CHEMICAL HERITAGE FOUNDATION

# MIGUEL ANGEL ONDETTI

Transcript of an Interview
Conducted by

James J. Bohning

at

Princeton, New Jersey

on

12 January 1995

(With Subsequent Corrections and Additions)

ACKNOWLEDGEMENT

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MIGUEL ANGEL ONDETTI

1930 Born in Buenos Aires, Argentina, on 14 May

## Education

1955 Licentiate, chemistry, University of Buenos Aires
1957 Ph.D., organic chemistry, University of Buenos Aires

## Professional Experience

1948-1957 Bookkeeper, Department of Energy, Argentina Government
1957-1960 Professor, Catholic Institute for Teachers
1957-1960 Instructor, University of Buenos Aires

The Squibb Institute for Medical Research, Argentina
1957-1960 Senior Research Chemist

The Squibb Institute for Medical Research, New Jersey
1960-1966 Senior Research Chemist
1966-1973 Research Group Leader, Peptide Synthesis
1973-1976 Section Head, Peptides, Steroids, and Antibiotic Research
1976-1980 Director, Department of Biological Chemistry
1980-1981 Associate Director, Chemical and Microbiological Research
1981-1983 Vice President, Basic Research
1984-1989 Vice President of Research, Cardiopulmonary Diseases
1989-1990 Senior Vice President of Research, Cardiovascular Diseases
1990-1991 Senior Vice President, Cardiovascular and Metabolic Diseases
1991 Retired

## Honors

1981 Alfred Burger Award in Medicinal Chemistry, American Chemical Society
1983 Thomas Alva Edison Patent Award, Research and Development Council, New Jersey
1983 Ciba Award for Hypertension Research, American Heart Association, Council on High Blood Pressure Research
1986 Chairmanís Edward Robinson Squibb Award, E. R. Squibb & Sons, Inc.
1988 Award for Contributions to Medical Science, Pharmaceutical Manufacturers Association and National Health Council
1988 Inventor of the Year Award, New Jersey Inventors Congress
1991 Perkin Medal, Society of Chemical Industry, American Section
1991 Warren Alpert Foundation Prize, Harvard Medical School
1992 Award for Creative Invention, American Chemical Society
1992 Herman Bloch Award for Scientific Excellence in Industry, University of Chicago

ABSTRACT

Miguel A. Ondetti begins this interview by describing his parents' immigrant background and work in Argentina, early interests in chemistry, and education at vocational school in Buenos Aires. Upon high school graduation, Ondetti began work as a bookkeeper, continuing studies at night to meet university entrance requirements. He began chemistry coursework at the University of Buenos Aires while supporting himself with accounting work for the government. Her he describes his broad training in chemistry, Argentina's political climate, and his Ph.D. scholarship and carbohydrates research for V. Deulofeu at The Squibb Institute. Upon graduation in 1957, Ondetti explored other opportunities before accepting a position with Squibb's alkaloid isolation group, where he remained until 1960, when after much consideration he accepted a job with Squibb, New Jersey. In New Jersey, Ondetti worked in the peptide chemistry group, synthesizing the nonapeptide bradykinin under M. Bodanszky, with whom he co-wrote *Peptide Synthesis*. He discusses adjusting to life and work in the U.S., and his advancement in the peptide synthesis field and promotion to group head when Bodanszky pursued a career in academia. Ondetti was part of a group effort to synthesize gastrointestinal hormones, particularly secretin, a peptide amide that stimulates the pancreas to secrete bicarbonate and water. While Bodanszky pursued stepwise synthesis of the peptide, Ondetti worked with E. Sabo on fragment condensation approach was used to obtain synthetic secretin for clinical studies, the results of which discouraged further development. Next Ondetti worked with Sabo to synthesize cholecystokinin, which stimulates contraction of the gall bladder and secretion of enzymes from the pancreas. Here he describes problems with the synthetic peptide's development, and its eventual use as a diagnostic agent; also discussed is the importance of his relationships with Sabo and Z. Horovitz. In 1967, A. D. Welch became Squibb's president, and changes in company research agendas led Ondetti to work on peptidase inhibitors. Ondetti describes acquiring venom for isolation of enzyme inhibitors, isolating phospholipase inhibitor, and learning to isolate and sequence peptides in competition with researchers at Brookhaven National Laboratories. In 1973, for practical reasons, Squibb's angiotensin converting enzyme [ACE] inhibitor work officially ended, but Ondetti's interest in the subject continued; prompted by discoveries of L. D. Byers and R. Wolfenden and interactions with D. Cushman, Ondetti decided to pursue synthesis of succinyl-L-proline, which was found to potentiate the contractile activity; after continued research, this work evolved into captopril. Here Ondetti describes human trials of this drug, problems with FDA approval, the effectiveness of captopril for hypertension treatment, and follow-up research leading to new therapeutic agents. The interviews closes with Ondetti's reflections on the fields of chemistry and pharmaceutical research, and his own career; highlighted are notions of success and rewards, collaboration between industry and academia, rational drug design, and leadership.

## INTERVIEWER

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

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INTERVIEWER: James J. Bohning

LOCATION: Princeton, New Jersey

DATE: 12 January 1995

BOHNING: Dr. Ondetti, I know you were born in Buenos Aires on May 14, 1930. Could you tell me something about your father and mother, and your family background?

ONDETTI: Yes. My father had immigrated to Argentina. My father's family was originally from Italy, but he was actually born in Paris, because the family had immigrated first to France and from there to Argentina. My mother also came from an immigrant family, but she had been born in Argentina. So the background is Italian, but I will say first generation Argentinean.

BOHNING: What did your father do?

ONDETTI: Well, my father had a craft, in the sense that he made garden furniture out of cement, but in imitation of tree trunks. I really don't know how this originated. My grandfather did it too. But unfortunately, when I was born—it was just at the beginning of the Depression—all these things came to naught, first of all because this was kind of not a very important commodity, and also because there was a change in the way that the people were living in Buenos Aires. They were migrating from large houses into smaller houses, or apartments where garden furniture was out of place. What my father was doing was really sort of dying down, in the sense that the demand was less and less.

I remember my father still working with it from my very early childhood. It was a memory that somehow got burned in my mind, the carve work. By the middle 1930s he was already looking for another type of job, and he finally found it by the early 1940s. He got a job as a night watchman for one of the big companies in Argentina, and that's what he did until he retired in the middle 1950s or so. My mother was a housewife. She spent all her time with us.

BOHNING: How many children were there?

ONDETTI: We are only two brothers. My brother is two years older than I am. He still lives in Argentina. He's an accountant, and that was actually what I was supposed to become. Since they were difficult times, from the very beginning our vocations were sort of oriented towards obtaining a job very early. So we went to what in Argentina is called a commercial high school. It's kind of a vocational high school that it is specifically oriented to train people who'll become bookkeepers and then eventually accountants—except that to really get a degree of certified public accountant, you have to go to the university. But when you finish the high school, you get a degree they call—I don't know what the correct translation would be—a bookkeeper. That's what I did.

When I was sixteen years old, I actually got a job. So I had to finish school going to night school. In Argentina, you could do all your high school either during the day, or at night for people who had to work during the day. I finished at night. But then, I was already interested in being a scientist, I think probably from the year that I started high school. It probably was on my mind back to those years.

I must say I wanted to be a chemist. Well, you see, I wanted to be a scientist very early, in the very early teens or even before that, through my readings at the library. I used to get books or borrow books for school from a public neighborhood library, and they had a very good collection of all types of books. That's the reason, among other things, why I became interested in being a scientist.

But the big surprise was that when I finished this vocational high school or this commercial high school, the university refused to accept me. They said I didn't have what at that time in Argentina was called the baccalaureate. It was obtained at a high school that was specialized for people who wanted to go into academic training. They said that without that degree, they would not take me, that I had to go back and do the high school again, but in the academic orientation.

So I had to do that. But I didn't do that in the regular fashion; I did it as a free student, for a while. You were allowed, if you wanted to—I guess everybody could do that—register as a free student instead of going to school, and at the end of the year, pass the exams of all the subjects. So I had to go. It was very, very lengthy. They compared what I had studied for bookkeeping with what I had to study for an academic high school, and they said, "You have to take thirty exams," so I did all that. It took me two years. I got the degree. Then I had to take the entrance examination like everybody else, and finally I was admitted into the school of chemistry in Argentina.

BOHNING: Up to this point, you had no real laboratory experience in chemistry.

ONDETTI: No, none. Well, when we were very young my brother and I set up a chemistry lab at home, as many people do. [laughter] The only thing I remember is getting an electric shock when we were trying to do an electrolysis of copper sulfate. [laughter] Like a stupid dumb ass, when we were working with the electrolysis—to get this thing covered with copper, I said to my brother, "Juan, let's try it with a regular knife." I put the knife inside the beaker and bang, I got a very big shock. [laughter]

I was interested in doing experiments, but I guess didn't know how. I must say, it was one of the moments of doubt when I really got into the university and I had to go to do real laboratory practice. Of course by that time I was also working for a living.

BOHNING: What were you doing when you were working?

ONDETTI: I had to use my training as a bookkeeper. I worked in several places, but I usually would be working with public accountants and taking care of the bookkeeping. At that time, when I finally entered the university, I was at one of the government offices, the Department of Energy. I was in the office of accounting in charge of the payroll.

It was very convenient, because the government offices used to work seven hours straight. People would come at one and leave at eight, or something like that, but I managed to work in the other shift, to work from 7:00 a.m. to 2:00. I said, "I have two hours to overlap with the rest of the people, and we can exchange information there." It was a great advantage to me because in the afternoon, I had to go to classes. I had to do the lab work. You could miss the theory, but you couldn't miss the lab. I had to do all the labs in the afternoon. Working in the morning I had the double advantage, not only that I could go and do the labs in the afternoon, but in the morning there were very few people. Whenever I had my work done, I could study.

Coming back to your question, my first real lab experience was at the university. For a moment, it was a little bit of a shock because it was quite different from what I was used to. [laughter] But still, I never really hesitated.

My basic interest was always biology, but early in my readings, I realized that you couldn't really understand biology unless you knew chemistry. Now it's obvious to everyone, but some people, even in spite of that, don't like chemistry enough, so they stick to biology. They figure they have enough with a couple years of chemistry. I got very interested in chemistry, but I always had a sort of biological orientation in the back of my mind.

In Argentina the higher education is patterned after the French, after the continental European style, not after the English like the Americans are. There's no, quote-unquote, "college," so you go directly from the high school to the university for the specific career you have chosen—chemistry, medicine, et cetera. High school is much more extensive and deeper

than in this country. From there you go directly into your professional training. Once you get into the chemistry like I did, you only have to study mathematics, physics, and chemistry.

I went to school in the 1950s, in the early 1950s. There was another situation that was quite different from nowadays. Teaching at the school of chemistry was very, very general. There was only one school of chemistry, and the graduates had to be prepared to go either into the paint industry, or into oil companies, or they had to go into the synthetic pharmaceutical industry, or they had to go into doing clinical analysis, or doing food analysis or whatever.

We had a program that had five years of just studying different types of chemistry. In those five years, you had to learn everything from inorganic chemistry all the way to biological chemistry, going through inorganic analysis, clinical analysis, food analysis, biological chemistry, and physical chemistry—the whole gamut. By the time I finished—it was in 1955 or thereabouts—they had changed the study plan. They had decided that in the fourth year, you had to pick an orientation. I was probably one of the last to receive a degree that was very general.

This very broad background was, I think, very good for me. During the last year of my career and for just a brief period of time, I thought I was going to become a chemical engineer. That was the first offering I got to really specialize. I did like it. I remember, we used to use American books on unit operations, and I thought it was a lot of fun. So I said, "Gee, this is what I should do."

When you finished the five years, you got a degree that was called *Licenciado*. The *Licenciatura* meant that you had all the subjects that you needed to know; it is more or less like what in this country would be a master's degree. But if you wanted to go for a doctorate degree, you had to actually, like here, find some advisor and someplace to work on your thesis.

I was then still working as an accountant, or really as a bookkeeper. I didn't know what I was going to do in terms of a thesis or if I was going to switch into really working in chemistry, when a friend of mine who was also a classmate at the university told me of this opportunity for a scholarship for training in research that was offered by Squibb.

That was a very difficult time. It was at the end of the Peron regime in Argentina. There was a great upheaval in higher education, because the students had been very angry about this type of politics. The university had been politicized to such an extent that all the good teachers, the good professors, had left the country or left for private jobs.

Actually, one of the leaders of organic chemistry in Argentina, Professor Venancio Deulofeu, had left the university to become the head of chemistry at Squibb. Squibb had a very particular position in Argentina, because during the time of Peron, they were given the monopoly of making antibiotics in Argentina. They were the only company that had been authorized, or given a license by the government, to make antibiotics.

BOHNING: Had Squibb been there before Peron, or did they come during his regime?

ONDETTI: They came during the time of Peron, in the early 1950s. They set up a very large fermentation plant. It was the first in Argentina. They made, of course, penicillin, and they made a lot of money. But Peron had established a regulation that they could not export all the money that they made. There were regulations that they had to invest part of it in Argentina.

So they agreed to set up a research lab, and they built one of the best research labs available at that time in Argentina; they had instrumentation that was not available any place. They did research in antibiotics and other natural products. They had managed—first because they had the labs, and second because of this political upheaval in the university—to get some of the best professors of the university working there as directors.

Dr. Deulofeu had been my professor of organic chemistry and was really one of the leaders in organic chemistry in Argentina. He was very well known worldwide, had studied with Heinrich Wieland in Germany, and then with [Edward A.] Doisy in St. Louis. So he had a great reputation. He was a man of personal fortune. At that time, he was the head of chemistry research at Squibb. His boss, who was the head of the whole institute, was Dr. Alfredo Sordelli, a very well known microbiologist and also a man of worldwide reputation. Together they had set up a first-rate research institute.

