparing heterocyclic analogs of azulene. Yet in your original paper, the sidelight was your work with hydrazine (2).

LOS: Right. I am just writing up a little thing for the Industrial Research Institute (3). I received one of their awards. When I was giving the talk there, I talked about anomalies—otherwise known as luck, or serendipity, or any of these other things—and the part they play. That's how the hydrazine part came about. It had really nothing to do with what I was doing there. But we were making a pyrazole, which you do with hydrazine easily. I had mixed the hydrazine, and I'd put some porous chip in there. I put it in early because it had to be evaporated—it was being run in alcohol. But I didn't get down to evaporating it, and I left it overnight. What should have been this deep yellow color, because it was a dye—a phenol-diazo

pyrazole, I was making—instead of the bright yellow color, it had gone completely colorless. I said, "Gosh, that was strange." [laughter]

From that simple thing, it developed into a really interesting little project. Somebody else in the States discovered the nice reducing power of diimide. It really is the reducing agent there. But that's how research should be. I liked that part, and that's played a major role in what I have done since.

It's rather interesting. I was just reading this article by Sir John [W.] Cornforth in *Aldrichimica Acta* of 1994 (4). There's just one little piece in here which talks about finding new reactions, new things—discovery, in other words. He says that nowadays, everybody has x-ray facilities. You know what you've got before you've got it, and all these other things. He says that in the old days, with a lot of natural product work, you didn't know exactly what the result was going to be, so you looked for things. Then he says, "Similarly, if you plan a synthesis and leave its execution to less-skilled people who have been told what to expect, you are likely to miss observations and opportunities that you would not miss if you allowed yourself to be taught by the experiments, instead of trying to teach nature how she should behave." I think that's rather interesting coming from a man who must be eighty years old, probably, now.

BOHNING: Oh, yes. [Louis] Pasteur said, "Chance favors the prepared mind"—as I see it, being open to the fact that there could be possibilities other than what you expect.

LOS: Absolutely.

BOHNING: In some respects, the refinement of our laboratory techniques today—in which we can detect incredibly small amounts and be very sure of exactly what's there—may limit discovery possibilities.

LOS: I think so.

BOHNING: It's an intriguing thought.

LOS: Yes. In the work that I went through in these fourteen-odd years that I did, these observations of these anomalies really led to different directions. I'm afraid that for instance, in an industrial setting, many people don't, or cannot or will not, follow up on these observations which say that there's something not quite right, or something is different. You know, you have projects; you have timelines; but it's really not the way to discover things if you get exactly what you expect, I mean. We think we know what we want, so we ignore what we didn't get—

or what we did get which we didn't think we would get. That's a serious drawback, I think, of the way a lot of the research, particularly in industry, is going.

BOHNING: Roy [J.] Plunkett told me that in 1938, when he was a young organic chemist at DuPont, he was asked to synthesize a new gaseous refrigerant (5). He ended up with one of his gaseous reactants turning to a white powder, which later on turned out to be Teflon. I asked him what his reaction was. He said that at the time, his reaction was, "My God, we have to start over." His assignment had been to make the gaseous refrigerant. [laughter] To his credit, however, he tested that white powder and found unusual properties, which later led to Teflon.

I've used that example to say that he did not have a closed mind. He knew he had an assignment, but here was something new and different and unusual, which he pursued. However, today's economics and industry are probably different than they were in 1938, and he had the flexibility to do that at that time.

LOS: That's right.

BOHNING: We'll pursue this line a little later when we discuss your other work here. Returning to Stafford, you said that he was the one who directed you to Canada.

LOS: Yes.

BOHNING: Could you say a little bit more about that?

LOS: He was very good to me in many ways. I actually finished my Ph.D. in two years, essentially, which is fast even for the UK. But one of the reasons that I could do that was that I was given a scholarship by the Carnegie Trust to do a Ph.D. I didn't have to teach, which a lot of the other students had to do to make some money. They didn't have to pay tuition or anything then, if they taught. I was very lucky in that respect. My dad really didn't have to pay anything more after I graduated. I could really get on.

I was lucky in that he actually gave me some assistance, which was unusual also. I actually had an undergraduate student who was working with me. He must have thought I was doing all right or something. That was very nice. I was able to get a lot of work done. We worked hard, though—I mean, we worked long hours, too—but being able to get finished, he helped me a lot in that respect.

Then he said, "Well, you've been doing all this synthetic work. I think you should get some experience in structural chemistry"—meaning isolation, structure determination, working

on small scale, this sort of thing. He said that the National Research Council in Ottawa, Canada, had this fabulous group. It really was. It's hard to imagine that that actually stopped.

Professor Leo [E.] Marion was running the organic section. He was world famous for his natural product work. I applied to him, and he said yes. The stipend was remarkably good for that time. I could actually go over there and take my wife as well. I got married just before I left.

I mean, there were teachers from Australia on sabbatical. There were people on sabbatical from Yugoslavia, from Canada, from England, from the U.S. It was a really diverse group, but one that brought a lot of different strengths to it. That was probably the best move I made. I mean, that was really a great time. I got exactly the experience that I was looking for there. You never really think about it now, but we used to take an IR Spectrum of a sample and then recover it from the Nujol that we had mixed it in.

The National Research Council had just built its own NMR machine—the first one. It took the whole room. You had to take all your keys, all your money, and all metals out of your pockets before you were allowed to go into the room. It was my introduction to this powerful method.

It was just a wonderful experience. I just learned so much there. Probably the happiest time in my life was those two years I spent there.

BOHNING: Were you able to develop any gas chromatography techniques at that time? That was pretty new.

LOS: No, no, we didn't. I did some of that in Edinburgh, still. There was one professor there, John Knox, who has had many prizes for his work on gas chromatography. He was a lecturer there at the time. I used some of his equipment as well, in that time. So yes, I was familiar with that.

BOHNING: You had a number of papers with Marion and [O. E.] Edwards (6). I'm not sure who Edwards is.

LOS: That's right. Edwards was the other permanent staff member. When Marion died, Ted continued that group.

BOHNING: Again, you were looking at structures derived from alkaloids and plants.

LOS: Yes, yes.

BOHNING: I'm intrigued to see how that keeps showing up. [laughter]

LOS: Yes, it keeps showing up.

BOHNING: At one point, George [H.] Büchi supplied a critical suggestion.

LOS: Absolutely, yes.

BOHNING: I'm curious about how that came about.

LOS: It was the structure of hydroxylycoctonine. I think we had all the pieces, but we didn't know how to put them together, quite. I mean, Büchi was up there, and he gave a lecture, I remember. We spent a lot of time around the table talking about it. Actually, I think it was some synthetic work that directed to suggesting a structure for hydroxylycoctonine, which we could then prove or disprove. He proved to be correct.

It was a race, actually, between the Karl Wiesner group, which was also a very good group with [Z.] Valenta at the University of New Brunswick in Canada. They were working on the same project. I'm not sure whether we beat them or not, but it was neck-and-neck, anyway. There was quite some rivalry on this natural product work going on at that time.

BOHNING: The Büchi connection came about as a result of his visiting your group.

LOS: Yes, that's right.

BOHNING: That's interesting. What had you been thinking about during your postdoctorate work, in terms of your life beyond Ottawa?

LOS: I thought I was going back to the UK. I mean, my family was there; I told them I was going to come back. Then I sort of realized that there were such tremendous opportunities for the choosing, at this stage, things I might do. There were a number of organizations that came to the National Research Council to interview people for positions. It was a very good time, at that time. There were lots of positions available. There were a lot of teaching positions

available. Many of my colleagues from NRC went to teaching positions in the UK and Britain or back to their own countries in Germany and Holland, I know.

I'm really not sure what drove me. I didn't feel I was a person to teach. I was very shy, and I really didn't want to get up in front of people. Seminars and what have you really frightened me, almost. We were not trained in that way in the UK system. I mean, I didn't give one seminar while I was at Edinburgh—not even on the work that we were doing, for instance. It wasn't done.

I essentially looked for an industrial job. I thought, "Well, I'll just write to some companies, too, and go and visit to see what's available." I visited Upjohn; I visited Sterling Drug; and I visited Lederle, which is our pharmaceutical division. I think I was offered positions in all of these places. I think there were small things that decided that I would eventually go to Lederle—well no, it's not quite as simple as that. I went to Lederle. They said when I got back that there really were not any positions available anymore in that area, but they would like me to come back because they were establishing an agricultural research division, and they would really like me to come and interview for <u>that</u> position. I decided to do that and came back. They offered me a position.

