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KOJI NAKANISHI

Transcript of an Interview
Conducted By

Leon Gortler

at

Columbia University
New York, New York

on

15 February 1985

With Subsequent Additions and Corrections

THE CHEMICAL HERITAGE FOUNDATION
Oral History Program

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KOJI NAKANISHI

1925 Born in Hong Kong on 11 May

Education

1947 B.Sc., chemistry, Nagoya University
1954 Ph.D., chemistry, Nagoya University
(Mentor: Y. Hirata)

Professional Experience

1950-1952 Garioa Fellow, Harvard University (with L.F. Fieser)
1955-1958 Assistant Professor, Nagoya University
1958-1963 Professor, Tokyo Kyoiku University
1963-1969 Professor, Tohoku University, Sendai
1968-1977 Director of Research, International Centre of Insect Physiology and Ecology, Nairobi, Kenya

Columbia University
1969-1980 Professor
1980- Centennial Professor
1987- Chairman, Chemistry Department

1979- Director, Suntory Institute for Bioorganic Research, Osaka, Japan

Awards

1954 Award in Pure Chemistry, Chemical Society of Japan
1968 Asahi Cultural Award
1978 Ernest Guenther Award, American Chemical Society
1979 Chemical Society of Japan Award
1979 E. E. Smissman Medal, University of Kansas
1979 Centenary Medal, British Chemical Society
1980 H. C. Urey Award, Phi Lambda Upsilon, Columbia University
1981 Remsen Award, Maryland Section, American Chemical Society
1985 First Research Award, American Society of Pharmacognosy
1986 Alcon Award in Opthamology
1986 Paul Karrer Gold Medal, University of Zurich
1987 Honorary D.Sc., Williams College

ABSTRACT

This interview covers the life of Koji Nakanishi from his early education in Egypt to his current work as Professor of Chemistry at Columbia University and Director of the Suntory Institute for Bioorganic research in Japan. He discusses his education in wartime Japan, his fellowship years at Harvard University working with Louis Fieser, a succession of positions at various Japanese universities, and his eventual decision to go to Columbia University. His research on the structure of natural products and, more recently, their mode of action, and the development and use of infrared spectroscopy, NMR, and circular dichroism is discussed in some detail. The interview concludes with a brief discussion of his avocation, magic, and some general comments on the future of organic chemistry.

INTERVIEWER

Leon Gortler holds an A.B. and M.S. (chemistry) from the University of Chicago and a Ph.D. in chemistry from Harvard University. He has been on the faculty of Brooklyn College since 1962, where he is currently Professor of Chemistry. This interview was conducted as part of Professor Gortler's long range study of the development of physical organic chemistry in the United States.

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INTERVIEWER: Leon Gortler

LOCATION: Columbia University
New York, New York

DATE: 15 February 1985

GORTLER: This is Leon Gortler interviewing Professor Koji Nakanishi in his office at Columbia University on 15 February 1985. Professor Nakanishi is currently Centennial Professor of Chemistry at Columbia and is also the Director of the Suntory Institute for Bioorganic Research in Osaka, Japan.

I know you were born in Hong Kong on May 11, 1925, but I know absolutely nothing else about your family or your education. How did you happen to be born in Hong Kong?

NAKANISHI: My father was with the bank--what is now called the Bank of Tokyo. It used to be the Yokohama Species Bank. And like the Bank of Tokyo today, this bank has branches all over the world. In fact, I was simply born in Hong Kong. After that we were two or three years or so in Lyons, and then three or four years in London. I got my primary education in Alexandria, Egypt at the British Boys School. I first came back to Japan with my parents when I was about twelve or thirteen years old. At that stage I started learning Japanese. So, I'm not a typical Japanese in that sense. I was born in Hong Kong and I've got three brothers, all younger. One was born in Lyons, one in London, the third one in Alexandria. Four boys.

GORTLER: Did any of your brothers become scientists?

NAKANISHI: My third brother, yes. I was in Egypt, Alexandria and there still existed a strong influence of the French at that time because of the Napoleon years. I went to a school called The British Boys School, and it still exists. I have met two other chemists who are quite well known, who come from the same school. They are Steve Hanessian and Wilfred Armarego (Australian National University).

GORTLER: Well, that explains your ability in English. Can you give me your father's name?

NAKANISHI: Yuzo. He died about twenty years ago.

GORTLER: And your mother?

NAKANISHI: Yoshiko.

GORTLER: Aside from taking you around the world, and giving you that kind of background, what other influences did your parents have on you?

NAKANISHI: Well, not much. My father was hardly at home because he was rather busy. But I feel grateful because when I was in Egypt, the first language was French. That's what I spoke best. And then number two was English and a little Arabic and Japanese. Only Japanese is oral, no reading, no writing. I spoke with my brothers, in fact, in French. And when I came back to Japan--this was when I was about twelve or thirteen years old and I didn't like the idea--my parents sent me to a missionary family on a private basis. This was an American family and their son was about my age. So every Saturday afternoon I was sent there by force, you see. Well, it was all right.

GORTLER: And what did you do there?

NAKANISHI: I just played with the son so that I would not lose my English. As a result, I have kept my English. I've lost most of my French. But I am grateful for being forced to keep up my English. Because of my English ability, I was treated as a special student during my middle and high school days in the Japanese school system. Then, I was one of the earliest Garioa fellows, the predecessor of what we now call the Fulbright fellows. During the war in Japan, English was an enemy language, so all English education was stopped. After the war, and I remember it was in 1950, I just went to a friend's place. We were living in the same apartment block and I just went there for drink and chat. He said, "Koji, do you know that tomorrow there's going to be the Garioa exams for going to the States?" So I just went there, without any preparation of course, and I passed the exams and that brought me to the Harvard Chemistry Department and since then I've become a chemist. So it changed my career.