They had established grants or scholarships for training in scientific research, so I applied for one of them. To make a long story short, I got it. I had very good grades in school, so I got the scholarship. But since I've been always a sort of pessimistic kind of person, I decided not to leave the government, but to ask for a leave of absence without pay. They gave it to me.

I went to Squibb and for a year I worked as a research chemist at the Squibb Institute for Medical Research—Argentina's branch. Scholarship-holding researchers were not actually considered employees of the company. As a matter of fact, the year that I worked there with a scholarship never counted on my record. I worked exclusively on my thesis. I mean, I didn't have any obligations to the company.

Deulofeu was interested in natural products, and his basic research was either on carbohydrates or on alkaloids. He asked me to work on carbohydrates. That I hated. [laughter] But of course, I wasn't in a position to choose a topic, so I worked on carbohydrates. He had worked with some of the great carbohydrate chemists in Germany, and so it was a very deep-seated tradition to work in carbohydrates in his group. I knew that all that I was doing was just working on the thesis (1).

I had a very hard year working there. Then at the end, he offered me a job with Squibb. I turned it down, because Deulofeu was an outstanding scientist, but he was very cold in the interaction with his collaborators. I mean, you never knew how you stood with him. I thought I had enough of this; I was willing to try something else. I left, and he understood, but I still had to write the dissertation for the doctoral thesis, which kept me in contact with him.

I got a job with another chemical company in development, but I lasted only one week. I soon realized how spoiled I had been by this year of doing research in a very outstanding lab. When I got into this industrial lab everybody was only interested in what were the requests of the manufacturing plant, and I just couldn't take it. In one week, I said, "Now, if this is going to be work in chemistry, I'll do something else."

Fortunately, as I told you, I had not resigned from my job as a bookkeeper with the government, so I went back. I still had a job but I was very, very depressed. I thought, "Well gee, I spent five or six years doing chemistry. What am I going to do now?" It was a very sad time.

Fortunately, I had to write a thesis, so I needed to see Dr. Deulofeu just to show him what I was doing. I finally decided to swallow my pride and said to him, "Do you still have the job that you offered me?" [laughter] He said, "No, I don't. But I have another one." "Oh," I said, "well, I'll take it." I did not even ask what the salary was. [laughter] I don't know whether it was the same job or it wasn't.

It was 1957 then. I became an employee of Squibb. I knew, because I had been in touch with the people working there, that I wasn't going to work on carbohydrates. If you can set your mind back to the 1950s, it was the time when everybody was enamored with natural products. Ciba had made a tremendous success out of reserpine, an alkaloid antihypertensive agent isolated from rauwolfia serpentina. Since in Argentina there is a great wealth of plants—because the northern part of Argentina has a subtropical climate—Squibb had botanists and they would send samples to us to look for alkaloids. We would extract them and determine what kind of alkaloids were there, and whether they were new or they were not. I mean, we had to extract them, crystallize them, and look a little bit into the structure to determine whether we had a new alkaloid or not.

If we were successful and we had a new alkaloid, we would send samples to the States to be tested, because, really, The Squibb Research Institute in Argentina was a branch of The Squibb Research Institute in the States. At that time, Squibb had the research in New Brunswick, New Jersey, where the manufacturing plant was, so we functioned, really, very much in relation with them.

Besides the alkaloid isolation group, Squibb also had a very important antibiotic screening program. That was probably the most important project. In Argentina I never worked in antibiotics.

[END OF TAPE, SIDE 1]

ONDETTI: That was my work for, I guess, 1957 until 1960. Periodically, we would get visits from the research people here. Particularly, the head of the institute in the U.S. would come and discuss the research. I only saw these people when they were given the usual regular tour of the labs. We used those visits to practice our English.

At that time, the head of the Squibb Institute for Medical Research was a microbiologist. His name was Asger F. Langlykke. He would, as I say, come once a year to Argentina. On one of those visits, I got called by the secretary of Dr. Deulofeu. By that time, Deulofeu had become the head of the institute because Dr. Sordelli had retired. They asked me to go to his office.

Now, normally, that was kind of unusual, because Deulofeu was a sort of a peripatetic researcher. He would go to the labs; you never had to go to his office. He would come to the labs and see what you were doing, and ask you how things were going, and so on and so forth. So it was kind of strange that he would call me to his office.

I went. Langlykke was there. Deulofeu said, "Dr. Langlykke wants to talk to you," and he left. Langlykke didn't waste a lot of time in introductions. He said, "We'd like you to come and work in the States, in the labs in New Brunswick." "Gee," I said. I think he already knew that I had been accepted by The British Council as a recipient of a scholarship for training in the U.K.

The British Council, I think, is all over the world. They promote the educational relations between different countries and the U.K. They provide grants, and you select the academic place in the U.K. where you want to study. Deulofeu had got me accepted to work with a Professor A. J. Birch, a famous Australian chemist who was then in Manchester. I had to wait until September for the beginning of the new academic year.

I explained all this to Dr Langlykke and he said, "Oh, we'll be glad to wait for you. I mean, you can go to Manchester. When you finish there, you come to the States." But it was obvious that The British Council was not going to be very happy about that. I told them that I was going to go from the U.K. to the States. They said, "No, scholarships are for training people who go back to Argentina." So if I wanted the job in the U.S., I had to resign the scholarship. The funny thing I always remember about that interview with Langlykke was that it might have been like a Thursday or a Wednesday. I told him, "When do you want me to decide?" He said, "Well, I have to know your decision before I leave." I said, "When are you leaving?" "The day after tomorrow." [laughter] "Wow," I said. "How long would I have to stay there?" He said, "As long you want. We are offering you a permanent job."

I was married and my wife Josephine had already gotten her degree. She was a dentist. She did not have a private office, but she was working in different hospitals. She was an only child, so leaving the country was a very hard and difficult decision to make. I called her out because I had to decide quickly; I could not wait. We got together, I remember, in a coffee house in downtown Buenos Aires, and we talked about it for as long as we could since I had an evening job as instructor at the University. We thought, "What the heck." They were paying for everything, and if we did not like it, we could always come back.

It was wishful thinking. It's not that easy to go back, as we learned later on. But we didn't have any children at that time, so we said, "Well, if we don't take advantage of this opportunity now, we'll never do it." We knew that we could choose to go to England with The British Council scholarship, but the British, with their usual carefulness, were going to make me sign a waiver that I would be wholly responsible for my wife, if I took my wife to the U.K. They were not going to pay for her trip, her expenses, or even her medical insurance. They even advised me not to take her along.

On the other hand, Squibb was paying all our expenses, including the moving expenses for all our furniture. At that time, I remember, they offered me a salary of seventy-eight hundred dollars a year. Now it looks like a pitiful amount of money. In 1960, it was nice. [laughter] It was March 1960. It was not a bad salary.

When I got here, I got a raise right away, on the spot. They told me, "No, no, we are not going to pay you seventy-eight hundred dollars. We will pay you eighty-five hundred dollars." Of course, I didn't object. [laughter] In 1960, it was not a bad salary. I was looking at the figures today in the newspaper, the figures comparing inflation between 1960 and now. A 1960s salary has increased like anywhere between six and seven times. So it would have been now fifty, sixty thousand dollars. When I retired, in 1991, we were paying incoming Ph.D.s that amount. Now they might pay even more than that.

BOHNING: How did that compare with your salary in Argentina?

ONDETTI: It might have been six or seven times higher, but there was no comparison. In Argentina, I couldn't buy a car. In Argentina, I couldn't have a telephone—not because it was expensive, but because you had to apply for a telephone and wait two or three years. We couldn't get married for two years because we couldn't find an apartment. Here, in New Jersey, I could find an apartment in a day. A visiting scientist from Squibb New Jersey showed me the newspaper with lots of apartments for rent. I said, "But this is unreal. I mean, don't you have to pay money to the previous occupant, like in Argentina?" "No," he said, "only one month's deposit to the landlord, and that's it." I mean, it was the difference between day and night.

In Argentina at that time, I had the job at Squibb and two other jobs to really make a decent living. I was an instructor in organic chemistry at the university, and I was professor of organic chemistry at an institute for high school teachers. I worked very hard—I mean, I never got home before nine o'clock—and I worked Saturdays too. Commuting alone would take two or three hours a day. When I got here, even if I really wanted to work hard, I would get home at six o'clock. [laughter] They also told me, "Oh yes, you can buy a car the moment you step into the country." I got a used car, two months after I arrived, for two hundred dollars.

So it was difficult to turn down such an offer, except for family reasons. For a moment I almost got cold feet, because I talked to Deulofeu. As I say, he had stepped out when I talked to Langlykke. But later on I talked to him, and I said, "You know about their offer." He said, "Yes, yes, I know. I recommended you, so I know that he offered you a job." But he added, "Well, you know, you have to make your own decision. This not my decision to make." If I went to England with The British Council scholarship and then came back, Squibb Argentina was not going to have a job waiting for me. I would have had to go to the university.

Even though the politics had improved in Argentina after Peron, there were not that many possibilities. He said, "Well, I'm sure that you can eventually get a job as a professor." In Argentina the professorial positions are filled by public contest, so you have to apply whenever one becomes available. He said maybe there would be one open after I returned, but he did not know. Well, I mean, it was obvious that the future in Argentina was not that clear.

So we decided to go, and we arrived here by the end of July 1960. I didn't know until probably a month before in what particular lab I was going to work, because Langlykke, as I said, was head of the institute, but I was going to work within the department of chemistry. I didn't even have any idea if the people in chemistry knew that a job had been offered to me. Two people were offered jobs by Langlykke, myself and another fellow who came later. He couldn't enter the U.S. at that time because he had been a postdoc with R. B. Woodward at Harvard, and according to the immigration law, he had to stay out of the country two years. So he accepted the job and came to the States in 1963, but he didn't stay at Squibb too long. He left in 1965 to join Coca-Cola in Atlanta.

BOHNING: What about language?

ONDETTI: Well, that was one of the major fears that I had. We had English in high school, and then we took private lessons. A lot of the books that we used in chemistry were not translated, and I had to be able to read English. I mean, to understand a large part of the original chemical literature you had to read English fairly well, except that the English of chemistry is not that demanding in terms of English literacy.

We had a private teacher who was a British fellow, a retired bank employee. We had to change to an American teacher when we decided we were coming to the U.S. instead. [laughter] We found a native American lady who was a very good teacher, but it was a big shock to change from British to American English. When I came here, it took me a while to get adjusted to speaking American English full time. I soon found out that it really makes a big difference if you're in an environment of people who are well educated. They make allowances for your accent and limited fluency. The big shock for me was to go out on the street and talk to people, where they don't make allowances. Even today, sometimes it annoys me when people say, "What?" [laughter]

It was hard to adjust to a new country. It was not so at the lab. It was a very nice environment. Besides, as it happened, I came to the peptide chemistry group, where the head of the group was a Hungarian refugee. So they were all acquainted with foreigners. [laughter]

The real big difference for me had nothing to do with language. Working for Squibb in Argentina was like a world apart from working here. I mean, in Argentina, we had to send most of the stuff to be analyzed to the States and wait several weeks for the results. Here, we could walk around the corner and say, "This is a sample. Give me the percentage composition of carbon, nitrogen, hydrogen, sulfur, et cetera," and we would have the results in one or two days.

Another big difference was the field of chemical research I was going to work in. The head of the department of chemistry at that time was Dr. Fried, Joseph Fried, who had made quite a reputation for himself in steroids. I knew him because he had visited Argentina. I thought that I was going to be in steroids or something like that, because at that time that was the largest research effort in Squibb. But no, they put me in peptides. That was a brand-new research group for Squibb and for most of the other pharmaceutical companies.

We were a little bit segregated from the rest of the chemistry department. Peptide chemistry is a bonafide part of synthetic organic chemistry, but the techniques are somewhat different from those used in other areas of synthetic organic chemistry. For many chemists peptide synthesis is rather repetitive and not very interesting. Originally I felt the same way, but I grew to like it because in peptide chemistry I had a very large contact with the biologists, and that is what I always liked. So, in retrospect, I am happy that that's what they asked me to do.

BOHNING: [Miklos] Bodanszky was head of the group, is that correct?

ONDETTI: Yes.

BOHNING: What kind of a person was he to work for?

ONDETTI: Well, Bodanszky is now retired, and he came back to live in Princeton. He lives not far from here. He's an outstanding gentleman. He's very much in the old European style of scientist, with a very broad education. He had been trained as an industrial chemist. He had worked in the chemistry of peptides from the very beginning. He came to Squibb from du Vigneaud's lab in New York, one of the pioneering groups in peptide synthesis in America. He escaped Hungary in 1956. He got a job with du Vigneaud because he had already worked on peptides in Hungary, and he worked with du Vigneaud until he came to Squibb.

He was very willing to train and teach people. In 1967 he left Squibb for Case Western Reserve University. He had always wanted to be an academician, a professor. Working with him was a very good training ground for me. He paid a lot of attention to my grounding in peptide synthesis. This area was new to me.

Bodanszky is in some ways a hard man to work with, because he's very strongly opinionated. He had very definitive views on peptide synthesis methodology, because he pioneered new methods in peptide synthesis. Even to this day, he's always resentful when people don't give him proper credit for his contributions. But for me he was a tremendous help, because as I say, he's very knowledgeable. He's not only knowledgeable in peptide chemistry, but also in medicinal chemistry in general.

Being a foreigner like I was, it made us a little bit closer than we would have been otherwise. But it was obvious that he didn't like the industrial environment that much, so very soon he was already looking for other positions. If you remember, the 1960s were a time when there was a lot of money from the government to create centers of excellence in academia, and many professorial jobs were created.