I know why I didn't go to Sterling. It was the interviews that really turned me off Sterling. I don't know, I was so surprised, the sorts of questions they asked of me—like, for instance, "Give me all the methods you know of how to make an aldehyde." They also turned over all the papers and turned all the bottles around when I arrived. You know, "We don't want you to know what's going on, or see anything here." I got the feeling that I really didn't want that. I thought, "If my training's worth anything, that's not how it should be used. We already know how to make an aldehyde. I can go to a book if I want to." That was not what I wanted.

[END OF TAPE, SIDE 2]

LOS: The nice thing about the interview I had, at agricultural research division, was that they brought out some spectra and they said, "We've got no clue as to what this is. Can you make heads or tails of this?" They said, "We've heard a little bit about NMR. Do you know anything about it? Tell it us about it. Should we have one?" It was these sorts of things, and an opportunity to tell them about my own work. Then when I asked them about what I would be doing when I was here, they said, "Well, you would set up a program." It gave me a right sort of feeling, that this is really where I wanted to go. It was a young organization—they were just setting up—so there were a lot of enthusiastic people.

At Sterling, they were very well established people. Obviously, there was a very well established way of operating, and things like that. That's basically why I can't remember too much about Upjohn either, actually.

BOHNING: Had you selected these pharmaceutical companies because of your background in biochemistry?

LOS: Biology, biochemistry—yes, absolutely. The difference was small. I was going to be in the animal part of the agricultural division, so it was really a sort of pseudopharmaceutical research, anyway. It was going to be drugs for animals. That satisfied that criterion as well, and that was very good.

BOHNING: Was this at Lederle?

LOS: This was at Lederle.

BOHNING: Where was that located?

LOS: That's in Pearl River, New York—just where the Garden State [Parkway] crosses the border, actually.

We had good interactions, anyway. Although we were in the agriculture division, we were actually very involved with the pharmaceutical people.

BOHNING: Whom did you report to when you first arrived there?

LOS: A man called Dr. Milon [W.] Bullock. He was a very earthy individual from the Midwest—grew up on the farms and what have you, too. He went to Ohio State. He was, in many ways, a remarkable man. I think he could probably do anything he set his mind to. That would be fixing cars, or building a house—and he did both of those—or doing some very, very good chemistry.

He also gave me a tremendous amount of freedom. I think he trusted me and he trusted my judgment, and boy, is that ever important. He was my boss here until I left to go back to Scotland. That was from 1960 to, I think, 1969. So yes, he was a very good boss and gave me a lot of support. I guess he fought for the programs in the management line and supported me to the end. I mean, it was a very good relationship. He's retired now. I still see him occasionally—still a good friend.

BOHNING: You made an interesting comment that's been showing up in our talks with other people. That is, the idea that he fought for the support to keep you going.

LOS: Yes.

BOHNING: That's so crucial.

LOS: Absolutely. It is. Being in the position that I am in now, I can just see how crucial it is. I mean, it is so easy to say no—especially as a manager. You're not likely to get into much trouble. In fact, you're more likely to stay out of trouble if you say no. So you've got to have somebody who will actually fight for the programs. That means that you, as the researcher or the bench person, have to be able to convince your boss that what you're doing is not outlandish. It's well directed; it has a reasonable focus on what the company or the business wants to try to go after—but the way you're going at it is a very reasonable way with a good chance of success, and things like that. I mean, that this is a well worthwhile project. Yes, you've got to have the support up there. Otherwise—and I've seen it happen—projects are really killed for not very good reasons.

BOHNING: Even when you start out as a bench chemist, you really have to sell to someone else.

LOS: Yes, to someone else.

BOHNING: As you moved up the research ladder, as it were, you found yourself in the middle. You were no longer the bench chemist. You had to sell someone else on projects, and you had someone selling to you.

LOS: Both ways, both ways. But I think your past certainly impacts on you a tremendous amount. If you've had failures and done skunk work, for instance, and things like this, it really impacts how you view these projects or proposals of how the work should be done, or what work should be done. I think that it makes a difference. If you can see success having come not through an absolutely pre-planned process, you can appreciate some other people's view on how you might get there. There are different ways of going about things, different ways of looking at problems. Just because they're not your way, they're not the wrong way. I think it's a little easier if you've traveled some of the paths that they are going on.

BOHNING: When you first started there in 1960, and during this nine-year period, did they tell you, "Synthesize this compound," for instance? Or did they tell you, "Here's generally what we're interested in. How can you help us?"

LOS: They had a specific project in mind for me when I was hired. It was at the time that Dr. Peter Karlson, in Germany, had discovered the insect molting hormone. This hormone was required for the insect to molt through its various life-cycle stages. The thinking was—and I think rightly so—that, "Here's a new nice method that we might be able to apply for insect control." The problem was that Dr. Karlson was working with silk moth pupae, which he had imported from Japan. He couldn't get enough, so they couldn't isolate enough materials to do structure work. Then, if it was available, they would only have very small amounts. Now, how are you going to do the structure? That was where they thought I could help, since I'd been working on natural products. I didn't know all this at the time. This is why there had been a lot of work, and questions on NMR and things like that. They were sort of feeling me out.

It's rather an interesting story. They decided that working on silkworm pupae was not an option. They decided that there must be a way of catching an insect just before or just after it had gone through a life cycle change. Reasoning had it—and this came from the entomologists and other people—that presumably, there should be a reasonable concentration of this molting hormone at that stage. So somebody had the bright idea about the mayfly. It emerges within about two days out of the Great Lakes. I've never seen it myself, but there are swarms of them. They said, "Ah, this must be a good source of the molting hormone." So they contracted with Battelle in Columbus, Ohio, to build some kind of collecting device for these mayflies as they came out of the lake. They would extract them by a procedure that was now published, based on silk moth technology. Then I would receive this extract, and then I would go to work.

Within the first two weeks that I arrived, I think, I was sent to Columbus to pick up this flask. It was just a five-hundred-milliliter round-bottom flask. It had this evil-smelling black goo in it. [laughter] I came back, and I carried this thing in my hands all the way back. We did some bioassays—these were done by someone at Cornell for us—but lo and behold, it was completely inactive. I think the cost of that was sixty thousand dollars in 1960. It was a lot of money, anyway, for that one extract.

That then was the start of my career with Cyanamid. I don't know where that flask is. It may still be at the Lederle Labs, for all I know. [laughter] No one was very keen to throw that out—I mean, it was liquid gold. But that never worked, and the thing was dropped.

So I was given a different project. It was one which involved animals—in particular, cows. There were two parts of the project. There'd just been a lot of work on anabolic steroids—how they increased muscle and what have you. They thought that if they could get a suitable material for animals, they could feed that to them, increase the muscle part of the cow, and so, in these feedlots, make them more productive.

That was one part of it. The other part was, they wanted to find something that would regulate the estrus of the cow so that they could use artificial insemination. They could get them all up at the same time of the cycle, and then the vet would go in there and artificially inseminate the whole lot of them in one visit. That's actually done nowadays. But actually

what we did is—which seems farfetched, almost, when I look back on it—we started on a steroid synthesis program. We developed a lot of methods, and we did a lot of testing in rats and rabbits, and so on. To cut a long story short, we did a lot of pretty good chemistry. We got a few publications out of it—mostly on anomalies, reactions gone wrong, which we also investigated—and many patents, actually, as well. But it never amounted to anything that was commercially valuable. It was not one of the more successful commercial projects, I'm afraid. [laughter]

BOHNING: I counted five papers during that period (7).

LOS: Yes, yes.

BOHNING: I wanted to ask you about the attitude of the company towards publishing scientific papers. Many companies have had the attitude, "We don't want to reveal anything we're doing."

LOS: Correct. In my opinion, at that time, there was not a very consistent attitude. We were divided in sections. There was the veterinary part and the plant side—different management, and they had different attitudes. I think the animal side was very much more for scientific publications. So the onus was on the scientists themselves—did they want to go to the trouble? You still had quite a bit of work to do. I mean, there were certain barriers that you had to overcome. You had to go through the patent people. You had to go through the other lawyers. You had to go through management, so you had to get clearances at different levels. It took quite a while. They'd come back and they'd nit-pick it, so you had to be pretty well a stickler yourself—otherwise you'd soon give up on it. A lot of people did.