Bodanszky was a friend of a George Olah, and Olah had moved from Canada to become the head of the department of chemistry at Case Western Reserve University. I believe that Olah was very influential in getting Bodanszky this offer to be a professor of chemistry there, and he left. Besides, Bodanszky was very well known in this brand-new field of peptide synthesis. He had been asked by John Wiley to write a book on peptide synthesis, and he offered me co-authorship (2).

So he was very helpful to me, to make myself known in the field. Through him I was soon invited to participate and organize some of the first peptide meetings in this country.

I don't know if you're very familiar with peptide synthesis, but peptide synthesis is kind of a narrow, very limited field. I mean, the kind of chemical techniques that you can use are very limited, because in essence, you spend all your life making amide bonds. Once that is said, you have to realize that due to the variety of amino acid involved in these amide bonds, the variety of chemical problems is quite extensive. It gives you a feeling of confinement,

claustrophobia, in the sense that if you're a synthetic organic chemist, you feel that you'd like to experiment with other techniques once in a while. [laughter]

I don't know. If I look back and think, maybe if Bodanszky would have stayed at Squibb, maybe I would have looked for another job to be able to grow more independent. But then, when he left, it was not a problem anymore, because then I was offered the position of head of the group. I think I was probably at the right place at the right time.

As I say, when we decided to come here, we said, "We are going to stay and see how it works out. If not, we can go back." In the interim we made a number of new acquaintances. You know, when you're brand new in a country, you get in touch with people who are also new, who just came here. We were living then in New Brunswick, where Rutgers University is. We met a number of very interesting Spanish-speaking people who were teaching there. We got to meet a lot of people who were very happy being here temporarily, but they said, "No, you don't want to stay here."

Then we slowly drifted away from that kind of group and got to know more people who were either Americans or foreigners who had immigrated here to stay. We grew to enjoy living in this country. Slowly, the thinking of our going back was beginning to fade. The children were born. My parents died, and slowly our links to Argentina began to weaken.

In 1969, we did have an offer to go back to the school of pharmacy at the university in Buenos Aires as professor of chemistry, but things were not very stable in Argentina in 1969. I did visit there. I was invited a couple of times, but it became obvious to me that it was going to be as hard to get adjusted to living back in Argentina as it had been to adjust to the United States. Besides, I never trusted the political situation in Argentina, and I was right. It was going to get much worse than it was in 1969 before it got better in the 1980s.

In any case, it was a hard decision, because we knew that if we decided not to go back, that would probably be our last chance to return. By that time, we had a house. My position with Squibb was very solid; I was by then the head of the peptide group. We finally decided to stay here.

Only on very few occasions did I entertain the idea of leaving Squibb. It was really never a major concern. I always liked the ups and downs in the pharmaceutical industry. In the 1960s, it was a difficult time. You remember the Kefauver bill that actually created all the machinery of the FDA, which made the registration of new drugs much more cumbersome. When I came, people were taking steroids from the laboratory into clinical research in a couple of months. There was very little toxicology done on them. There were some safety studies but not very extensive. When the new regulation came in, people said that that was the end of research in the pharmaceutical industry. For every new chemical entity to be advanced to clinical studies you had to file an IND [Investigational New Drug] application and carry out a large number of studies, and then file an NDA [New Drug Application]. After a lengthy review

you could get approval for marketing. They said, "You'll never survive that way." Well, most of the pharmaceutical companies managed to survive, and they are doing very well.

The pharmaceutical industry is always changing, and sometimes drastically. I saw a lot of changes, but the motivation for research was always there. I just happen to like that kind of work, in the frontier between chemistry and biology, so I never felt a strong urge to leave.

[END OF TAPE, SIDE 2]

BOHNING: How large was the peptide synthesis group when you joined it?

ONDETTI: When I joined it, we were only three Ph.D.s and two assistants with a B.S. or M.S. We were only five. On and off, we had stayed being five almost to the time that, actually, the company officially decided to get out of peptide synthesis. That was in the early 1970s. It never grew to be a large group.

BOHNING: Why was the decision made to start it in the first place?

ONDETTI: I think the decision was mainly made by Gus Fried, the director of the chemistry department. He was a very progressive and innovative kind of chemist. I think the group started in 1959, just a year before I came. That was a short time after du Vigneaud had gotten the Nobel Prize for the synthesis of oxytocin. People felt that peptides were going to be the new area for drug discovery, like alkaloids and steroids had been before. There was a great deal of interest. It was arguable—there were a number of points against it—but he felt that you had to be in this field. I think it was a reasonable decision. In a sense, synthetic peptides never fulfilled the promise of becoming very important drugs, but they are really very important tools in pharmaceutical or even medical research. I mean, you couldn't really ignore them now.

When I joined the group, the idea was actually to make a drug out of a peptide, so Bodanszky continued to work in oxytocin and vasopressin, like he had done in du Vigneaud's lab. Companies were already selling natural oxytocin, but that was a very small market. The only really large market for peptides was insulin. For a while, we cherished the idea of working on the synthesis of insulin, except that in the 1960s, it was a major undertaking, because insulin is five or six times as large as oxytocin.

We actually started working on insulin. It was in the middle 1960s when the Chinese reported a total synthesis of insulin. That was in the period just before Mao's Red Guards revolution, and soon after that most of the scientists who had been in the lab synthesizing insulin

ended up in the countryside doing all kinds of farm work. [laughter] Many years after that, I met some of them in Shanghai. The synthesis of insulin wasn't a practical proposition at that time. After the Chinese, an American group also published a total synthesis of insulin, but it wasn't reasonable from the commercial point of view. It was about that time that we started a collaboration with the Karolinska Institute, synthesizing gastrointestinal hormones, and actually we made a product out of one of them.

Peptide products have to be given by injection, and in this country this is not considered to be a very reasonable way to administer drugs, except in emergencies. So slowly, pessimism set in and only the companies that had a very strong research base continued. As a matter of fact, by the time Squibb was considering getting out, Merck had already gotten in, and always maintained a very active peptide group. They had a much larger group than we had. A lot of the companies that at that time, in the late 1960s, were involved with peptides, slowly, in one way or the other, left the field. Most of the research in peptides begun in the late 1950s was done by European pharmaceutical companies, like Ciba-Geigy—well, at that time it was only Ciba—Sandoz, Hoffman-La Roche, Schering, AG Bayer, et cetera.

As a matter of fact, when I came to this country, my first need in a new language was not English but German, because most of the chemistry on peptides was published in German. I had to actually take classes in German from a private teacher retired from Rutgers, because I needed to at least be able to read some of the literature. Most of the more important research was published by *Helvetica Chimica Acta* or *Chemische Berichte*. You had to read German to understand some of the experiments, in order to duplicate them.

But slowly, as I say, the pessimism on the future of peptides as drugs set in by the end of the 1960s. Our last big project in peptides was the venom peptides, converting enzyme inhibitors. After that, we drifted between small projects. Then, as it usually happens every four or five years in a pharmaceutical company, there was a reorganization of research and they decided that they didn't want to do any more peptide chemistry, that we should work on antibiotics.

Some people at that time were saying, "Why don't you just quit and go? You have a reputation in the peptide field. You're better off going to a place where you might take that reputation." It just didn't occur to me. I thought it was fun to work on antibiotics. But little did they know that we were eventually going to be working on peptides. [laughter]

BOHNING: Before we get to that point, I'd like to review some of the other things you did. But before we do that, I want to ask you about Merrifield's solid-phase techniques. When did they come in? How did they affect your work?

ONDETTI: Oh yes, that was a very interesting story. At the time when Merrifield published his work—I think his first paper was in 1963 or thereabouts—Bodanszky had hired another Ph.D., Saul Lande, who came from the labs of Klaus Hoffmann in Pittsburgh, also another academic laboratory strong on peptide synthesis.

Saul was an interesting fellow. Later on, he left Squibb to go to Yale University as an assistant professor, and then left to become an M.D. But when he joined our group he was interested in actually making peptides by a technique similar to that of Merrifield, and he tried some things, but Miklos wasn't very keen on that type of research. Miklos had been so strongly grounded into classical organic chemistry that the idea that you would make compounds without purifying the intermediates sounded to him like anathema. He thought that this was one of the stupid things that only American chemists did. [laughter] Saul tried some things, but half-heartedly, without much success.

Then we saw the first paper by Bruce Merrifield (3). It was the synthesis of a pentapeptide—not a great achievement from the point of view of a classical peptide synthesis, but it was a little bit unbelievable as a new approach for larger peptides. But then came the synthesis of bradykinin, and that paper opened quite a few eyes. Bradykinin is a nine amino acid peptide not easy to synthesize by standard procedures. Merrifield showed that the compound he made was not only pure but had the full biological activity of the natural compound, but there was still the concern that solid phase would always lead to mixtures that in many cases could not be purified.

This was the source of considerable discussion at all meetings on peptides. At the beginning of the 1960s, there was already a European peptide symposium that met, I think, every other year. It was very exclusive. Only a very few Americans got invited, because as I say, the largest contribution of peptide synthesis was in the hands of the Europeans, big pharmaceutical companies mostly, and academicians. I guess it was because of a little bit of jealousy, or because of the exclusive policy of this group, that a group of American peptide chemists got together to organize an American Peptide Symposium. As a matter of fact, I was one of them, but I wasn't really the instigator. I eventually became one of the members of the organizing committee. The first one was at Yale. By that time Saul Lande had already left and was at Yale. He offered to have the first American Peptide Symposium there in the summer, when the facilities of the university, dormitories and conference rooms, could be obtained at a low price.

During those meetings there were acrimonious fights between the people who did synthesis by what used to be called solution synthesis or classical synthesis, and solid phase synthesis. There were just endless arguments about whether solid phase could ever become an accepted technique for the synthesis of pure peptides.

Well, the short and long of this was that eventually the technique improved. People began to realize there were shortcomings that had to be overcome, and they worked on them,

and eventually it became an acceptable way of making peptides. Now it has become obvious that there are certain peptides that you couldn't make any other way because it would be very, very laborious. I think even Miklos, now, got convinced. He tried his own variations of the solid phase technique. After he left Squibb, we also started to use it. If you use the proper care you can synthesize pure peptides by solid phase. I mean there were limitations, but those limitations could be overcome. Solid phase made a big difference in peptide synthesis. Yes, it made a big difference.

At that time, you see, there was a big difference between Miklos and myself, in the sense that he was a very strong-in-methodology kind of person. He was very interested in trying new chemistry applied to protection, activation and coupling of amino acids to form peptides. I liked that, but I wasn't that keen on it as much as I was on trying to make biologically active compounds. I was more interested in the end product. I said, "Miklos, okay, I agree that we have to make pure compounds. But once I get it, I don't care how it was made." I mean, I don't care about making it in solution, or by solid phase. There were other questions that we have to deal with in the pharmaceutical industry, such as, "Are peptides useful? Can you make compounds that can be orally absorbed?" We had very extensive discussions on those things, because he was very much a chemist, and for him peptide synthesis was chemistry. The people who used solid phase synthesis were more interested in the biology. Solid phase peptide synthesis, as chemistry, is very tedious because its procedures are repetitive, and that is the reason that it can be and it was eventually fully mechanized

My assistant Emily Sabo was a very good chemist and quickly learned to run solid phase peptide synthesis with a small hand-operated machine. At that time there were no automated machines. She had been an old hand at making steroids, and she used to poke fun at this kind of kitchen chemistry. [laughter] But you could make good peptides with it, if you were careful.

I think the solid phase technique was a great invention. I believe it was proper to give Bruce Merrifield the Nobel Prize. Other people had tried similar approaches, but he took the trouble to perfect it to the point that it could work in everybody's hands. Many details were later modified by other people, but that doesn't change essentially the fact that he made the greatest contribution.

BOHNING: Your first assignment was a synthesis of a nonapeptide. You published two papers, I think in the mid-1960s, on biologically active citrulline peptides (4). The interesting thing is that, once you have the ability to synthesize something like this, you then look at analogues to improve its capabilities. That didn't work, as it happened. It turned out not to be the first time you found that analogues didn't work, or didn't have the same activity as the entity you wanted to synthesize.

ONDETTI: In those days, to make just an octapeptide, like bradykinin was supposed to be, was very hard work, very laborious. I mean, it meant months of work. Bodanszky had made, before, compounds of that size, but he had tried to synthesize bradykinin on the basis of the wrong structure and he did not get a biologically active product. So he told me when I came, "We now know what is the right structure for bradykinin, it is a nonapeptide and not an octapeptide. Why don't you make it?"

I started, as I said, in July. I didn't have a sample to be tested until December, but it did turn out to be the right compound. To make several analogues of that structure was very, very cumbersome. That's the reason why people felt that the need was there for some better technique to make variations, because the number of analogues that you could make based on a nonapeptide was astronomical. I mean, how could you make those things if it took six months to make one? Making modifications is sometimes very depressing, because you don't get the biological activity that you're looking for more often than not. [laughter]

Interestingly, we never published the synthesis of bradykinin itself. I don't remember what it was. Somebody else had already published it and Miklos felt that we were too late. But the analogues were new compounds even if they did not have the antagonistic activity that we hoped to get, and so we published on them (5).

BOHNING: All right. What was the company's attitude about publishing in the scientific literature?

ONDETTI: I think it was pretty good. I mean, we never found serious problems in that respect, because the managers up to the level of associate director of the institute were people who came from the research area, so they had the same interest at heart that the people in the lab had. The only thing was that when they got to a higher position they had to be more sensitive towards the proprietary interests of the company. They always wanted to have the manuscripts cleared by the patent office, and they wanted to know if we were disclosing information of value for the competition. That became very critical in the time of captopril.