But if you stuck with it, you could get them through, and those ones I did. It was nice if you could do the anomalies-type thing. They didn't really encourage you that much to work on those, because that was sort of for-science-only work. You could get those published reasonably easily, but on your main topic of research, it took a little work to get them through.

BOHNING: How large was the group you were in? Were you the only chemist, or were there other chemists?

LOS: No. I was in Bullock's chemistry group, and there were probably eight of us. I always had one junior person working with me, sometimes two, even up to three.

BOHNING: Your instrumentation was state of the art?

LOS: Yes. Yes, I would say so.

BOHNING: You had the physical facilities that you needed, then.

LOS: We had the physical facilities. Yes, I think we had good facilities for doing research.

BOHNING: You essentially carried on this steroid synthesis work for a good part of nine years. Is that correct?

LOS: Yes, just about.

BOHNING: How did the lack of commercial results affect keeping the program going?

LOS: It's a little hard to know what went on in the inner sanctum here. But when I left, it wasn't long afterwards that that project died. So whether it was the fact that I was in it that it kept going or not, I don't know. I mean, I don't know what the inside story is on that. But obviously, they were willing to go for quite a long time on this.

They had a strong steroid program in Pearl River. That was probably one of their strongest. I had very good relations with these people, and we exchanged information quite a lot. In fact, when it stopped here, they took over quite a bit of the chemistry that I had developed here. I think that was maybe also a reason for continuing it—that there was some interest, not only in the agricultural part, but also on the pharmaceutical side.

BOHNING: You've talked about the importance of anomalies. However, at this point in time, we reach an anomaly in <u>your</u> life, in that you went back to Edinburgh and worked on prostaglandins.

LOS: That's true. I had, for the last couple of years, thought that I might like to teach. I'd grown a little more self-confident, I think, at that time. There were certainly avenues that I would have liked to have pursued, that I felt—and my boss certainly felt—that I couldn't. There was too large an avenue to do it sort of under the table. In some ways, I'd become perhaps a little bit disgruntled by that. There was, I think, also the fact that my family was still over there. That had something to do with it, but I think primarily, it was that I thought I would like to teach and be able to set my own goals, set my own programs, and set the direction I wanted to go into.

I think that was one of the main driving forces.

BOHNING: Why did you select Edinburgh? Was that going home, in a sense?

LOS: Well, I knew some people there. It was a senior research fellowship and involved very limited teaching, but it also allowed me to get a research program started. Actually, what I did was join the professors' group there and take over a part of the work there. I knew about prostaglandins and so on, and it looked like a really up-and-coming, important area of pharmaceutical products. Certainly the way they work, and how they work, and what they control, was certainly important. It was a way to get started pretty quickly.

For instance, they had a GC-mass spectrometer, which to me was really the method to use for identification of the prostaglandins from body tissues and body fluids, and things like that. I mean, it was a real plus. Also, they were well funded. The Medical Research Council was funding them well. They had a good in with Upjohn, who was a producer of almost all the prostaglandins at that time. So that happened to come up. I knew about the position, and I happened to write—and yes, they would accept me. I decided to go.

So started probably one of the most expensive ventures I've ever made. [laughter] We sold all our furniture here, the house, and everything. I had four children. We all moved to Edinburgh.

I soon found out that things were not quite as easy as in industry, particularly. For instance, I needed a gas chromatograph. Well, we didn't have one. I was in the pharmacology department—it was a medical school. Well, the biochemistry department had one, but it hadn't been used for two years; some pieces were missing. They said, "Gosh, you know, if you want it, you've got to get it working again." Here, I'd just pick up the phone and ask for somebody to come in from some company and fix it. There, there wasn't the money, so you try to fix it yourself, and you buy the parts.

It was a whole new world, and it really didn't work out very well. Soon, after about eight months or so, I let it be known here at Cyanamid that if they had a position, I would like to return—having bought a house there, furniture there, and everything else there. [laughter] We weren't very happy there.

Now came a real problem. I talked to the director of chemical research, who was Dick [Richard J.] Magee, at that time. He said, "Well, we'd love to have you back, but your old job isn't there. You can't go back to your old job." I said, "Well, that's fine." He said, "But we can offer you a job on the plant side."

Well, I obviously had been here, and I knew what the plant side meant. It meant that you had to make anything, but it couldn't cost more than a dollar a pound. [laughter] You nitrated benzene, and then you reduced it. I felt rather dismayed by this. But I thought, "Well, you

know, optimistically, it's a way to get back. You'll see what happens when you get there."

It turned out, of course, that it was the best thing I ever did. I was a bit disillusioned for a year, but after a year, I was made a group leader, which I probably could not have expected had I stayed here all along. I don't know that the positions would have been available.

[END OF TAPE, SIDE 3]

LOS: I was made group leader, and that sort of changed things a lot. Now I had a little more say in what we did and how we did it.

BOHNING: You said that you were disillusioned in that first year. What were you working on during that first year, when you returned to American Cyanamid?

LOS: Well, the group that I landed up in was a support group for plant growth regulators. It was the belief of some that one would be able to regulate the way a plant grows, what they produce, how quickly they grow, or how good a crop they yield—by chemicals. People have found gibberellic acids, abscisic acids, and a lot of these other things, and they found that they could manipulate plants. There was a very sizable program going on. We were the support group for that program.

I had, not no faith, but very little faith in the biology that was going on with this program. It was very much, "Just apply the chemical and see what happens to the plant." Then you had to try to find out whether it was a good thing or a bad thing—and whether it worked out in the field, which it usually didn't. It was, I thought, very poor biology compared to what the chemistry could support. I thought we were making lots of compounds for not very good reasons. That's why the disillusion really came in.

But I was very fortunate. It turned out that it was this program that turned me on to what eventually turned out to be a very good program, but heading in a very different direction. At the time that I was group leader, in the early stages, I had this plant growth regulator program. We also were supporting the fungicide program, which was much more structured and had much better biological support than the PGR program.

BOHNING: It wasn't until 1980 that you had a paper on phthalimides as plant growth regulators (8). When did that work start?

LOS: That started in 1970. That was really the start of this whole imidazolinone project. It didn't start in my group. The phthalimides actually were herbicides that started the program;

they killed a few weeds. As the story goes, the herbicide chemistry group, which was headed up by Dr. Al [Albert W.] Lutz, tried to modify the structure to make it more active, and so on. But one of the compounds they made was completely inactive. The biologist noticed that the plants grew bigger, maybe better—and this is where I was in the right place at the right time. They said, "Well, this is obviously a plant growth regulant. We should optimize this biological activity." This then came into my group, and this was then a PGR project. We were supposed to then improve the activity from this point of view, rather than from an herbicide point of view.

BOHNING: However, the phthalimide came about from just random testing.

LOS: That was a compound that had been made at Pearl River, at our pharmaceutical labs. It was actually patented as an anticonvulsant. It was later sent down here for broad biological testing. So yes, that was also a random event.

BOHNING: You have written that in the chemistry that developed during the next fourteen years, your department took three approaches to discovering new herbicides.

LOS: Right.

BOHNING: It seems that of these three approaches, the random screening was still the most effective at that time. Is that true, or is it not true?

LOS: I think it is true. I think it's probably still true. In my position, I'm in charge of biological testing, and this still is the major approach. The more compounds we can get to test, the happier we are. Some of the other approaches are going on as well. But certainly, even within the last couple of years, the major synthesis projects have derived from compounds that were active in a random screening process.

BOHNING: What is the magnitude of the sample you are screening, let's say in a year's time?

LOS: At the present time?

BOHNING: Well, going back to the early 1970s, when this whole project got underway.

LOS: Oh, gosh. We were down to probably about four thousand compounds a year. We

needed a sample of probably three hundred milligrams or five hundred milligrams, something like that. So it was very different from today.

BOHNING: How was the screening done? That would still be a large number of compounds to be screening.

LOS: It is done at an arbitrary rate. You will screen it at a high enough dose that you will pick up any compound that has biological activity. You actually spray the compound on the plants that you want to control, or you put it on the soil, so that plants as they're coming up, they pick it up. That's called preemergence activity that occurs before the plants actually come up, or postemergence activity when there actually are already plants. So we do it. You test them both ways because some act one way, some act the other, and some act both ways.

BOHNING: That must be a pretty big operation.