When Gus Fried was head of organic chemistry, he was very supportive of publishing. If we did things that were not worthwhile to publish, he thought that they could not be very good for the company either. In a sense, we felt that we were working in an environment that had the same requirements of academia: that we had to publish to be recognized. Besides, the peptide field was even more so, because it was such a brand-new field and you had to be known. The only way to really become known in the field was publishing, or going to meetings and presenting papers.

We filed a patent on our work on bradykinin analogues, like everybody else, but it was never a possibility to really make anything of commercial value out of that (6). When we got

into the gastrointestinal hormones, we had more concerns about patents and so on. But in general, the environment at Squibb was very supportive towards publication.

BOHNING: In that case, it was somewhere in the mid-1960s when you joined the gastrointestinal hormone group. That's when you met Emily [F.] Sabo, with whom you had a long association.

ONDETTI: That was a very interesting story in itself. I don't know how we got contacted. I think that J. Erik Jorpes who headed the group on gastrointestinal hormone research at the Karolinska knew people at Squibb, and came and gave a seminar, and met Miklos. Miklos impressed him that we could synthesize anything for which they had a structure, so that's the way the people at the Karolinska were willing to let Squibb know the structure of secretin before publication.

Secretin was the first compound for which the name "hormone" was coined in the early 1900s. But it took like fifty years to actually learn the structure, and Jorpes knew the structure. He was going to publish, but first he wanted it to be confirmed by synthesis, so he agreed with Squibb—I don't know if Squibb also had provided him with some financial support—to let us know the structure in advance of publication. So Miklos started to work on that.

Miklos is a very intense kind of person. Very soon, he got very unhappy, because secretin has twenty-seven amino acids, so its synthesis was a major undertaking and Miklos was working alone. I did some work on that, but by that time I had lost my assistant. She had quit to go somewhere else. Miklos was very unhappy, so he let it be known to the head of the chemistry department. To pacify Miklos, instead of giving him more manpower, they offered him a proposal, the formation of what was called a "task force." It consisted of taking people from different groups and putting them to work temporarily on peptides.

Well, Miklos didn't quite like it, but after he had complained so bitterly, he couldn't just turn it down; but this task force approach had problems. The people called to form the task force were very unhappy about being pulled out of another job to work in peptides, for which they didn't have a great regard. They had a great regard for Miklos, because Miklos was not only well known in the field, but is an impressive fellow.

So they created this task force, but then Miklos complained that I didn't have anybody to help me, so the head of the chemistry department, Frank Weisenborn, said, "Okay, I'll give him my assistant, Emily." Emily was the only one who came very happily to be in the peptide group, because she wasn't very happy to work with Frank. That's the way I got to work on the secretin team. There were people who came from steroids, people who came from medicinal chemistry. I was the lucky one; I landed with Emily. As I say, that was supposed to be only for the duration of the task force, which I believe lasted for one or two years.

Then when the task force was finished and everybody went back to their groups, Emily requested to stay with our program. Actually, she played a very important role in finishing the secretin work, because the task force helped, but it finally was disbanded before the job was finished. We had to finish the work ourselves.

The task force approach became a technique to be used in other cases. I mean, in the case of captopril, it happened the same way. Captopril became such a major discovery that Frank Weisenborn, who was still the head of chemistry, pulled people from all over the chemistry department to work on the analogs of captopril. But, it was different. The compound was simpler, and each one had its own analogue to work on. I mean, secretin was a major collaboration in which people had to make pieces to be worked upon by somebody else, and that was very, very hard. Even today, I don't think it's a very good idea. [laughter] But sometimes you have to do this when you have no other way of getting manpower.

BOHNING: There were two different approaches you used for that synthesis. One was a step-wise approach, and one was a fragment approach.

ONDETTI: That was another of Miklos' peculiarities. Miklos, as I say, had initiated new techniques in peptide synthesis, in particular the stepwise approach using p-nitrophenyl esters. He believed in them so, so strongly that he wouldn't touch any other approach.

This technique, which he really implemented for the first time in the synthesis of oxytocin, is actually similar to the approach that is used in solid phase synthesis. You start with the amino acid at one end, the carboxyl-bearing end, and keep adding one amino acid at a time. It's very good in many respects, but it's got one major problem. You cannot work in different portions at one time. It's not a convergent synthesis, but he believed that that was the only way—that, coupled with the method of using active esters that he also had pioneered.

So he said, "I'm going to do secretin that way. We're going to start with the first amino acid and go all the way to the end." For everybody who worked with him, the only function they could have had was to come after him. He was making, shall we say, the breaking-ground amount, and everybody was repeating it in larger scale. People didn't like that, that much. [laughter] Since Miklos wanted to have a sort of fallback position, he said, "Miguel, you like to try other things. Why don't you do the other way, by fragment condensation." That's what Emily and I did, in collaboration with a couple of other senior chemists. We made different portions to be later put together.

[END OF TAPE, SIDE 3]

ONDETTI: Miklos finished his synthesis first. He actually got enough material to send to Sweden and to prove that they had the activity that they thought that was the same as the natural product. He completed his work. By that time he had this offering of a full professorship from Case Western Reserve University, and he left.

But the company had committed itself to actually make secretin for clinical studies, so while we were working on small scale, the development group was making a very large batch. They were following the procedure that Miklos had used, but they ran into a big problem. By the middle of the synthesis they had such a mixture that they couldn't purify it by any available procedure. I mean, it was just impossible to go on. At that time Miklos had already left, so the project was in my hands, and the task force had already disbanded. We decided that we were just going to call it quits and take whatever they had made and purify it; but to be able to purify it, we had to remove all the protecting groups. It meant that we couldn't go back and continue the synthesis by the stepwise approach. With Emily, we took the impure material made by the development group, removed protecting groups, purified it and continued the synthesis the way we had made it, and we finally succeeded in preparing a pretty large amount of secretin.

At that time, as I said, the FDA regulations were in place. We had to do a complete toxicology study in order to move to clinical experimentation. Since secretin stimulates the pancreas to produce bicarbonate, Morton I. Grossman at the Veterans Administration in Los Angeles thought that secretin would be nature's antacid. He started a clinical study, but apparently continuous stimulation leads to an inflammation of the pancreas, so they had to stop this study. I think we spent most of the secretin that we made by giving it away to investigators in academic labs.

BOHNING: Was the arrangement such that if you had something that seemed to have some promise, there was another group—the chemical group—that scaled it up to larger quantities?

ONDETTI: Yes. This is the traditional way, but in peptides it became a big problem, because the techniques were so specialized that the development group had to build their own peptide group. They were not very happy about that, because it was very different from the rest of what they had to do. They finally did it, and by the time that we were working on the converting of enzyme inhibitors, they had hired some people who had very good expertise in that field. But still, it was also a very small group. That probably was one of the drawbacks of the peptides as drugs, that they really required a completely different kind of development group. They maintained it for a while, but it didn't lend itself to the flexibility that the people in development wanted.

BOHNING: In the case of secretin, it was actually you and Emily who made the large-scale amount.

ONDETTI: Yes, because by that time, since they couldn't finish and they couldn't actually purify the intermediate they had, we had to actually take it over. What we did was that instead of running the synthesis once in a large scale, we ran it several times in small scale until we accumulated enough material. The development people didn't like that because it created a problem between them and the regulatory group. It was done as an exception, and they were glad that we did it, in the sense that they had invested quite a bit of time in this project and they thought it was going to be a complete failure, but we managed to pull it out and finish it successfully. We've never done that again. I mean, from that time on, development had to make all of our larger batches.

Nowadays, it would be almost impossible to do, because the regulations are even worse that they were in the 1970s or late 1960s. The labs that produce material for clinical studies have to be inspected by the FDA. They have a number of regulations that are called GLPs, good laboratory practices. The benches have to be a certain size; the water has to come from certain sources; and so on and so forth. Our research lab would never be approvable according to those kind of regulations, so we never went back into doing development. [laughter] That was it.

BOHNING: But you were still involved hands-on at the bench at this time.

ONDETTI: Oh, yes. Except that things changed quite a bit after Emily came to work with me. [laughter] I think if I go back to my notebooks, it was the time of secretin when I really stopped carrying my own lab notebook, the reason being that Emily was so efficient that it didn't make any sense for me to do my own experiments. Emily could do by herself all the things I wanted done. It was much easier for me to do all the planning and then tell her to set up the experiment, rather than to set up experiments myself.

At that time, I had two assistants. One of them was Nina [J.] Williams, and then the other was Emily. It lasted a few years until we came here, from New Brunswick to Princeton. Then Nina left and we replaced her with a young B.S. chemist, Tom Kissick. For a few years I had still two assistants working with me. I never felt that I was away from the lab, because my collaboration with Emily was such that I felt that it was almost like doing the experiments myself. I stopped having an office within the lab in 1973, because I was asked to be section head for antibiotics. Then I had to have a separate office, but it was on the same floor and it was seconds away from the lab, so I spent a lot of time in the lab. I only felt the shock in the early 1980s, when I was promoted to associate director of the Institute and then I couldn't work with Emily anymore. Then I really felt that I had left the lab, period. But as I say, I probably stopped

carrying a notebook on my own in the late 1960s. By the time we worked on captopril I had really no experiments of my own. Emily would carry all the laboratory work.

BOHNING: What was her educational background?

ONDETTI: Emily had a bachelor's degree in chemistry from Ursinus College in Pennsylvania. Emily always sort of poked fun at her training as a chemist. She always felt that it would have been a waste of time being a Ph.D. She was extremely intelligent, but she didn't have that dedication to chemistry to make a full-time career out of it. She was very keen on participating in different sports like tennis, golf, et cetera.

She married a gentleman who was ten or more years older than she was, who was in the microanalysis department in Squibb. They had a daughter and Emily was always very involved in running the household. Also, I don't know, it was very difficult to say, but she got the attitude that she didn't care really about chemistry, but she could do chemistry better than anybody I've ever seen in my life. First of all, she had very good laboratory techniques. She was outstanding at crystallizing organic compounds. If Emily said that it could not be crystallized, we just abandoned it. [laughter] She was very efficient; she could run two or three preparations or sometimes more, at the same time. She worked with total concentration. She probably was the inventor of what is it now called flextime. She would come to work about 5:30 a.m. and she wanted to leave not later than three o'clock to be home when her daughter came back from school, and she had done equal or more than anybody else during that time. She would take a very short time for lunch. She was always a very outgoing kind of person and everybody liked her, but nobody would come to disturb her because she was concentrating one hundred percent on what she was doing and she didn't care to talk to people. She was a character in many respects.

We sort of hit it off right from the beginning because she shared my complete dedication to whatever we were doing. It worked perfectly. As I say, I got to the point that I would have sacrificed anybody else in the group, even Ph.D.s, except Emily. [laughter] She was the only person I wanted to keep. Actually, when they decided in 1973 that the group wasn't going to exist anymore, the only thing I asked was, "What's going to happen to Emily?" "Oh, they said, don't worry. Emily will still be working with you in wherever you think she should work." So I said, "Okay. We'll have no more peptides. We'll work on antibiotics." I didn't really care at all, provided Emily was still going to work with me.

As a matter of fact, Emily had already worked in antibiotics when she came to Squibb in 1951 or thereabouts. She had worked in antibiotic screening and things like that, and then on steroids. Working with Emily was quite different from having a collaboration with a Ph.D., in the sense that with a Ph.D., I would have to convince him or her that it was worthwhile to do what I planned to do. With Emily that problem did not exist because she would leave all the

planning to me, and I would trust her judgment in carrying out the experiments properly. What made it difficult for me to collaborate with Emily later on, when I got larger responsibilities, was that Emily could not go out and explore new methods of synthesis or do any major planning, because she wasn't very familiar with the literature. She couldn't really work independently. I mean, if I had been collaborating with a Ph.D., I could have said, "Okay, let's work in that area," and we'd get together every week or couple of weeks. That didn't work with Emily.

I think it was 1981 or 1982 that I was asked to be associate director of the Squibb Institute, and the demands on my time increased tremendously. I would go for days without being able to go to the lab, and Emily wasn't very happy because she didn't have enough things to work on, because when certain experiments didn't give what we wanted, she didn't know how to proceed. So we both almost simultaneously and independently arrived at the decision that it was not going to work. She said, "Well, Mike, if you want, I can work with so and so," and so she did. That was a very sad moment, because I thought that research was over for me. I think she worked like six or seven years more and then she went on medical leave, because her health had deteriorated significantly due to diabetes.

BOHNING: After the secretin work, you did work on sincalide.

ONDETTI: Yes, that came out from the other hormone that Jorpes and Mutt had isolated, cholecystokinin. It is the hormone that induces the gallbladder to contract. It's very important in digestion. But at difference with secretin, they have found, and we confirmed, that you didn't need the whole hormone for activity. With only eight amino acids you could have all the activity of the hormone. When we confirmed that we could make a small peptide that had all the activity of the whole hormone, it became reasonable to try to make a product out of it.

Actually, it wasn't that we could point out to any specific therapeutic use, but it could have a very important diagnostic use, because in order to do a gallbladder examination they used to give the patient a meal that had a large amount of fat, so that the gallbladder would contract and x-ray pictures could be taken before and after the contraction. With this, you didn't have to do that. You'd just do an x-ray and then give an injection of this product. Then you could see if the gall bladder had contracted correctly. If the patient had stones, you'd see the stones more clearly.

Again it was a very difficult job for development, but this time because the chemical means of purifying the final product were very few. The only way to really get a hold on the purity was a bioassay. The pharmacology department had to develop the bioassay. Finally, after considerable effort the company agreed to develop it as a diagnostic product. Actually, I think it still is in the market, because it slowly became used in a therapeutic fashion in people who have to be supported with intravenous infusions of amino acids. They need this stimulation of the

gall bladder to maintain a reasonable motility of intestines, because they don't ingest any solid food. I believe it still is a significant market.