LOS: It is. There are a lot of people involved. We have a group which does nothing but that. I mean, you have to grow plants and have them all ready. You have to have an operation of spraying mechanisms, so that you can do it accurately and simulate what happens in the field. You have to have the greenhouse space to leave them there for anywhere from three to five weeks, to grow them. You're going to have people water them. Then you're going to have people look at them and rate them. It's a big operation.

BOHNING: Is that rating quantified in any way?

LOS: Yes. Here we use a rating of one to nine, which is roughly zero to one hundred percent. Absolutely dead is a nine, almost dead is an eight, and so it goes down. There are different letters we use with a rating. A plant can be very stunted, for instance, although it's still alive. It will be given a seven rating with a letter behind it, so that we have a picture of what actually happened.

BOHNING: Is there a magic line you draw through this scale, for which you say that everything above this line is interesting, and everything below it is not?

LOS: In practical terms, yes. It also depends heavily on what species have the nine and the eight. So it's a combination.

If it's one special weed that is found to be controlled, and it's known to be a problem,

that can be a product. We have one commercial product, which is called Avenge. It controls essentially one weed, post-emergence. It controls a weed called wild oats. It's a real problem if you're growing wheat or barley. That made it as a product simply because, if you don't control it, you get all these wild oat seeds in the wheat. The bakers and the beer makers don't like that, so they dock you—you get a lot less money for your product. Plus the fact that this wild oat is a very vigorous plant, and your yield goes down—it's very easily measurable.

BOHNING: Once you found that the original phthalimide had activity, the next step would have been that you would modify the structure to increase the activity. There were three different ways, on that particular molecule, of changing the structure. One was the alkyl group; another was the amide group; and the other was the phenyl with benzene. Which of those did you attack first, in terms of modification?

LOS: The alkyl groups. The reason was that we knew that the amide function, in all they had done in the herbicide group, was required. I mean, the best biological activity was associated with that. We also knew that a specific substituent in the phenyl ring, which happened to be the 3-chloro group, changed the activity from being this herbicide to this plant PGR. So we took the other piece in the middle, and we made so many combinations—almost anything we could think of—small groups, a large group. Then we tied the two substituents back to make cyclohexane rings. We went the whole way, actually. The cyclohexyl group happened to be probably the preferred alkyl group.

Then, of course, you start trying to change the other things in the phenyl ring. The 3-chloro substituent happened to be really probably one of the better groups. A 3-CF_3 substituent—which is also a pseudohalogen, of course—happened to be a very good one as well, but much more difficult to make, so we didn't pursue that very much. But certainly, it was very good as well.

BOHNING: It must have come as quite a surprise that putting the chlorine on the benzene ring changed the function altogether.

LOS: From herbicide to PGR, absolutely. I mean, it's just not something you anticipate—which is a nice thing, right? I mean, that's what you like to have happen. As I said, I was lucky enough to be able to take hold of that and work with that.

BOHNING: I had been curious as to how you got the cyclohexyl group in there. However, you've answered that. You simply tied the ends together in different sizes. Again, that was not something one could predict. [laughter]

LOS: No, no. Absolutely not.

BOHNING: You were really pursuing two different things at one time. Is that correct? You were pursuing the PGR work as well as the herbicide group.

LOS: No, no. Fungicide work.

BOHNING: All right.

LOS: I mean, my directive for the chemistry group was to follow leads in fungicides and in plant growth regulants. It was only because of the change in biological activity that the herbicide group, which was not my group, gave this compound for me to follow up on. As soon as they had made the 3-chloro compound, it came to my group.

BOHNING: I was trying to think my way through the sequence of events here. As a result of activity of the cyclohexyl derivative, you needed larger amounts for field tests.

LOS: Yes.

BOHNING: Therefore, you needed to find better ways of synthesizing than what you were already using. Is that correct?

LOS: No, not necessarily better ways. But there were obviously a lot of alternative ways of putting the molecule together. Right?

BOHNING: Do you mean more efficient ways?

LOS: Well, I don't know. I mean, you start with cyclohexanone. You could make the amino acid derived from cyclohexanone. Or you could make the aminonitrile, the Strecker product; react that with the anhydride; and then manipulate the nitrile to the amide. Or you could make the amide first, and then react it. We wanted to see which combination of these different things would be most amenable for the people in the prep lab who were going to have to make this compound on a larger scale. What would be the easiest for them to handle?

The cheapest way was to go probably from the nitrile to the amide directly. But you had

to use concentrated sulfuric acid for that, which was not the easiest way or the easiest thing to manipulate. We just wanted to see whether it was better to try to do that first, some other way, or whatever. We looked at all the possibilities.

BOHNING: Yes. In one case, you had a molecule that you needed to cyclize, so you used trifluoroacetic anhydride.

LOS: Right.

BOHNING: This gave you an isoindole. This was still a plant growth of PGR, if I remember correctly.

LOS: Correct.

BOHNING: But now you had a new type of molecule to deal with.

LOS: That's right.

BOHNING: That wasn't the major product of the reaction, though.

LOS: No, no. The major product was what we were looking for. I can't remember, in actual fact. I mean, I did the experiment myself. Although I was group leader, and most group leaders didn't do any lab work anymore, I still had my own hood. I spent as much time as I could working in the lab myself, which had a lot of benefits. I didn't need to tell anybody about running an experiment; I could do anything I wanted. I also always had someone working directly with me, which many of the other group leaders did not. So I could work on my own ideas. You don't like telling senior people, you know—well, you shouldn't tell senior people how to run a reaction, or what to run, or exactly how to do something. They should have their own program and way of working at it. I encouraged that.

But I can't for the life of me remember why I used trifluoroacetic anhydride. It's very low boiling; it's very reactive—easy to get rid of. Maybe I thought this would be very easy for the prep lab to use, or something like that. But it was a happy circumstance. The material was formed in only a small amount, but it was a fairly easily isolated byproduct. The main product was very clean, but there was this fairly insoluble, nice crystalline product that I could isolate. I went through all the trouble of purifying it—and trying to get the structure, the NMR, and so on—and decided it was the isoindole. Naturally, we had it biologically tested. It looked as if it

had just the same activity as the non-ring-closed material.

We didn't know anything about this system. We thought it was probably pretty unstable. I think maybe the thought that it was unstable came from the fact that we saw the biological activity and thought, "Well, it must be just hydrolyzing back in the soil and going back to the cyclohexyl compound. It's the PGR. It's working just the way the parent is." Actually, that held us up in many ways. We treated those compounds with kid gloves often, and we kept them away from water. We did all our reactions in nonaqueous systems. It held us up. There were a lot of things that came out later that should have come out earlier, had we not based our work on this false assumption. Rather strange, actually.

BOHNING: The next step was that you set out to find a practical route to the isoindoles, as a class.

LOS: Well, we had to finish the PGR work first. There was a gap. That was sort of on the back burner, waiting—because the patent situation on the PGRs required completing first, and since everything seemed to be pretty important here. But yes, we had to find a way. We actually found several ways we could do it. Some of them were rather unusual. We thought of sodium hydroxide pels in toluene, which was an excellent way of doing it. It was used in very large scale to make some of these compounds.

BOHNING: However, in doing this, somewhere along the line—I'm not sure exactly what the sequence was—you found an herbicide, one of these isoindoles.

LOS: Yes, that's right. We decided that, "This compound is just like the PGR. We'd better make enough compounds so that we can apply for some patents and cover this area, because somebody's just going to do this if we don't do it." So yes, we had to continue working in this area. We started picking up as many of the phthalimide compounds as we could to cyclize them, to convert them into isoindoles. One of the ones that we did was the one that started this whole herbicide program—the one that Dr. Lutz started with in his program. When we cyclized that, we found, "Gosh, this is a much better herbicide than we've seen in any of these other ones." It was now a very active compound. So this generated quite a lot of excitement again, and also a whole new synthesis program.

BOHNING: It's intriguing that you can switch back and forth between PGR and herbicidal activity with minimum change in the molecule. At this time, was there much known about the real function of the molecule, in terms of any enzyme inhibition or anything of that kind?

LOS: No. But it's strange. A lot of these herbicides actually have PGR effects at very low

concentrations. You could show a good effect on the plant; it doesn't kill the plant. If, for instance, you plot the dose against plant weight—if you start at a very low dose, and you plot it—you'll find that the plant weight actually increases, and then it goes down as the herbicidal effect takes place. So at low doses, you can get a good PGR effect.

BOHNING: Now you had a molecule that had herbicidal activity. However, looking at that series, it turned out that the parent herbicide was the best one. The first herbicide that you made from the original phthalimide was still the best one.

LOS: Correct. It was the best one. That's correct.

BOHNING: Now, I'm not clear how we get to the next step. You studied a lot of the chemistry of this molecule—the reduction, the addition of alcohols, all kinds of things.

LOS: It's rather a little story in itself.

[END OF TAPE, SIDE 4]

LOS: We had made this material that you referred to—the best one in the series, the starting material. It was a very active compound. We didn't make enough material to go into field trials, to do some work outside. In order to do that, you have to have the compound formulated. So we sent this material down to the formulations group, and they made different formulations. It looked as if they had developed a good formulation.

It was in the spring. They had decided that they had gotten the formulation, and they let it stand for a while. When they were going to send it out, they noticed these nice crystals on the bottom, so they called me down and said, "What do we do now? What about the crystals?" I said, "Well, give it to me and I'll see what it is. It's probably starting material. It's probably just the compound crystallized out."

So I did it myself, again. I isolated the material, and I did some spectroscopy, and so on, on it—the usual. It's not the starting material. It's not the material that we gave them. NMR data said that methanol had added to the compound. I go back to the people. "What? There's no methanol in your formulation," but there actually was. There was like a half a percent of methanol in some solvent they had used.

We didn't know anything about the chemistry of these products. I said, "Well, it's not the material, so let me find out what it is." We made some guesses as to what it was. I said, "Well, I'll make some. Then we can test it." We didn't know quite how to do it.

One of the first reactions I did was, I took some of the starting material we'd given them, and I put it in methanol with sodium methoxide, base catalyzed. Something or other was going to happen. I did another reaction just with methanol—just let it sit in methanol. I did another reaction with some methanol with a little HCl gas in it, an acid-catalyzed methanol. I followed the reactions by thin-layer chromatography.

The one with the methoxide in there was over just like that. Good, clean product, clean reaction. I said, "Ah, this is great." I had isolated a product that's not the same as the one that came from the formulations. This happened to be the first imidazolinone. The one from the acid-catalyzed reaction turned out to give the same product as the one from the formulations. In the end, we unraveled what it was. The acid-catalyzed reaction induces the addition to the C=N double bond, and the base-catalyzed one opens the ring to give an imidazolinone ester.

That was the reaction that went wrong, that gave us this new series of compounds. That's how the imidazolinones actually started—a series of miscues.

BOHNING: What year would this have been when you conducted this experiment? I'm trying to think how much time elapsed between the time you started the PGR work and this point.

LOS: It must be about 1975, I think.

BOHNING: How long after you first discovered this imidazolinone did you realize you had something that had good activity?

LOS: That was probably within a couple of months. I mean, it takes a while for the compound to go through the system—probably about a couple of months.

BOHNING: Did it stand out? Was it one of those that was obvious?

LOS: Oh yes, it was obvious. There was no question about it. It was more active than anything we had seen thus far, but very poor compared to what was coming along. [laughter] That was the start of this whole new project now, again.

BOHNING: But now you were in herbicides.

LOS: Now we were in herbicides. Fortunately, they did not take the project away from us,

which could have happened.

BOHNING: That's why I asked.

LOS: I'm not sure why my boss—at that time, Jerry Berkelhammer—decided to keep it in my group, but he did. It was a very good occasion—I mean, a terrific happening. [laughter]

BOHNING: Was your PGR work still going on?

LOS: The biology was, not the chemistry.

BOHNING: You devoted all of your time to this, then.

LOS: All the time to this, yes.

BOHNING: How did you decide to approach the analogs? What was your target?

LOS: Well, we did the same things that had been done in the PGR project. The two alkyl groups there in the imidazolinone ring were varied—did the same rules apply as for the PGR project? We didn't know. Was the ester the best? It turned out not to be true. I mean, the acids were certainly much more active than the esters. What about the substitution in the phenyl ring? The most active compound, again, was the parent compound, but there were signs of selectivity which we had not seen in any of the other previous compounds. There was selectivity, if you did have some substitutions of the phenyl ring, particularly with alkyl groups. Was there something magic about the imidazolinone ring itself? Was that something peculiar and particular? We tried many, many combinations and differences. Could you put substituents on the nitrogen, for instance, or not? All of these questions were attacked essentially at the same time, and probably close to all the group was working on it, so we could attack these entities at the same time and sort of pull them together.

BOHNING: When did you realize that you had something commercially viable?

LOS: It was not as simple in this area. The compounds were essentially non-selective, as I said. The compounds that had some selectivity were not as active. We struggled. We finally found a compound—which was also a little bizarre, because that one was derived from 4-methylphthalic

anhydride. We're starting from an unsymmetrical intermediate. The product at the end is a mixture, so you end up with a mixture in which the methyl group is either meta to the carboxyl group or para to the carboxyl group. There wasn't an easy way to separate them. But this was the only compound—well, no, there was another one as well—but this was the real compound that showed some selectivity and some activity on some specific weeds. One of them was wild oats.

It didn't do very well in the field at the time. I'm not sure how this story actually unraveled, because if we look back at the data from the work that was done in the greenhouse, one would have said that the best way to test this compound is that it should be used pre-emergence. You put it down after your seeds are planted, before anything comes up.

In point of fact, it was tested for probably one or two years that way, but it seemed to hurt the crop. It didn't do as well. But there was one test in Spain that was done—people were late in getting it out, so the crop had emerged and the weeds had emerged. They sprayed it anyway, and it performed very much better that way. It's a very good commercial product now. It was from that observation that the testing changed. Somehow, we were fooled or the biologists were fooled, at that time, as to how that material should be tested. This product is called Assert. It's a very good product now, used in wheat and barley.

BOHNING: Each of the methyl isomers has different activity.

LOS: Different activities, yes. [laughter] It's good. I mean, it works out very well. One isomer is good on wild oats, and the other one is good on wild mustard. One's a grass; one's a broadleaf; and both are problems in wheat and barley.

BOHNING: That meant that you didn't have to go through separating the isomers.

LOS: No, that's right.

BOHNING: What year was that released?

LOS: What year was it sold?

BOHNING: When was it first sold commercially?

LOS: I don't know the answer to that.

BOHNING: Again, I'm looking at the timeframe from 1975 on.

LOS: Yes, but it's quite a long time after that. I mean, by the time we'd gone through registration and everything, it's got to be at least six years, maybe seven. So it's got to be in the 1980s.

BOHNING: Therefore, by the time this material reaches the marketplace, your patent has already had a significant part of its lifetime pass. Is that true?

LOS: It's probably true.

BOHNING: You've gone through the field tests, and you've now reached the point where you know what you need to do with this product. What happens next? You have to scale up production, but you also said there are regulations—you have to register it, and so forth.

LOS: No. Our research effort is divided into two. I am part of discovery. Then the other part is development, which goes on at this site. Discovery goes to the point where you know that you have a commercial-entity product. It then is taken over by development. They then start the program, and it's a broad-base program where you have to look at efficacy. You have to start toxicology work, and you have to start environmental work, and all these things. This one front starts moving down. So it's only up to the stage where you realize that you <u>have</u> a product that discovery is intimately involved.

We're still on the development committee, but the real task is taken over. Now you have to deal with projects and timelines, and agencies and outside labs, and all this sort of thing. Residue work, you have to start—and carry-over work, follow-crop work, and all this. There are so many things that have to be done, but that's just taken over, lump sum, by development. They put someone in charge of just that—the development of that one compound.

BOHNING: How often might something get from discovery to development but never make it to market? Is it pretty well assured that by the time it goes from discovery to development, it's going to make it all the way?

LOS: No, it's not a given. What is happening, particularly now, is that greater effort is made in trying to find what red flags there might be before it ever gets to this stage. So we do things now which were never done in discovery ten years ago. We look how it moves in the soil. We

look whether it has a problem with fish in water. We look whether it's volatile. A lot of things that would be red flags are looked for before they ever get to that stage. It never used to be like that, but now it just costs so much that we need to do that now.

BOHNING: At some point, another department—unless development does this as well—needs to put this on a manufacturing basis.

LOS: That's right. We provide them with an initial synthesis and perhaps some improvements, but it seldom is anything like how they will eventually produce it. It is also given to the chemical process development group to find the procedure that can be scaled up—that can be amenable to large-scale production.

In Cyanamid, the discovery effort was divided out from development in the 1970s, I believe it was. It was done for the very reason that, for instance, my chemistry group would not become involved in finding a process to make this thing on a large scale. We were discovery, and we would have a budget. We would have our own budget; we would have the directive to discover new things—not to be bothered with, once we discovered it, to take it on further.