At my retirement party, one of the speakers made the comment that the company can make more money on this product than on captopril because the clinical dose is only five micrograms, less than one-thousandth of the dose of captopril. This is sort of a funny twist, because that was one of the serious problems of formulation development, that each vial contains only five micrograms of peptide. They had to develop a special formulation adding salt to it. They tried different things. It was a big problem for a while.

BOHNING: Was that your decision, to follow up on that work?

ONDETTI: Well, yes. By that time, Miklos had left. I felt that being a smaller compound, we had a better chance of success with it than with secretin. But still it wasn't easy. I had to count on a lot of collaboration with people in the biological side, because a lot of the analytical work had to be followed by bioassay. All the biological work was done by Bernard Rubin and Zola, when Zola Horovitz was the head of pharmacology.

Bernie really had a lot of collaboration with other people in the pharmacy group, because we ran into all kinds of problems with the formulation—because if you put in five micrograms of one compound and five milligrams of something else as an excipient, all kinds of small reactions that normally would not happen, do happen due to mass action. For example, with lactose, we said, "Gee, well, lactose won't do anything to this peptide." But we found that there were so many hydroxyl groups available in the five milligrams of lactose that the sulfate on tyrosine would migrate to the lactose. Once you lose the sulfate on tyrosine, you lose the activity.

So, we had to go from formulation to formulation. At that time the quality control people did not have a good method for measuring five micrograms of any compound, so the pharmacologists had to step in and say, "We'll do bioassays," but they had to be quantitative enough to satisfy regulatory people. It involved a number of people. I must say, I was fortunate that we had people who were believers and supported us. For moments we thought that they were not going to go for it. Once it became the product, then they had a lot of people involved, and then it was easier. In a sense it was probably the only peptide that made it into a market product, because even the peptide that we made from the venom and got to clinical studies was never marketed. It was already prepared to be used as a diagnostic agent, but the company refused to be involved in that area again.

[END OF TAPE, SIDE 4]

BOHNING: Well, you've raised an interesting point, as sort of a general point. That is, somewhere along the line in the development of a product, there comes a time when you need to have a champion higher up to support your cause.

ONDETTI: Very much so.

BOHNING: You really have to convince that person of the worth of your project. They, in turn, probably have to convince someone else.

ONDETTI: That's right. I mean, no matter how enthusiastic you are, unless you have sold it to somebody who has, shall we say, a position of responsibility, who can put enough weight behind you, you're never going to succeed. That, in a sense, was the way I saw Zola Horovitz helping us tremendously during all my career. I mean, when I came to Squibb, he was already there. He had joined Squibb in 1959. He was a CNS pharmacologist, but very soon became involved in management as the head of the pharmacology department. In a similar fashion, you cannot really get a project off the ground unless you have chemistry and biology behind it. I mean, chemistry alone in a pharmaceutical company is not such a tremendous force. It's only something that you have to count on. I mean, a pharmaceutical company will not succeed unless it has a very good chemistry group, but when you're talking about new products or new drugs, you have to have the biological people behind them.

Zola was always very supportive of the communications between chemistry and biology, especially so in peptides. He was always that way from the beginning, when I was in the cholecystokinin work. I guess secretin wasn't that much of a concern for him because in secretin, we did most of the work with the collaboration of the people of the Karolinska. But in cholecystokinin, he became very, very important. He was very strongly behind it. Later on, he was actually the one who got me and the chemistry involved in converting enzyme inhibitors. So he was always very supportive of us. Since Zola got into a position of associate director much earlier than I did, he was the kind of person who was going to be critical to provide support.

So you're right, support is very important. Even after we actually decided to disassemble the peptide group, there was an interest in the pharmacology on what we were doing, particularly through Zola, who was always there. I mean, when we decided to restart the angiotensin converting enzyme inhibitor project before it was an official program, we knew that Zola's support was there. That was very, very important.

BOHNING: In 1967, Arnold D. Welch became president of The Squibb Institute. There was a change in research goals at that time. The peptide research was to continue, but not in the same vein as before.

ONDETTI: That's right. It was not that they really thought that the gastrointestinal hormones were not worthwhile as a research effort, but they felt the company was not commercially interested. They themselves were not very interested in that either. There was a time when people felt that instead of having too many areas of research, one had to concentrate. More or less at that time they had made the decision that cardiovascular agents were going to be one of the areas in which they wanted to concentrate.

Dr. Welch and his management group came in 1967. We might have been working on and off on gastrointestinal and cholecystokinin until 1970 or so, but it was not going to be the major part of the peptide group work. That, I guess, is why they were very positive about getting us involved in converting enzyme inhibitors, because they felt that that was a way of providing a different direction more in relation with the cardiovascular field.

BOHNING: You wrote in that recent write up—I think I'm quoting here, or pretty close to it—that you had become interested in the direct blocking action of peptidases (7). How did that interest develop?

ONDETTI: I was unhappy with the fact that we had received, continuously, the criticism of management that peptide had problems—that first of all, there were not therapeutic areas in which it was obvious that a peptide was going to be a successful drug. Then there was a problem that you had to make compounds that were small, so that they would be more likely to have activity, and so on and so forth. From the middle of the 1960s it was clear that we had to sort of look for other areas in which we could utilize the peptide expertise to make a more direct attempt at making, quote-unquote, "drugs," even if they were not exactly peptides, so that's when I started to get interested in peptidase inhibitors. Peptides might not be themselves important drugs, but they're important for body functions. They are very critical as messengers and are important intermediates, intracellularly or extracellularly. The reason why peptides are very short acting is because they're cleaved by peptidases. Therefore, I thought that trying to block that action could be of sufficient therapeutic interest.

For example, bradykinin was one of the first peptides we worked with. One of the concerns was that bradykinin had a hypotensive activity, but it is of very short duration, because bradykinin is very rapidly cleaved by peptidases. Interesting, and kind of ironic, is that bradykinin is actually destroyed most efficiently by the converting enzyme that makes angiotensin two. We were concerned with that, but we were not aware of that in the early sixties.

When John Vane came and presented his work and suggested that we get involved in the isolation of converting enzyme inhibitors from the venom of snakes, it sounded very, very appealing to me. They really didn't have to do much work to convince me to become involved in that area. I knew that management was not interested in gastrointestinal hormone, so that probably, whether I liked it or not, I had to change. What they were proposing sounded like it was a very good replacement for that project, so I was very gung ho. I was very fortunate that it happened at the right time.

BOHNING: You commented that, "It was an appropriate research endeavor for me emotionally" (7).

ONDETTI: Yes. First because it was a natural product research project. As I said, in Argentina, Venancio Deulofeu, my thesis advisor, had pioneered the isolation of biologically active compounds from plants, from frogs, et cetera; never from venoms. But I thought that this was a very nice twist to the idea. [laughter] I liked it. Even today, I find that whenever I talk to somebody about captopril, they think that the most interesting thing is to hear about the venom of snakes, [laughter] even though captopril itself had nothing to do with the venom of snakes. People have a fascination with the idea that you can make something beneficial out of a venom. [laughter]

BOHNING: Well, my interest in that was the fact that I visited the Serpentarium in Sao Paulo.

ONDETTI: Oh, you did?

BOHNING: About three years ago, I think.

ONDETTI: Is that a fact? How come?

BOHNING: Well, I was in Sao Paulo doing oral history interviews for Dow Chemical, the Dow Brazil operations. We had some time to see some things, and we went to the Serpentarium. So, when I saw that, I said, "Oh, I know exactly what that is."

ONDETTI: Well, we bought venom from them, because we actually ended up needing gram amounts, and you couldn't go around buying grams of venom anywhere else.

There was a company in Florida that sold small amounts of venoms, but we actually wrote to the Instituto Butantan in Sao Paulo. We said, "We need venom of Bothrops jararaca, because it is a Brazilian pit viper." They said, "Oh, we can get you that. How much do you want?" "Two hundred grams." [laughter] Well, we had this big box of venoms, and for years we kept them in the refrigerator, because we hadn't finished with the project. Finally, somebody asked me whether it was safe to throw them away. I told them it was, provided you do not spill them over your skin, particularly if you have open cuts.

For a while, everybody would come into the lab and see how the venom looked. It's just the kind of story that appeals to people. Natural products have a very strong appeal for people from the outside, and even for people within research. Pharmaceutical research is still interested in natural products. You probably have heard that recently Merck and some other companies made agreements with countries in tropical areas to explore the biodiversity of their plants and animals.

After the work on the venom, when other researchers were interested in finding compounds for which they had a new biological assay, I'd say, "Why don't you go and get some of the venoms that I had in the refrigerator and test the crude extracts? Maybe you'll find one that is active, and you can try to find the compound responsible for the activity." We did that ourselves later on. It was a very interesting story. We didn't publish because it was a big failure.

John Vane, as you know, got the Nobel Prize because of his findings about the mechanism of action of aspirin. He was the one who actually elucidated that aspirin inhibits prostaglandin synthesis, and that is one of the reasons for its anti-inflammatory activity. Now, very near the end of his consultantship with Squibb—before he got a job as the head of the research for Burroughs-Welcome—he used to come and talk about this. I told him one day, "Listen, from my reading of the literature, I found that some Argentineans found that in the venom of a snake, there is an inhibitor of the enzyme phospholipase, and this is the first enzyme in the cascade that leads to the synthesis of prostaglandins. Wouldn't an inhibitor of this enzyme do the same as aspirin?"

He said, "Yes, why don't you go ahead?" He convinced the company that I should work on isolating from the venom of the snake an inhibitor of phospholipase. At that time, the people who could support us biologically were not the same people who worked with us in converting enzyme inhibitors, and they were not as cooperative. So with Emily, we learned how to run the enzyme assay ourselves with egg yolk, so that we could follow the isolation.

Then we kept following the active compound by paper electrophoresis and paper chromatography. We used to cut the chromatogram in pieces and test every piece after washing the compound out with water, and in this way we knew where the activity was. It was easy to get it, to find the activity, but slowly it became more and more difficult to follow it up with

chemical reagents, because it would not give any chemical reaction whatsoever. It came to be very, very disquieting to me, because I said, "What could it be that it migrates toward the negative pole in electrophoresis, like it has a positive charge, but it doesn't react like any kind of amine?" Finally it came to me that it had to be a metal ion, like iron, copper, zinc, et cetera. Finally we proved that it was zinc; the venom of the enzyme had a lot of zinc from the salivary gland. The snakes concentrate zinc in the salivary gland. The zinc inhibits the enzyme strongly, and that fooled us. We spent like four or five months, but it was a big fiasco. [laughter] You know, there might have been another compound that inhibited the enzyme, but if there was one, we lost it following the metal that was present in larger amounts.

BOHNING: When you started out in the isolation of angiotensin converting enzyme inhibitors, you said that you were in competition with a group that had extensive experience in protein sequencing.

ONDETTI: Yes, because the way it really happened is that when Vane came to talk about this idea that you could block the formation of angiotensin, he really had come up to this kind of observation because the Brazilian pharmacologist, Sergio Ferreira, had carried this crude venom from Brazil to his lab. Sergio Ferreira was a pharmacologist, and periodically he went to visit John Vane's lab, to do work there. He brought with him this interesting crude venom extract. He had shown that it potentiated the action of bradykinin. Through a number of studies they did in Vane's lab, they also found that it blocked the formation of angiotensin, too. That kind of information made John Vane say, "Well, this might be something very useful therapeutically. It might be something that Squibb would be interested in."

By that time, Sergio Ferreira had begun fractionation of the venom in collaboration with a biochemist at the Brookhaven National Laboratory, Lewis Greene. They had already isolated one of the inhibitory compounds, a pentapeptide. Greene was the one who had expertise in protein sequencing. They wanted to get supported by Squibb, and they said, "Well, you do the synthesis. We'll do the isolation." For some reason—I don't remember exactly why, but I think it might be due to patent reasons—the company refused to get into a collaboration with Greene or Ferreira. So we said, "Well, all right, you go your own way, and we'll also do the isolation in our own labs."

For us, this situation created a little bit of a concern, because we knew much more than they did how to synthesize peptides, but we didn't know how to isolate and sequence peptides. We had to sort of learn on the run, because I couldn't really say, "Well, I'm going to take a sabbatical and go to some other lab and learn how to sequence peptides." We just had to try everything. That's the reason we sort of cooked up a strategy that was very different from theirs. When we finally met at the meeting, we realized that we had gone very, very different ways—not because I thought it was a better approach, but because I had to acquire the practice right on the things that I was doing. To practice I needed a large amount of compound, so I did not try to

isolate the most active compound, as people usually do, but the one present in the largest amount. With that compound we did our experimenting in sequencing peptides. Fortunately, most of the inhibitors present in the venom had somewhat similar sequences, and what we learned with one was useful with the others.

The fact that we could do synthesis very efficiently was also very critical, because at the end, we had sometimes a number of alternatives for each structure. We synthesized them all and then compared with the natural compounds, and in this way we confirmed the sequence. That approach created a problem when we had to publish. The referees were never kind to us, because they said, "Well, but this not a way to do sequencing" (8). Oh, I said, "But we can show you that those are the right sequences." [laughter] It was exciting, because we knew that we had to do it fast in order to get to the end before they did and so claim patent rights. We couldn't wait long.

At that time I was working not only with Emily, but also with Nina Williams. Nina was more adept to doing this kind of fractionation in which you have to do paper chromatography. In order to have enough material to do the next step in the degradation, you have to run chromatogram-cut the area of the paper you are interested in and sew it to another paper in order to do further fractionation. Emily didn't like that kind of thing. She didn't like it at all, so Nina would do that, and whenever we arrived at a sequence, Emily would synthesize it. It worked pretty well. They were both very good.

BOHNING: The problems that continued, however, were the oral aspects, even as you went on to look at analogs. You finally even did random testing.

ONDETTI: Yes, I guess that would thoroughly discourage a company from continuing in the peptide area, because we had a compound that was very interesting according to the clinical studies, but we could not really produce something that could be used every day. We had a lot of clinical investigators interested in taking the compound, and we did a number of clinical studies. The only people who were going to use it were going to be the large research hospitals, where it could be given by injection. The company felt there wasn't a big market on that basis and that unless it could be used by every physician, they were not interested. What was most discouraging was that we made a number of compounds and we tried different ways of attacking the problem of lack of oral activity, but we never fixed it.

BOHNING: The ACE inhibitor work stopped officially in about 1973, then.

ONDETTI: Officially, I think it was 1973 when it actually stopped, because they said, "Miguel, we need you for something else," and then the whole peptide program was discontinued. By

that time, I guess, I was already doing work on the phospholipase inhibitor project and other small things. A significant number of clinical studies had been done with teprotide, the synthetic nonapeptide identical to one of the inhibitors isolated from the venom, and some clinical trials were still going on. John Laragh from Cornell Medical Center came in for a consulting visit and tried to convince the commercial group to market teprotide as a diagnostic agent in the treatment of hypertension, but the company declined. For a while, everybody thought it was the end, but it wasn't.

[END OF TAPE, SIDE 5]

ONDETTI: I'm trying to remember when John Laragh came; I think it was in January 1974. In March or April 1974, we went back to work on this area on our own without having requested official approval.

BOHNING: Why did you decide to go back?

ONDETTI: We went back because we were still deeply interested in the project. Many times in a research organization you get people to work in one field, but their soul is not into that. They take a project, they do the best job they can, but if they do not succeed they move on. But for us it was a project that we really wanted to make work, that we wanted to succeed. When we left it, we left it regretfully. When we found the first chance of going back, we didn't care what we were working on. We said this was the kind of thing that we <u>had</u> to do.

Sometimes I try to explain that to people. We have occasions in which a project comes from up on high, and you have to impose it on the people in research. But if you don't convince people that it is a worthwhile thing to do, you're not going to be very successful, because people are not committed mentally to that project. They just do their job—professionally, okay—but their minds are not committed to it and their hearts are not in that. I saw it again and again later on, when I had managing responsibilities, that if chemists and biologists were very committed to something, it was a completely different kind of program and it made a big difference. I think this is what really moved us to go back.

Actually, our going back into the project came around in a kind of trivial way. Dave [David W.] Cushman in a routine review of recent literature had found an interesting paper on enzyme inhibitors and he sent me a note saying, "Look, this guy made this interesting inhibitor of Carboxypeptidase A; wouldn't it be nice to have something like that for ACE?"

He didn't really send it to me. As I said in my paper, he sent it to Zola (7), and Zola sent it to me asking if we could make or get some of this particular compound to test. Since I

realized that that was not the way to go about it, I called Dave and we got together to discuss the question in detail.

BOHNING: When you saw the card with the paper by [L. D.] Byers and [R.] Wolfenden (9), what was your immediate reaction? Perhaps you thought, "This is it. This is the answer."

ONDETTI: Well, there was something like that. We knew a number of things about the enzyme. From the activity of the compounds that we had made, we had learned something about what the enzyme active site looked like. It had the properties of carboxypeptidase. What the paper said was that they had found a very good inhibitor of another carboxypeptidase, Carboxypeptidase A. It was like somebody gave us the piece to complete a puzzle. From all we knew and what they said, we believed that it should be possible to make a new type of inhibitor of angiotensin converting enzyme. What was striking is that the first compound we made worked, so we believe that our assumption was correct. That really was an eye opener.

What is also interesting is that we didn't even agree with the assumptions that they had made on how the compound that they made worked. It was just a question of making a compound that we believed would be specific for our enzyme.

Later on I learned—I was told, but I don't know if it is a fact—that the people at Merck had actually seen the same paper and made the same compound that we made, but they decided there was no future in it until we published the captopril story. Then they went back. [laughter]

It's interesting how, from the same compound, they drew a different conclusion. I can't understand it, because the compound was active, even though poorly active. But, of course, we were probably coming from different points of view. As I think I said in the paper, when we stopped the peptide group, somebody had this great idea that we were going to test everything that we had on the shelves as potential converting enzyme inhibitors. We did all that screening, but we could never find any compound that was good enough, so I guess that's what made the big difference for us. We had tested like, I don't know, three thousand compounds out of the Squibb files without finding anything really active. We made this compound just from scratch, and we got a result that was better than any of that, so we believed that there had to be something there. I mean, we were much closer than we ever were by testing three thousand compounds. I think that because of that background we thought this very poor activity was still very interesting. Maybe also because, as I sometimes say when telling this story, I was sick and tired of working on antibiotics and I wanted something else. I just took any kind of suggestion. [laughter] No, that's not true. I enjoyed antibiotics, but antibiotics weren't my lab work. I mean, it was other people's lab work. I was just a supervisor.

BOHNING: It was March of 1974 when you would have seen that paper. At some point, you went to the internal medicine team and said, "We've got something here that's good." How long was it between those two points in time?

ONDETTI: We might have done that by early the next year, I think, because at the time we presented that to the team, we had not really gotten into making things like captopril. We were just still wandering around in the same kind of chemistry, but we were making compounds that were better than the ones that we had made at the very beginning; I mean, I guess ten or one hundred times better than the ones that we had started with. So we knew that we could improve the activity. We also had the specificity we wanted, and at that meeting we told this story. At that time, we still had the same president of the institute who had actually called for discontinuation of the work on peptides, but nobody said, "Gee, who told you to go back into peptides? They just said, "Good work. Good luck to you." [laughter]

Really, at that time, we were very few people involved in that effort. In chemistry it was Emily and myself, and I still had responsibility on antibiotics, and that took a considerable amount of attention on my part.

BOHNING: You were also getting good indications of oral activity at this point, were you not?

ONDETTI: I don't remember if we had it, at that meeting. I think the oral activity experimenting was done by the pharmacologists by themselves without discussing it with us—I wouldn't say out of desperation, but to sort of galvanize the interest of the company to allow us to continue. Zola was associate director of biology for the institute. Similarly, there was an associate director for chemistry, and to this person reported chemical research and chemical development. So, the biologists wanted to convince him to put more chemistry into that, because they thought that Emily alone wasn't enough. I believe that was the reason why Zola prompted the pharmacologists to show that there was an inkling of oral activity.

So the pharmacologists gave a huge dose of the best compound we had at that time. Normally, as a hard and fast rule, if a compound has significant oral absorption, you have to give no more than ten times the dose that you give intravenously to show the same level of activity. But I think they had to give a hundred or several hundred times. [laughter] It meant that oral absorption was very small, but that the activity was there. So they said, "Oh, the compound is not very good, but you can get oral activity while you can not get it with the peptide inhibitors." It was interesting, but it wasn't earth shaking.

When they decided that they were going to give us more chemical support, it was a sort of half-hearted decision. They decided that the assistant department director of chemistry, Jack Bernstein, who also had an assistant working with him in the lab, was going to let his assistant

work with Emily and I in a sort of mini task force. So now there were two people in the lab, a one hundred percent increase in manpower. [laughter] That was, I guess, the reason for doing the oral activity studies.

BOHNING: You became interested in using the sulfhydryl group. How did you latch onto that idea?

ONDETTI: As I say, we did not quite agree with the paper of Byers and Wolfenden (4, 5) regarding the interpretation of why the compound they had made was a very good inhibitor. They postulated that the inhibitor bound to the enzyme like the two products of the enzymatic reaction, and they called it a "bi-product analog." We thought that they had not given a good test to the idea that the compound would bind to the zinc at the active site through one of its carboxyl groups. They gave some arguments that were not bad, but we thought it was not enough. So we kept on the idea that it was very important somehow to coordinate with zinc on the active site. Because of that, I said to myself, "Let's change that and make other compounds that have groups that would be better binders or better ligands for the zinc." We started making hydroxamic acids, and we did get better activity.

I wanted to make the sulfhydryl compounds, but I didn't do it right away. The reason was that during my years in peptide synthesis, I had had a great deal of trouble making certain peptides containing sulfhydryl groups, because they were unstable. It's one of those things; I don't know many times you face the same situation. I'm now a consultant for another company in a program that is also a peptidase inhibitor program. You find out that you discuss with people and say, "Well, let's make this compound or that compound." But they don't usually make them; they make something else. You say, "Why?" And in the long run you learn that it was because it was easy to make that other compound. [laughter] So, normally you make first the easy compound. Slowly, if you run out of ideas or nothing works, then you say, "Well, let's make the real McCoy."

In a way, it was the same then. We kept sort of postponing it. I had enough other ideas that we wanted to work on, and there were not that many people, so we sort of kept putting aside the more difficult ones. It really happened that way.

One day, looking among the new catalogues and advertisements that one gets everyday in the lab, I saw an advertisement for a new compound to derivatize proteins. This compound, they said, "If you are interested in putting some sulfhydryl groups into proteins, use this compound. It will react with the lysine epsilon amino groups, and right away, you can have a new sulfhydryl group." I said, "But gee, that's exactly what we need to do." If you had come from scratch, you wouldn't have used that kind of chemistry, because it's kind of involved to synthesize this new reagent. But it was easy if you could buy it. I said to Emily, "Why don't

you order some of that, and we'll try it." And that was how we got into this new class of inhibitors that were going to make a big difference.

So we ran the reaction and got the compound we wanted, but we got problems. They could easily oxidize and give all kinds of side reactions that you had to fight with. But, you could overcome these difficulties. It was not an impossible task. Once you overcame the first barrier, then it became easier. Emily learned how to make the same compound by other routes, and, if they got oxidized, you had to reduced them. The final products were oils, but she managed to crystallize them directly or make crystalline salts, and things like that.

The first sulfhydryl compound we tested was so much more active than any of the previous compounds that everybody was excited and running in all directions. They wanted to know how much we could make, and how fast. Every day, everybody wanted more for some new test. The funny thing is that we didn't need to get a lot of increase in manpower to do that. By the time that the large increase in manpower came we already had made captopril. It was very exciting.

BOHNING: That activity was what, a thousand times?

ONDETTI: Yes. Well, I mean, it depends on what you compare it to. If you compared it to the best compounds that we had made so far, captopril was like a thousand times or more. But if we compare it with the first compound that we made when we read the paper by Byers and Wolfenden, the first sulfhydryl compound was probably close to ten thousand. But we knew that that still wasn't the end, because we could make up one that was even ten times better than the one that we made first. When we made captopril, right away everybody said, "This compound we're taking to the clinic," because we couldn't figure out that we could make anything more active. [laughter] Then later on, with increased manpower, we made a lot of derivatives of captopril, some of them even more active. But it was obvious that with captopril we had come into a completely new field.

[END OF TAPE, SIDE 6]

BOHNING: The first disclosure of this came in 1977, in an article in *Science* (10). What kind of reaction did you get to that?

ONDETTI: Well, what were more interesting about that paper were the internal arguments about the publication, because some people didn't want us to publish. They just said that we were going to create a lot of competition for ourselves—and it was true; it did create a lot of

competition. But we told them that the clinicians were going to publish whether we published or not, and they did. As a matter of fact, the first clinical study with captopril—the first human studies of captopril—were done in Lausanne, in Switzerland in December 1976.

The reason for not doing the study in America was a technical one. The study consisted of showing that if you give the volunteer angiotensin one, blood pressure goes up. But if you give captopril beforehand, and then give angiotensin one, blood pressure stays the same, because it has blocked the conversion of angiotensin one into angiotensin two that is the agent that increases blood pressure. Now, in this country you couldn't do that, because angiotensin one was not an approved drug, and you could not give <u>two</u> non-approved drugs together. You needed to do a special toxicology, a separate and more cumbersome study. But they said, "In Europe, you can do that."

So we went to this investigator who was very well known in the field, Hans Brunner, and we set up this study in Lausanne. When they got the extremely positive results, in December of 1976, they said, "Now we're going to publish." There was no way of holding them back. Since they had to approve their publication, they finally approved our own publication in *Science*. As a matter of fact, they published in *Lancet* (11) a few weeks <u>before</u> our paper came out in *Science* (10). Some people read only one of the papers, but a lot read both.

Our paper really created a stir because, by that time, the paper in *Lancet* was known and everybody knew about the efficacy in humans. Everybody realized that it was going to be a completely new approach. I mean, hypertension had been sort of in the doldrums for quite a while because there were not very good compounds. The last new type of antihypertensive agents that were introduced in the late 1960s in this country—they were introduced in Europe much earlier—were the beta blockers, and they had a lot of problems.

There was a tremendous amount of interest and some of that was kind of interesting. I always remember that Squibb always had a kind of competitive position vis-a-vis Merck, because they had worked against each other in the field of steroids from way back. Some of the top managers in chemistry knew some of the key people in research at Merck, and they were surprised by a call from them saying that they wanted to meet, just to talk about how the new discovery came about.