BOHNING: Sometimes in the discovery phase, a department is doing some beautiful chemistry, but that doesn't necessarily translate into large-scale production.

LOS: No. We developed some very nice chemistry throughout this whole process, I think. But most of it was laboratory chemistry. You know, you can't use butyl lithium—not very easily, anyway. [laughter]

BOHNING: Assert was the first herbicide you discovered, then.

LOS: Yes.

BOHNING: At some point, you made the decision to replace the benzene ring with a pyridine analog, or at least go to a heterocyclic structure of some kind. Why would you put a heterocyclic molecule on that ring?

LOS: We had been working in that benzene series, and we'd made the naphthalene analog, but we didn't seem to make very many advances—not very active compounds, really, and we didn't see anything different. We were down, actually, to one person working on this project. It was at a time when, at some review meetings, I still remember, some people in management were

saying, “Why are you still working on this project? What’s in it?” We were really being encouraged to finish.

You know, it’s not so easy to find good leads. It wasn’t then; it isn’t now—particularly in the area where your chemistry is your own. You’ve got a lot of background that others don’t have. You maybe think, a little bit, you know what you’re doing.

It seems so trivial now. I said pyridines, but pyridines were expensive. Pyridines were tough chemistry. You couldn’t do simple benzene reactions on pyridines. They did different things. They weren’t symmetrical any more. But I decided that there was this 2,3-pyridine anhydride available from Aldrich. I said, “Gosh, got to do this.” I say three people tried; it actually reminds me of those statements about doing the reactions yourself, actually. [laughter] We never really knew why, but I think I know why now. It was very poor quality. I think the anhydrides had essentially gone to acids and the junior people really hadn’t checked it out.

So it actually took the three people—three different people, at three different times—actually to get the reaction to work. What was also bizarre was that, you know, we knew that we should get two products from it, but we could only isolate the one. This one person, Jack [John J.] Hand, did it. It had to go through chromatography. The yield wasn’t very good, and we were lucky to isolate this one material. This is where we had a real quantum jump in biological activity. I mean, it was incredibly active compared to what we had seen before. This is the time, very early, that all hell broke loose. I couldn’t believe how active these compounds were, compared to what we had seen before.

So we were lucky on two counts. We could have used the 3,4-anhydride, which would have led to inactive compounds. We could have isolated the other isomer from the 2,3-anhydride; it would have been the end of the story. As it was, we isolated the only active isomer that saved this project. That was pretty lucky.

BOHNING: Yes. It was sheer good fortune that that was the only such isomer that Aldrich had in its catalog, as you thought.

LOS: Yes.

BOHNING: If Aldrich had had several of them available, it might have been a different story.

LOS: It might have been a different story. Yes, I’m very thankful. [laughter]

BOHNING: I heard a similar story to yours, in the development of the original Freons by [Thomas] Midgley. Somewhere along the line, his team needed antimony trifluoride, and they

ordered five bottles. They used the first one, and what they had worked fine. It turned out that the other four had contaminants, so they didn't work. But of those five bottles sitting on the bench, if they had picked one of the wrong ones—when the chance was only twenty percent that they would get the one that worked—that project would have never gone forward. Somehow, they managed to pick the right one by chance. [laughter]

That led to Arsenal and Pursuit, I believe. They're both pyridines.

LOS: They're both pyridines. We have just announced another pyridine, which will come onto the market, we hope, maybe next year. This is another pyridine.

BOHNING: Is there a name for it?

LOS: I think so, but I don't know what it is. It's the 5-methoxymethyl derivative.

BOHNING: Who makes up the names?

LOS: The trade names we sometimes have a competition for, here. They say we need a name. Often they ignore the names and say, "The marketing manager will pick one." Then it has to go through all this screening, of course, to make sure it's nobody else's and everything else. Also, the common name has to follow some rules, I'm not sure what they are. Like in imazethapyr. Is that the common name? Is that what it's called, the common name?

BOHNING: Yes. When I saw those names, that was a new set of names for me.

LOS: Yes. There's going to be an imazapyr; there's imazamethapyr; there's imazamethabenz, and so on. But yes, Pursuit and Arsenal came out of the pyridine studies.

BOHNING: Then in the next step, you added another benzene ring.

LOS: We put another benzene ring on there. See, what had happened was that this project had become so big—actually, it had become probably the biggest project that we'd ever had in Cyanamid's agricultural division—that two chemistry groups were shifted onto this project. So it was divided up, and the other group was going to make the quinoline analog. It was actually made before the pyridine analog. It was the first big surprise, in that it was the first compound that showed this terrific selectivity in a crop. You know, Assert had as well, but this was the

compound that was very active as well. I mean, there was a real difference here. Arsenal was completely nonselective—it killed everything, essentially. But the quinoline analog, which is now called Scepter, was very selective in soybeans. It has become a big product for us.

BOHNING: There was also something called Cadre. I'm not sure what that was.

LOS: Cadre is the 5-methyl derivative, and that will be on the market next year also. Its prime target will be for use in peanuts.

[END OF TAPE, SIDE 5]

BOHNING: When was the biological mechanism determined? That is, when did you determine what enzyme these compounds interfered with?

LOS: Yes, that was done in the early 1980s. It came out of a project that Cyanamid had with a biotech company in Minneapolis called Molecular Genetics. The joint project was one in which we were going to try to see whether we could get a corn plant that was tolerant to these herbicides, so that you could use any of these herbicides on corn and they wouldn't hurt the corn. We found selectivity on a number of crops, but never corn. It's still true.

So this project was started. There was one person from Molecular Genetics, Paul Anderson. There was also one person here who sort of guided the project, and this was Dale Shaner. Through tissue culture work, they were actually able to find cells that tolerated these herbicides very well. These were mutants. Now they had the mutant, and they were able to regenerate a plant from the cells. Now they had a plant that was resistant, and they had a plant that was not resistant to these herbicides. There was obviously a difference. So they decided to work on the mode of action of these compounds.

One of the things that they did was to determine what the composition of the free amino acids was. I'm not quite sure why that was particularly done. But they had a lot of parameters they could look at. They could look at incorporation into DNA; they could look at incorporation of acetate into fatty acids, and things like that. This allowed them to eliminate certain processes.

They looked at what the amino acid pool looked like. They found out that for three amino acids, there didn't seem to be any in this treated plant, but they were present in the resistant plant. Then they went back and they treated the sensitive plant with the herbicide, and also fed these three amino acids as well. The plant survived. They decided these three amino acids were important, so they looked up the biosyntheses of these three amino acids and found they had some common pathways. The two of them decided which step, in each path, each would look at to find out which one was involved. Well, the first one that Dr. Anderson at

Molecular Genetics looked at happened to be the correct one. This was the combination of two molecules of pyruvic acid to give acetolactate, the first step in the biosynthesis of the three amino acids—valine, leucine, and isoleucine. So it was this enzyme, acetohydroxyacid synthase, which was being blocked by these new imidazolinones.

BOHNING: How much did the organizational structure change as all of this developed? This would have had to be one of the major effects of putting all of these products out at this time.

LOS: There was a major expansion here. I don't know as much about it, but I think we probably grew half as much again during this period. It required a tremendous effort. Of course, when they started selling the products, the money was there to support this effort. We've sort of grown continuously up till the last couple of years or so, when we have completely grown out of space and everything else and have slowed down. Plus, now we're under new management as well—which is, we try to find out exactly how things will or will not change.

BOHNING: I want to ask you about that aspect of your work in a few minutes. However, you were essentially a group leader until 1984, almost fourteen years, while all of this work was going on.

LOS: That's right.

BOHNING: Were you content in that role, or had you thought that maybe you should have been given some more responsibility?

LOS: No, I was very happy in the role. I was—and probably still am—first and foremost a scientist, and here I had a group of people who reported to me. I had a terrific group. We worked very well together and caused successes—just tremendous things for a group. We were highlighted—I mean, we were recognized. So the rewards were there. I mean, the satisfaction was just enormous. The drive of the group and the enthusiasm to extend this was exhilarating. There was really not much thought at that time.

BOHNING: In 1984, you became a senior group leader. However, by 1986, you were a manager of crop protection chemicals discovery.

LOS: Yes. But before becoming a manager, I became a group leader of a biology group. So I went from senior group leader in chemistry to senior group leader in herbicides, which was a

biology group.

BOHNING: I see. That would have been the period from 1984 to 1986.

LOS: Yes. Now people have asked me, "Why did you do that, particularly at the height of success? Why would you change?" I was offered the job probably several times.

I think that a change like that can do wonders for the vitality and the enthusiasm of a researcher. It gave me something that I had to learn from scratch, although I'd been involved in the biology to a certain extent. But it really gave me a new lease on life as well. Mind you, there was terrific apprehension. I talked to a lot of people, upper management as well, in that. But in retrospect, I think I probably did the right thing. Yes, the projects went on without me in chemistry. The same project went on for a while without me. I really had some new mountains to climb too, which was really a lot. It kept me going very, very enthusiastically, I think.

I don't know whether other people have found this or not. I don't know whether other people have even considered it. It's not an easy thing to do, to change like that, but I think for me it was very good.

BOHNING: You were still at the bench, as it were.

LOS: Well, not so much. Not so much. I was becoming more of a manager than a bench person after I changed into the biology part.

BOHNING: Was that by design or by circumstance?

LOS: By circumstance, more than anything. It was a much larger group. It also involved a fair amount of travel. We did testing around the world. I got to visit strange places like the Philippines, Japan, and Brazil—places like that. But it also brought me one step closer to the development part. It was not the chemistry that pushed things into development; it was the biology group who pushed things into development. So I got a little closer to a different sort of action—a little more structured, a little more committee driven, almost. It was a little less the cavalier discovery-type work, in many ways.

BOHNING: How did you feel about that?

LOS: It took quite some time before I really accepted that. I mean, it's very difficult, because

the biology and chemistry groups obviously interact very closely. You sit at a meeting where you are in charge of biology but really you're a chemist, and the other people are running a program that you sometimes wonder, "Well, gosh, I wouldn't do it that way"—but you can't really say that, because it's none of your business. [laughter] You can say it, but it's not the same. So yes, there were times that I said, "Oh, what did I do?" But I think things have worked out.

BOHNING: From there, you steadily increased in managerial responsibility.

LOS: Yes, that's true.

BOHNING: I noticed the name of crop protection chemicals research, which sounds like somebody's idea of broadening the coverage.

LOS: Well no, that's not correct. The title is not correct.

BOHNING: All right.

LOS: You see what it actually says.

BOHNING: Yes.

LOS: That was at the time when I was manager, I think. Is that correct?

BOHNING: Right, yes.

LOS: Yes. For a very short interim period—and I knew it was a short interim period—I was in charge of both herbicides and insecticides.

BOHNING: All right.

LOS: That was an interim position, sort of a manager of that, until they split it up into what it is today.

BOHNING: That is crop sciences.

LOS: Crop sciences. Right.

BOHNING: Do you utilize academic consultants?

LOS: Yes. I must say that during the chemistry part of this we had one consultant, who is still a consultant and a good friend. He's Professor Mike [Michael E.] Jung of UCLA. He is just a terrific consultant. He was such a good man to bounce ideas off. He'd come up with ideas for specific syntheses of specific molecules that we wanted to make, and things like that. A really terrific guy.

We do the same on the biology side. We have people come in from universities, from USDA [U.S. Department of Agriculture]. We may even just use them as a consultant for a day. We may have a mini-symposium, which we've done on a number of times. Well, we get a number of them in just for discussions on specific projects that we're interested in. So yes, we use them, and they can be very valuable.

McNULTY: Did your interest in teaching ever resurface?

LOS: No. Maybe now—I mean, I've thought about it. I toyed with the idea of perhaps of joining the Peace Corps and teaching chemistry or something in that sense, rather than university teaching, if it were necessary.

BOHNING: At this point, we've covered most of these areas on this agenda that we had sent you, but there are a few things I'd like to explore a little bit more. One area deals with changes in the company's attitude toward supporting research and development during your career here at Cyanamid. Have there been any changes?

LOS: No. For the major part that I was here, we've had two CEOs. The one who was there during most of the work on the imidazolinones was a George J. Sella, Jr. Probably he was an unusual type. He was very, very supportive of research. Here is a man who was the CEO of a four-billion-dollar company—at that time, about four billion dollars—and he would come down at least twice a year and spend the whole day with discovery. Not development, discovery. We would have a room, and he would spend the day talking on different projects. It was not necessarily the group leader, not the manager, certainly not the director, who'd speak to him. It

would be most often the bench people. He would listen to them, and it would be one-on-one. There was no congregation. He would put his feet up, actually. He didn't have that great a training in science, but he was a tremendously smart guy.

My introduction to the very top manager of the company occurred when I was talking about my project to this man sitting across the table from me—being, you know, somebody way up there, talking to me. So throughout this time, there has been a tremendous support for research and the development, because things come out of research that require development. This has gone on throughout the whole time I've been here. I mean, there has been terrific support. They've increased the research budget some ten to fourteen percent per year. It has been very well supported. Probably the reason why it's been so well supported is that it's been very productive. There's been a steady stream of new products that have come out of it—not only herbicides, but in the other areas as well.

BOHNING: We've talked a little bit about teamwork. Certainly, in your case, you've needed to have different people involved—such as the biology component and the chemistry component, for example. From your experience in an industrial environment, how important is having the cooperative effort of a large number of people?

LOS: Probably more important than anywhere else. I think perhaps, in discovery, the group in itself is where it has to start. We had a custom, and we used this the whole time, that every morning at coffee time we all met together. This would be for probably half an hour. This was every day. We would meet, and it wouldn't necessarily have to be anything to do with the project—it could be of someone's family; it could be some sporting event; it could be anything. Very often, it was some discussion of something that had gone wrong or something that was working very well, or somebody who had an idea and just wanted to put it on the board. But it became a very close-knit and a very cohesive group. I think this played a large role in the success of it.

I don't know, maybe other people use other techniques, but I found that that single thing was probably one of the best things that we did. [laughter] Apart from that, obviously, we needed to work with a lot of other groups—be it field teams, be it biology testing groups—setting up schedules and timelines, and this sort of thing. It makes or breaks a project—there's no question about it.

BOHNING: Did you ever have an occasion when someone wasn't a team player or otherwise, for whatever reason, didn't fit within the group?

LOS: Talking in general terms more than specifics here—for all the time that I've had groups—it's unfortunate in many ways that the most creative, the most innovative people are the most difficult to manage. They don't want structure, and they don't want to be told. It becomes a

real challenge for the person in charge. Yes, there have been people who have been like that. Sometimes, it's been so bad, it just doesn't work. I mean, it's so disruptive for other parts. Most times you can handle quite a bit of disruption for what they produce, what they add to the group. But I think it's true, though, that these most productive people are often so difficult to handle.

BOHNING: You had commented earlier that, for the most part in your career, the manager above you was always very supportive of what you were doing. You also have discussed, briefly, what it's like now that you're on the other side. How do you react to those situations that you were in earlier?

LOS: I like to give them as much freedom as possible. I mean, there are certain limits, and they realize what the limits are. There's a broad target. How you get there is not necessarily that important. I give them as much freedom as I possibly can, in that way.

I have three good-sized groups who are reporting to me now, and it has worked very well. Those three groups have to work well together as well. So they can't go off, particularly in crazy directions. They know this. They are very bright people; they are there because they are bright. You don't take away that from them, that ability to chart their own course, in other words.

[END OF TAPE, SIDE 6]

BOHNING: What do you look for in finding creative people?

LOS: It's probably one of the toughest parts of our jobs, and it's not always very easy to tell. I think this is one of the problems that frequently arises in chemistry, for instance—that the training for a Ph.D. person, in my opinion, is not so much a training as a pair of hands for a professor. I think it's unforgivable for a professor not to allow students to make mistakes, to think out their own answers to problems. Give them a problem. I know students who have gone through a year working on a single reaction that is in a multi-step total synthesis. To me, I don't know that that's necessarily a training for someone to learn how to think a problem through, or how to tackle problems—particularly in some of these big schools, where they have thirty graduate students.

How do we look for them here? You have to depend a lot on people giving you their opinions. Particularly when you're hiring, try to get people who've had postdoc experience so that you can see whether there's any trend, and this sort of thing. It's not a simple thing. You have to think very carefully of the questions you might ask them. It's not so easy.

BOHNING: You're not going to ask how many ways they know how to synthesize aldehydes.