They were not interested in any collaboration, because they knew that that couldn't work. They said that when the paper finally came out, it attracted a lot of attention at Merck because they had worked to some extent in that area. "How dumb," they said. "Why didn't we think of this?" [laughter] Then the story changed, because we ran into some troubles in the clinical studies, and everybody thought that it was from the sulfhydryl group. So Merck's feeling was then that they had to make a compound like captopril, but without the sulfhydryl group. The head of research had told all the chemists that, "Don't even think about making any compounds that are similar to captopril. They have to be as good as captopril, but they have to have no sulfhydryl groups." [laughter]

The paper really made a big impact (10), but a lot of what happened with captopril was not really quite in the works at the time that, actually, we started doing those studies. A lot more came later; some of the medical applications were not even dreamed of when we actually got into this field. A lot of the therapeutic implications of the renin-angiotensin system were only uncovered because of the availability of ACE inhibitors. There were some studies that had been done with the peptide ACE inhibitor teprotide in heart failure. In renal failure, myocardial infarction and diabetes, nobody had done anything. It all became possible because we had this compound.

It's interesting, because in the mid to late 1980s, one of the researchers in Lausanne had an award for the most cited paper. I don't know what you'd call it. They gave it for one of the first clinical studies in captopril.

BOHNING: Citation Classics, that's it.

ONDETTI: Citation, that's it. They gave it to this clinical study on captopril, but I went back to check, and we found that our paper was cited more than their paper.

BOHNING: That's interesting.

ONDETTI: Now, I don't remember what the number of citations was, but it was a lot.

BOHNING: Well, we had just finished talking about the public announcement and the reaction to all of that.

ONDETTI: Yes, that's true.

BOHNING: You did about ten years of follow-up research, then.

ONDETTI: Yes. I think what happened was that once captopril was actually released for clinical studies we were still fairly far away from actual clinical use, because we still had to complete all the long-term toxicology and things like that. But we more or less had a fairly good idea that it was going to be effective. Usually you have to try to support it, in case something happens to that compound. So right away, as soon captopril was thought to be a very useful

drug, then the company turned a tremendous amount of effort into it. I mean, going back to this idea of the task force, practically everybody said, "Maybe, except for some few people in antibiotics, we'll ask everybody to drop whatever they're doing and work on captopril analogs."

Very soon after that, in 1980, we got the disclosure that Merck had another compound. That created another big stir. So one after the other, there were different type of approaches tested. We had a large program that used only compounds that were analogs of captopril, and another program on compounds that were of a completely different kind of chemistry. We eventually came up with a phosphorus-containing compound that was longer acting than captopril.

All this got fueled-up by a number of disappointing clinical results. Clinical investigators, with this enthusiasm for finding a beneficial use, started using at the beginning very large doses of captopril, like one gram a day or more, and they ran into trouble. They got problems with side effects, rashes, things like that. Then all of a sudden people began to say, "Oh, gee, we've got problems."

Now, this was one of the drawbacks in being the first in a new clinical area: you have to learn everything by trial and error, because you don't know what difficulties you're going to encounter. We didn't realize at that time, or the clinicians didn't realize, that not all hypertensive patients could benefit from captopril. Slowly, it became known that there are certain types of patients; there are certain types of hypertension that are not going to respond to captopril, no matter how much you give them, unless you add the diuretic to the treatment.

It took a long time to learn all that. In the process, all the bad publicity did a lot of damage to the image of captopril. People were saying, "It's not a safe compound, because if you get too much, it can cause trouble." The people who came after us benefited from all that knowledge and they never got into trouble, because they never used large doses. They knew that, to give you just an example, in Blacks, angiotensin-converting enzyme inhibitors are not as efficacious as in Whites, because their hypertension is controlled not by the tone of their vascular bed, but by the amount of retention of liquid. Their blood pressure is sort of more due to the fact that they have too much blood, too much volume of liquid in their vascular system. To those patients you can give captopril until the cows come home, and nothing happens. You have to also give them diuretics, so we developed a combination of captopril and diuretics, and everybody after that did the same.

But through those years, we had a lot of bad publicity. You probably are aware that the FDA approval is in three phases: phase one, phase two, and phase three. At the end of the phase three, the results of the clinical studies with the drug are submitted to a board of experts, called the advisory board or the advisory committee, that is formed by people who are recruited by the FDA among the specialists in the field. They are asked to give their opinion about whether the drug is safe and effective. Then the FDA makes up its mind, and it doesn't have to follow their advice, but usually it does.

The advisory board meeting on captopril happened on a Friday. It went into history as "Black Friday." They could not say that it was not a very worthwhile drug, because they knew that it was the first drug of its class in the field and that there was definitely a beneficial effect. They had so many concerns that they finally agreed that they would recommend it for approval, but only when every other drug had failed. That was a very serious drawback. The approval was given by the FDA in record time. You see, captopril was made in 1975, but really the first clinical study was done at the end of 1976 and it was released in 1982. But it was released only to be used on those patients who had failed to respond to any other drug. That's a very restrictive use. Captopril managed to survive and do okay, but it was nowhere what they expected it to be.

So right away, the company had to set up completely new clinical studies to prove that if it was used with limited dosage, it was not dangerous. We had to screen the population so it was not used in patients who would not respond no matter what. Those studies took, I think, another two or three years. Captopril was finally released again for unrestricted use as a hypertensive agent in 1984, so there was a lot of time lost. Captopril comes out of patent (12) next August or in February of the year after.

During all this period, there was a great upheaval in research as to whether you should make another compound that would be like captopril or would be different from captopril. We did a tremendous amount of research, also under the pressure that other pharmaceutical companies were coming out with other compounds and things like that. It was only, I guess, by the end of 1985 or 1986 that we advanced two other compounds into clinical studies, one a more potent analog of captopril, and the other a phosphorus-containing ACE inhibitor which was eventually approved for marketing under the generic name of fosinopril. I don't think anybody has any research in ACE inhibitors now. I mean, there are too many of them already.

By that time I had a lot of responsibility in directing research in various areas of cardiovascular drug discovery, but I had not really much direct input into the lab bench research. It was a different kind of a game.

BOHNING: How did you feel about being moved out, as it were, from the laboratory area and into an administrative position?

ONDETTI: Well, it was very difficult for me. However, I can say in retrospect, "Well, given the same situation, I would do it exactly the same."

I think that it has something to do with the organization of a company. When I became responsible for research management, many times I faced similar situations with laboratory researchers reporting to me. Companies try to set up what they call parallel ladders. First we

used to have separate promotional ladders for assistants with B.S.s or M.S.s and Ph.D.s. Eventually we had three promotional ladders, two for B.S.s and M.S.s, and one for Ph.D.s.

One of the biggest problems was always, how do you keep people contented in the lab? How do you take people into management or into supervisory positions? Now, that was always a big problem, and we never found a really foolproof way of doing it. I don't think there are foolproof ways of doing it. Some people have systems that are more or less successful than others.

I think there are several reasons for it. In some cases, it is that a lot of people, when they get into research, very soon realize that the advance, if they stay in the lab, is limited. So they, themselves—if they are sort of ambitious people—want to get out of the lab. Now, that's one of the problems.

Sometimes, the problem is that some research people can become—or are—good supervisors, or can become good managers. In other cases, it's just sheer ambition, without any real base on capabilities. Once researchers are promoted out of the lab, if they turn out to be not really not good managers, it's very difficult to bring them back into the lab.

What happens in my experience is that people who are good scientists sometimes make good managers, and sometimes don't. I find that the problem is with those people who are not good scientists. They want to become managers to make more money, since they know that they can not advance in laboratory careers because they are not really good in research. In my experience it is better to lose them than to try to improve the situation by moving them to administrative positions.

But the other problem is, what happens if the person is really a good scientist and does not want to get out of the lab, but he or she still feels torn by the situation that they are never going to make it up the career ladder. We have no solution for that. Sometimes we've given those people a different position, such as research advisor or what have you. But still, they've got to report to somebody. They cannot be completely independent, and they cannot be separated from the overall research effort of the company. Otherwise, they are out there and nobody is really going to care about what they do or they don't do. So you end up losing them anyway.

Now, in <u>my</u> case, it was a different kind of a thing. It's the situation that develops when somebody in a company tells you, "We want to promote you to be head of the department." You can't just say, "No, I don't want to," because then you're never going to be paid any attention. You're never going to be supported any further. When it happened to me and I sort of said, "Gee, I'd really rather stay in the lab," they didn't like it. So I thought about it again and I said, "Okay, I'll do it."

For a while it didn't matter, because as head of the department I had an assistant who could still work in the lab with me, but then when I became associate director, it was impossible. By that time, I knew that I just couldn't say no to the promotion. What do you do? You say to yourself, "Well, okay, let me see what I can do that can be of benefit for the company. How can I get involved in the planning of research so that I can use my expertise?" And you can. I think it's fun, but it's not the same fun. I never really enjoy it as much as I enjoyed working in the lab, because working as a manager of research, I do have to do a lot of administrative stuff. This is the very difficult part, but it has to be done, so I have a lot of respect for good managers. Telling people, "Listen, you're not very good," or "you're not the guy we want," is difficult. Everybody, when they get into research, thinks that they are good. I very seldom find anybody who says, "Gee, I'm not that good." [laughter] They all claim that they are very good, that they are not recognized. So when you have to bring in the news and tell them, "Now, listen, we think you're not that good," that's difficult.

Of course, there are a lot of things that are not fun in doing research either, for example when things just don't work. But it's different. Besides, in my opinion, when you're successful in research directly, it's much more fun than being successful as a manager.

The other side of the story is that people in bench research believe that the money is usually not distributed in proportion to their contributions; that is, if they do some major breakthrough, they're not necessarily going to get recognition. The companies usually recognize people who make good contributions. I cannot really complain in my case. The company will recognize you. But usually, they recognize your boss better.

I found this a predicament that I could not escape. When I was a director of research, I couldn't go to the department director and say, "Well, we're going to give fifty thousand dollars to that guy because he made a tremendous contribution, and to you I'm going to give, say, forty thousand. If I give to the guy in the lab fifty, I have to give the boss sixty. It's just the way it works. I mean, it's impossible, or almost impossible, to do otherwise. So, everybody wants to be a boss. I don't think anybody has figured out how to resolve this dilemma.

When I was head of antibiotic research, I had responsibility for the research on antibiotics at our facility in Regensburg, Germany. The people there were ruled by the German laws on patents. The German laws on patents demand that the inventor gets a percentage of the sales of the product covered by that patent. In this country, you know, you assign the patent to the company after filing, and that's it; but there, the law demands that the inventor gets a percentage of the sales.

Of course you say, "Well, that's the solution." Well, it might be. If I would have gotten point-one percent of the sales for captopril, I would be very well off. But there is a problem with that system. I suffered with that system in Germany. There was a continuous fight over who was inventor on any patent. We couldn't set anything to rest. The guys would fight each other like mad. I mean, the bosses would put their name on all patents, and we'd tell them that

they couldn't. So everything degenerated into a legal argument within the company. We had to call the patent lawyers into the dispute. The lawyer had to interview everybody who said they were inventors, and the lawyers had to decide who was and who was not. That did not always solve the problem completely, because the animosity was still there, since they knew that there was so much money at stake. Most of the time, the patents were of no commercial significance whatsoever, but I tell you, we spent oodles of time deciding who should be on the patent, because they knew that if they were on the patent, they had a piece of the action.

I don't think the American system is going to change in that direction, but at least we don't have any of those problems. However, the question of inventorship is very important. When we patented captopril, I told the patent attorneys, "Listen, there are other people involved." Since this was a very serious event, the lawyers did not take my word. I believe they interviewed Dave Cushman, Bernie Rubin, and myself. They decided that Dave Cushman and I should be coinventors in the patent, because we had discussed this thing from the very beginning (12). I had made the compounds, but we had discussed them on and off, so we couldn't separate the contributions.

But neither he nor I were going to get a piece of the action. It was the question of the regulations of patent law. We didn't want anybody who might have been involved in the conception to be left out, because if somebody is left out, the patent can be declared invalid. The company couldn't risk that. But if you put somebody on who is not an inventor, it could also be declared invalid. It was a serious matter.

[END OF TAPE, SIDE 7]

BOHNING: You made a few comments in your *Annual Reviews* article that I wanted to follow up on (7). You said, "There is no successful research project in drug discovery that does not involve the close collaboration of biologists and chemists. We often try to enforce this collaboration through the specifics of administrative organizations, but it has always remained a matter of personal chemistry."

ONDETTI: Yes, that is correct. I lived through a number of different structural changes. When I came to Squibb, we had a research organization by discipline. There was the department of chemistry, the department of pharmacology, the department of microbiology. Research teams were formed by people from one department and the other department, but still, the research teams did not manage the research. The research was managed by the department directors. Then, people thought that in order to get good collaboration among disciplines, you should make departments according to the different therapeutic areas that the company is involved in, so all the chemists and all the biologists in one area will be all together and report to the same boss.

In the middle eighties we changed to that type of organization. Then, after the merger, and through a collaboration with a consulting firm, we went back to the old system. Interestingly, I started with this system by discipline. Then I became director of research on the new system by therapeutic area, and then I recommended that we go back to the old system, and that was implemented. The funny thing is that when they went back to the old system, I, a chemist, ended up being director of biology. [laughter]

What happens is that in medicinal research, a drug has to come out of chemistry, but it can only be proven useful by biology. So it is, by necessity, a joint effort. I mean, in industry, no matter how good a chemist you are, you cannot thrive on chemistry alone. The people who are really adamant about doing chemistry in the pharmaceutical industry end up in chemical development, because in development the key to the problem is a chemical one, so they have to solve it by chemistry.

I had a chemist who reported to me who finally came and said, "Miguel, I just don't care to understand or know any more biology. I want to do chemistry." He is a very valuable fellow and is now the head of chemical development at Squibb. But if you really want to stay in research, you've got to be interested in biology. There's no other way out, so what happens to chemists is that very soon they become very knowledgeable in pharmacology—but then again, they're not grounded in that discipline, so they have to depend on a good biology and/or pharmacology collaborator.

There are all kinds of collaborations. Some are based on enforced collaboration. If you say these guys are supposed to be responsible for a project, as I said, the department heads of chemistry and biology to whom those individuals report have to figure out why these people don't work together or why they've got problems. They have to intervene. If you've got the system in which both report to the same boss, that boss must decide who is guilty.

Sometimes nobody is particularly guilty; it's just that people don't get along together. But sometimes they do. You can, after having worked with people for a while, realize who are the guys who are going to be good collaborators—people who listen to other people. Sometimes the only way is just to sort of let them get together on their own.

As I said, after we had the merger, I recommended that we go back to the old system, because I believe that there's something more detrimental about having the chemists and biologists under one boss. This is particularly so for chemistry because, in general, the directors of therapeutic areas are biologists—I was an exception to that—and in general end up with a weak group of chemists. I think that if you want to have a very strong department of chemistry, it has to be headed by chemists. I think this is more important than anything else, so I said, "Let's go back to the old system. We'll have good chemists and let the management worry about how chemists and biologists collaborate together. If they don't, we'll keep changing them until we find people who do; but at least we'll have good chemists."

The only thing you have to try to impress upon people is that this collaboration is a very important part of the research—that nobody's going to be the only factotum in a discovery process, and that you have to get together and contribute.

But it still depends on the personalities involved. Some people are very good, but they just don't work together because they're either too ambitious, or just so sensitive that they can't accept any kind of criticism; or sometimes because they think that they know more than the other people do and don't want to listen to suggestions, et cetera, et cetera.

BOHNING: That brings us to another of your comments. You said that, "The formula for successful research is also listening, thinking, and doing" (7).

ONDETTI: Well, I found that people who usually cannot collaborate are the people who just don't listen. In research, when it comes to doing experiments, people realize that you have to pay attention to what the evidence tells you. I mean, if you insist that you know what the results have to be and you don't pay attention to what the results really are, you're going to be a bad researcher. That's obvious—well, most of the time; some people sometimes insist on misinterpreting the results. But in terms of the collaborative research, it's not that obvious. You are at a meeting and people say something. The other people are only waiting for their time to say what they want to say, but they just won't listen to what the other people say. They don't say, "Gee, maybe he's right. Maybe I should just look at this or that." I think this is critical. I mean, if you're going to collaborate with somebody, you have to have a certain amount of respect for the person, their ideas, and opinions. You have to listen, even if you finally make a decision based on your own judgment.

Many times people sit together at a group meeting, or even at a personal meeting, but they really are not together, you know; they are not really open to that kind of interaction. When it doesn't happen, I found that it is very difficult to change that. Sometimes we try and we get some degree of success, but it's not as good as when you see it develop naturally.

Now, when I was the head of the cardiovascular research, I saw people who really worked very well with each other—chemists and biologists—because they had this mutual respect for each other's opinion. I think that's the only way you can do it, but it doesn't occur as often as one would want it, and the collaboration is usually enforced by the heads of the corresponding departments who have the administrative responsibility for the projects.

What people sometimes don't realize is that this kind of collaboration has to go to the level in which the people are at the bench and they don't have, actually, administrative authority over each other. When your boss tells you that you have to collaborate with so and so, you're

going to do it even if you don't like it, unless you have another job and you know that you're going to leave. That's not usually the case.

BOHNING: You also mentioned, in that article, "The necessity of close interaction between industrial and academic research."

ONDETTI: Yes. I guess I have been particularly aware of this because I always worked in areas of frontier research in which academic research was strongly interested. Being in peptides from way back put me always in work with compounds that were of a great academic interest, so I always had a very close contact with the people in academia. I mean, I was very often contacted by people in the universities saying, "Can we have some of your compound? We want to do this; we want to do that." Sometimes they tried to interest us in working with them. Sometimes they tried to interest us in supporting their studies.

I was always very close to whatever was being done in the academic labs. But also, I think it cannot be denied that in the pharmaceutical industry in general, you work on the basis of what a lot of times is being discovered in academic laboratories. I mean, a lot of what we did started by being based on what was found in other institutions. For example, they got us interested in gastrointestinal hormones, in angiotensin converting enzyme inhibitors, and so on. We were interested in the angiotensin-renin system because of what was being done in academic research. We took the risk of following up an area that was very controversial, but only because some people in that kind of field said that it was important. Some others said that it was not.

The same is true in any novel research area, I think, unless you're working in the medicinal chemistry area that now is called me-too research; that is, you're just making another compound like the one previously discovered by somebody else. You always want to be—and really, you have to be—very close to what is being done in the forefront of academic research.

Now companies do a lot of very advanced or very forefront research, particularly in some of the biotechnology companies, but still, most of it is done in academia. So I think it is very critical to the success of the pharmaceutical industry that it is surrounded by an environment that does a lot of the very basic research; because companies can do some basic research, but most of it is still going on in academic institutions.

It's very useful for a pharmaceutical company to be constantly in touch with academic research. We have different systems, not only seminars. Bristol Myers, even before Squibb merged with it, had a system in which they have an award for the most successful research in therapeutic areas of their interest—cancer, cardiovascular, and so on—to keep them sort of connected to the academic environment. Sometimes these connections are considered detrimental for the freedom of academic research. That can be very serious when there are connections that involve clinical testing of drugs, but I'm talking more about connections that

involve basic research. You have to keep close to these people, because they can really be the source of new ideas. This is very, very important.

BOHNING: Apparently, this was the first example of what was called a rational drug design. Did you coin that term, or did someone else coined that term?

ONDETTI: Well, I don't know how this thing got started. We didn't use the word, "rational." We used the words, "drug design," to sort of emphasize that the compound had not been obtained by screening of randomly obtained compounds, but by just looking at an enzyme or looking at a target and making a compound that was geared to that particular target. I think that somehow, the word got to be used in connection with the adjective rational. I think it's misleading, because the tried and true procedure of doing screening of compounds from a large series of sources of natural products or other chemicals is also rational. I mean, there's no such thing as irrational drug design. [laughter]

I can't understand why they got to use it; it's not an appropriate use of the word. I think design is correct, in the sense that you want to differentiate between finding the drug by screening and finding it by looking at the target. That is the difference there. But both are very rational approaches. Even today, people are going back to screening, because if you really want to find a completely new type of chemical, sometimes the only solution is to do some random screening.

The captopril case was, in a sense, the first time in which one said, "This is the target that we want to hit. Let's look at its properties, and let's make a compound that will fit this target." It might have been done before in biochemistry, in the sense of making inhibitors or other enzymes, but it hadn't been done in terms of making a drug. So that's the reason why in our first paper in *Science*, we called it a drug design (6).

BOHNING: Doesn't computational chemistry play a large part in that today?

ONDETTI: Yes. I was asked some time ago what was the role of computational chemistry in the discovery of captopril. It didn't have one, because at that time we didn't have good computer tools. Besides, even today, there's no three-dimensional structure of angiotensin converting enzyme available to use in computer-aided molecular modeling. It's going to have more and more of a role to play, except that sometimes its role may be overestimated. I mean, to make a drug you have to build into a molecule not only what you get from the molecular design, but also the ability to be absorbed from the gastrointestinal tract, and the ability to survive metabolism and those things that we don't know enough about and can not be learned by just

looking at the x-ray structure of the target. You have to do it by using whatever knowledge has accumulated in the field. There is still a lot of art to drug making.

BOHNING: I have just a few more questions. We talked about the importance of teamwork. What changes did you see in the company's attitude towards research and development during your career?

ONDETTI: I think we should really talk about changes not only in the company, but industry-wide. Since I got involved in medicinal chemistry research, we migrated from an environment in which there was only random screening research into an environment in which there was more emphasis on identifying targets that would be useful for drug discovery. And, even if we have in many cases gone back to screening, it has been done with the emphasis on specific cellular or molecular targets.

At the time I started with Squibb, the emphasis was on having in-vitro testing systems and in-vivo animal models of the different diseases. Then you had to make compounds and test them. Now, there's more emphasis on the mechanism of the disease, and what part of that mechanism you're going to target for drug discovery. I think that is mostly due to the fact that there has been a tremendous increase in the knowledge of molecular biology. This kind of knowledge didn't even exist in the 1960s. In that respect, there have been worldwide—industry-wide, I should say—changes.

Companies' research policies change, usually, with the industry. Certain companies—it's probably true in other industries—are more willing to follow these changes than others. I haven't seen companies that are so rigid that they would stand on their own and say, "We'll do things our way, and that's it." There are companies that are more likely to try completely new approaches or look for new therapies, and others that are a little bit more likely to try to work on the areas that are already well known. Nowadays, everybody's moving, literally, away from me-too compounds, because of the regulations in terms of pricing and things like that. It's very difficult to survive without having some new types of drugs, what are called new chemical entities.

As I say, changes are more industry-wide. The companies just follow along whatever happens to be the particular wisdom of the times. People used to believe that there were companies that were more research oriented than others, but I think that this is debatable. There are companies that have been—if you're looking over periods of thirty, forty years—more innovative than other companies. We have seen in different periods, companies that have brought out very innovative drugs. Then they go into sort of a decline for a while, but they might come up later on. It's very difficult to say, but many times these changes are due to changes in management teams.

In general, all the companies move along with the spirit of the time. If the philosophy changes, all the companies change. One may be faster than others, but they all have to follow the philosophy of the time.

BOHNING: We've covered just about everything else on my list. I have just one last question, and that is, what did it mean to you to win the Perkin Medal?

ONDETTI: Well, it was a surprise, because I sort of lived in the rarefied atmosphere of medicinal chemistry. I always thought that the name of chemistry, without any other modifications or any other adjectives, didn't belong to me; that I was more part of the pharmaceutical industry, not the chemical industry. So I said, when I accepted the award, that there's a certain peculiarity about being a medicinal chemist that makes one somewhat feel, to some extent, different from other chemists. It is the fact that in the pharmaceutical industry, chemistry is only one part of the equation, but biology is the other very important part of the question. So the chemists, once they join a pharmaceutical company, have to be willing to become—to some extent—biologists. Otherwise, they will not survive.

[END OF TAPE, SIDE 8]

ONDETTI: In some sense, if you really are very, very keen on being a chemist—just a plain chemist—you tend to migrate, within a pharmaceutical company, into chemical development. After I said all that, I felt that medicinal chemistry might be just medicinal chemistry, but it's chemistry after all. I think some of the most creative chemistry has been done in the medicinal field. So receiving the award was kind of like coming back to feeling again part of the brotherhood, like I felt when I first went into the school of chemistry. At that time, I still wasn't contaminated by any kind of adjective; I just was a chemist. When somebody asks me what I am, or what I do, I always go back to just saying, "I'm a chemist." I always felt kind of strange, in the last couple of years of my career at Squibb, being a director of cardiovascular research where all the people reporting to me were biologists. Of course, the reason why it was probably done was that I had become very knowledgeable in the field.

Many times I've felt like a fish out of the water, because I wasn't trained in biology. I wasn't a card-carrying member of the biologists' group, and I always felt more comfortable with chemists. So, in the end I felt very proud to be recognized by a group of people for whom only chemistry counted, even though I'm sure that my contribution made the splash it made because of the biology that went along with that particular compound.

It was sort of like going back to my roots. It was a very, very joyful moment. I'm always kind of sorry that when I left, one of the things I didn't take out of my files on the

computer was my speech for the Perkin Medal, because there I tried to describe what it meant for me to be a chemist; what it meant being a chemist when I first came to this country, and how it changed over the years, and what it meant being in medicinal chemistry. That's more or less what I said to you.

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

ONDETTI: No, really, I think we've gone over everything pretty much in detail.

BOHNING: How did you feel about having the building dedication in your name?

ONDETTI: Oh, I enjoyed that. I was a little bit taken aback by the legend on the plaque. They gave me a copy of the plaque. [indicates] That's a copy of the plaque that they are putting in the building. It was originally planned to be in one of the not yet completed biology buildings, but I understand that it was finally put on the front of one of the chemistry buildings.

BOHNING: Just for the record, I'm going to read this, so we have it on tape. This plaque says, "Miguel A. Ondetti Laboratories. To Miguel Ondetti, Ph.D., who led the team that discovered captopril and demonstrated that a highly selective drug could be logically designed through an appreciation of the structure of a target enzyme. Captopril has transformed the lives of more than twenty million sufferers of hypertension. Dedicated on this date, April 24, 1991. Bristol Myers-Squibb Company."

ONDETTI: I never really looked at myself as being a leader, unless it's only in the sense that I'm a real doer and I push people to do things along with me. I mean, I like to get things done. I'm not the kind of person who likes to tell people, "Do this and do that." I like to step in and do it, with them or without them. So when the captopril effort came about, if I was the leader, it was because, as I say, when we saw that there was something that had to be done, I went in and I did it.

That was my experience during all my years at Squibb. No matter how critical or negative people are, in general, when they find somebody who is very eager to do something, they end up helping. People are carried off by the enthusiasm of people who are doers. Whenever I wanted to do something, they perceived that it was very important for me and ended up saying, "Okay, I'm going to help;" they all put their shoulders to the grindstone, and we did it. So, in a sense, people perceived that I was the leader, but none of those people who were involved in the captopril story reported to me, except for Emily. [laughter]

I also spearheaded the project because I was the chemist, and without me being willing and eager to make new compounds, nobody could follow through. If I hadn't moved—if the message that David Cushman sent to Zola, which ended up in my place, wouldn't have been acted upon—that would have been the end of it. But once I decided what we had to do, then people helped tremendously. It was very important.

BOHNING: On that note, I'd like to say thank you very much for spending this time with me today. I've appreciated it.

ONDETTI: Thank you for the attention.

[END OF TAPE, SIDE 9]

[END OF INTERVIEW]

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