LOS: No, not at all. [laughter]

BOHNING: At the time that you won the National Medal of Technology, which was a year or so ago now, I was struck by the massive amount of publicity that was given to that by the agricultural community. How did you react to that?

LOS: For more than one reason, I was amazed and so happy that somebody in agriculture received this award. Agriculture, particularly the agrochemical industry, has been such a target, in many ways. You know—we pollute; we poison; we do all the bad things. Yet in this particular instance, we have been recognized. Of course, I very much include Dr. George Levitt and the DuPont efforts here.

I think it's an indication—or maybe, it's a recognition—that yes, you have to use chemicals if we're going to feed all these people and do it efficiently, and not use up all the land that's left. But we can do it in a way that's not very harmful, if harmful at all. Information from many companies and the agricultural industry has indicated that there are other ways that you can achieve what you want to achieve, and that you can achieve them in essentially a benign way. There are many different ways now that people are looking for active molecules. They are gearing up, for instance, also in biological methods.

I think that has probably had an effect on how we do things—maybe not the award itself, but what the award was given for. I think people realize now that yes, there are targets that are exclusive, or unique rather, to plants, that these new products are used in such small quantities and are so non-toxic that they have such a minuscule effect on anything else—and that yes, we can do these things in this way. I think that's really gratifying.

Things are changing. I mean, now the regulatory authorities are saying, "You show us that you have a product that's like this, and we will put it on a fast track for registration. Instead of the eight years, we'll push it through a lot faster than that." There have been consequences to this that I think are really far-reaching. That's probably one of the best things that I think has come out of this.

BOHNING: Well, I've come to the end of my list of questions. Bernadette, do you have anything that you would like to add?

McNULTY: No, I believe you've pretty well covered all of my areas.

BOHNING: Is there anything you'd like to add that we haven't covered?

LOS: Let's see if I had anything noted yet among my notes at all here. No, I think that sounds right.

McNULTY: Did any of your children go into the sciences?

LOS: You would have to ask that. [laughter] No. The closest I came to it is that my daughter is a nurse. My eldest son, he's actually a very good mathematician, and I thought he was going to go into chemical engineering. But he switched to business, and he's in the stock market and things like that now. No, I'm afraid not.

BOHNING: That, by the way, is not unusual.

LOS: Isn't it? No, I didn't know.

BOHNING: That's one thing we had looked at, over a number of interviews—not just this project, but other interviews as well. It is very unusual for chemists, particularly, to have offspring who are chemists. It is not the norm, but rather unusual.

LOS: My wife would probably say that I turned them off chemistry in many ways, inadvertently—because they would do chemistry, and if they had a problem, they would come to me. My wife would say, "You'd look at it, and it would be so trivial to you. You'd wonder why they couldn't understand it, and you didn't have the patience to get down to their level." I can now. [laughter] I don't know whether that also has colored their perceptions or not. I really didn't have the patience with them—you know, "It's so <u>obvious</u>." [laughter]

BOHNING: Some people might say that the setup for an academic chemist may be responsible for that phenomenon, at least in the academic arena. An academic chemist can rarely spend any time at home, because keeping his lab and his group and everything going is really an almost around-the-clock function. His children may then say, "I don't want to have to do all of that." [laughter]

LOS: That's true. That's true.

BOHNING: The one outstanding exception I know of is the family of Jerome and Isabella Karle, the Nobel laureates (9).

LOS: Yes, yes.

BOHNING: They have three daughters, all of whom are scientists. But the daughters grew up with a mother who was also an accomplished scientist. Whenever Jerome and Isabella Karle traveled to meetings, the children went with them. They met all of these wonderful people, and other scientists, also. Isabella kept up with her work, but raised the family as well. I think theirs was a much different situation than usual, because both the father and the mother were scientists. Additionally, the mother and father have a tremendous relationship. So I think the whole thing is a very interesting picture.

LOS: Yes.

BOHNING: Of course, in the case of the Polanyis, the son [Michael] won the Nobel Prize, but the father [Michel] did not. [laughter]

LOS: That's right.

BOHNING: However, the norm is that scientists' children, chemists' in particular, do <u>not</u> follow in their parents' footsteps.

LOS: That's interesting. Herbert C. Brown, his son [Charles A. Brown] is a chemist.

BOHNING: Yes, that's right. I interviewed him for this project back in November at Purdue (10).

LOS: Oh, you did? Yes.

BOHNING: It was very interesting.

LOS: What's the son doing? I don't follow chemistry as much as I used to, but I haven't seen

him. Is he in the academic arena?

BOHNING: He was, yes. I don't know if he still is. We didn't talk about Herbert Brown's son that much. He was an academic chemist, but I don't know if he still is or what he's doing now.

LOS: Yes.

BOHNING: H. C. Brown has approximately eleven hundred publications. More than half of these have been published since he's retired. However, in his area, every reaction is a new molecule. When he gets into one of these areas, every experiment is another molecule and another publication. They're all new. He doesn't have to worry about patents or things like that.

LOS: No. That's been good though, and it's still exciting. I mean, there's still a tremendous amount going on.

BOHNING: Well, I think that's one of the keys, to find it still exciting.

LOS: Oh gosh, yes. To get a phone call from somebody, "Come down and have a look at this." You know when there's a real breakthrough, too. I mean, it's pretty obvious.

BOHNING: Well, on that note, I thank you very much for spending the afternoon with us.

LOS: I've enjoyed it.

McNULTY: Thank you again.

[END OF TAPE, SIDE 7]

[END OF INTERVIEW]

NOTES

1. G. O. Aspinall, M. E. Carter, and M. Los, "The 1:4-Lactone of (±)2:4-Dihydroxy-2-hydroxymethylbutanoic Acid, A New Saccharinolactone," *Chemistry and Industry* (1955): 1553.

   G. O. Aspinall, M. E. Carter, and M. Los, "Degradation of Xylobiose and Xylotriose by Alkali," *Journal of the Chemical Society* (1956): 4807.

2. M. Los, J. P. Saxena, and W. H. Stafford, "Heterocyclic Analogues of Azulene," *Proceedings of the Chemical Society* (1957): 352.

   W. H. Stafford, M. Los, and N. Thomson, "Reduction of Azo Compounds with Hydrazine," *Chemistry and Industry* (1956): 1277.

3. Marinus Los, "Researchers Need Freedom to Pursue Anomalies," *Chemtech* (1995): 19.

4. Sir John W. Cornforth, "The Trouble with Synthesis," *Aldrichemica Acta*, 27 (1994): 71.

5. Roy J. Plunkett, interview by James J. Bohning in New York and Philadelphia, 14 April and 27 May 1986 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript #0037).

6. O. E. Edwards, M. Los, and L. Marion, "Isolycoctonine and the Structure of Hydroxylycoctonine Salts," *Proceedings of the Chemical Society*, 192 (1959):192.

   O. E. Edwards, M. Los, and L. Marion, "Hydroxylycoctonine," *Canadian Journal of Chemistry*, 37 (1959): 1966.

7. M. Los and A. G. Mighell, "Acid-Catalyzed Rearrangement of 4,4a,5,6,7,8-Hexahydro-5-Hydroxy-4a-Methyl-2(3H)-Naphthalenone," *Tetrahedron*, 21 (1965): 2297.

   J. J. Hand and M. Los, "Fragmentation of a 6-Hydroxybicyclo(3,2,1)Octan-8-One," *Chemical Communications* (1969): 673.

   D. J. France, J. J. Hand, and M. Los, "Total Synthesis of Modified Steroids. I. 8-beta-Methyl-D-Homo-B-Norestranes," *Tetrahedron*, 25 (1969): 4011.

   D. J. France and M. Los, "The Direct Formation of a cis-Bromohydrin from an 8-beta-Methylestrane Derivative," *Chemical Communications* (1969): 1513.

   D. J. France, J. J. Hand, and M. Los, "Total Synthesis of Modified Steroids. II. 8-beta-Methyl-D-Homoestranes," *Journal of Organic Chemistry*, 35 (1970): 468.

8. M. Los, C. A. Kust, G. Lamb, and R. E. Diehl, “Phthalimides as Plant Growth Regulators,” *Horticultural Science*, 15 (1980): 22.

9. Isabella and Jerome Karle, interview by James J. Bohning and David K. Van Keuren at the Naval Research Laboratory, 26 February 1987, 15 June 1987, and 9 September 1987 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript #0066).

10. Herbert C. Brown, interview by James J. Bohning at Purdue University, 11 November 1994 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript #0117).

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