GORTLER: I see. I think we have to go back because I've lost a few years. I knew about your going to Harvard but I assumed you were already destined for a career in chemistry. Let's go back and work our way through that period.

NAKANISHI: I jumped a little bit.

GORTLER: When did your interest in science begin? Do you remember your earliest scientific training?

NAKANISHI: Well, I'll just tell what went on during the war in Japan.

GORTLER: Okay. That would be good.

NAKANISHI: It's really jumping way ahead with that Garioa business. During my high school years the war started and it became more and more difficult.

GORTLER: Where were you were living then?

NAKANISHI: I was living in Osaka. My parents were living in Tokyo. I was in a boarding house in a private high school. The classes were starting to shorten and we started working in factories, iron manufacturing factories. And all these high school kids, and university students, all of them were working. My last year in high school there were hardly any academic classes. And, frankly, we were all brought up in that militaristic mentality and I thought that one day we were going to be killed. I mean, the Americans will land in Japan, and we would just sharpen our bamboo spears and would be killed. That's really what I thought.

GORTLER: That must have been very frightening.

NAKANISHI: Yes, but you get used to it. The whole of Japan was mass hysteria. So I entered the Nagoya University. I'll tell you what I first wanted to become when I was young. I wanted to go into shipbuilding. I liked model ships; I made a lot. But then that was not appropriate, so I decided to go into applied chemistry at the University of Tokyo.

I was, I think, in my class, at the very top. And so under normal circumstances I would have gotten into the University of Tokyo. In those final years of the war there was no written examination. It was all based on school records. So I would have gotten in, except that there was a military training course--military drilling--and my grades there were not good. So I was the only one in my class who did not get into the University of Tokyo. I remember my mother's shock. It was the most prestigious school and I failed becoming a student of applied chemistry there. And, if you didn't become a student, you would be drafted. Nagoya University at that time was a new university and we looked around and there happened to be an opening in the chemistry department so I became a chemist.

GORTLER: There was an opening for a <u>student</u> in the chemistry department?

NAKANISHI: Yes.

GORTLER: Now, this is still while the war was going on?

NAKANISHI: Yes. It is just before it ended. And then, my first year in the university we were practically drafted as students and we were taken to an arsenal where they make bombs.

GORTLER: An armory factory?

NAKANISHI: Well, but in basic research. We were taken into the deep mountains in Japan because all of Japan was starting to get bombed. And then we were supposed to be making explosives. But it was our first year in the university and I didn't even have any organic lab experience. All of a sudden we're supposed to make explosives. It's crazy, what happened in Japan.

In my very first experiment, I had a big five-liter round-bottom flask, and a small amount of some liquid in the center of the heated flask. Then I was dropping some KOH solution from a dropper. Instead of going into the small amount of solution in the middle, it touched the side of the hot flask, the whole thing cracked and everything was finished. In those days, a five liter round bottom flask was not easy to get. In fact, I had made a special trip back to the Nagoya chemistry department in the overcrowded train packed like a sardine to fetch it. It was simply a good excuse to meet my girl friend in Nagoya (who is my wife now). And this stupid failure left a very bad impression on me about synthetic organic chemistry. I don't know whether that's the reason but since then I have not felt close to synthetic organic chemistry.

Anyhow, soon after that the war ended. Since our university was bombed, we were still in the mountains for one year or so. We found many sacks of crude dark-brown glucose hoarded by the army. I remember us having handfuls of dark glucose which made our teeth black and then shoot absolute ethanol into our mouth with a syringe. Then we came back to Nagoya and started working seriously on chemistry.

GORTLER: This is still 1945 or 1946?

NAKANISHI: It was 1946. I finally got my bachelor's in 1947.

GORTLER: That was still fairly fast.

NAKANISHI: Totally insufficient training though. Nagoya University was at that time a new university. It was an Imperial University.

GORTLER: Imperial meaning it was state supported?

NAKANISHI: The seven Imperial Universities which were the most prestigious before the war were: Hokkaido in Sapporo, Tohoku in Sendai, the University of Tokyo, Nagoya, Kyoto, Osaka, and Kyushu. Before the war there used to be another one in Taipei and one in Seoul, which are now the two prestigious national universities in those cities. The seven Imperial Universities are still the most prestigious of the federal universities. Of course, they're not called the Imperial Universities anymore.

Nagoya University was just started and I'm the third graduate of that university. All the professors at Nagoya University were an elite group of highly motivated, young, assistant professors brought from the University of Tokyo. They came there to start this new university. And there was only one organic or biochemist and that was Professor Fujio Egami. Unfortunately, he died prematurely a few years ago, and if he were living now he would be in his mid-seventies. He was very well respected, probably one of the most active biochemists in Japan. He was in charge of the organic group. He discovered, for example, ribonuclease T_1 and ribonuclease T_2.

In the Japanese system, as you probably know, there is a full professor, an assistant professor, and two assistants. Fujio Egami was the full professor and under him was Professor Y. Hirata, as an assistant professor. When Hirata separated from Egami to start his own organic chemistry group, I went with him and eventually became Assistant Professor under Hirata.

GORTLER: But this is already later on, after you had gone to Harvard.

NAKANISHI: Yes. I guess Hirata formed the organic chemistry group around 1951, and I returned in 1952.

GORTLER: But you were already working with Hirata before the Harvard years.

NAKANISHI: Yes, I was there as a graduate student.

GORTLER: So you had started your graduate work right after you finished your undergraduate work.

NAKANISHI: Yes.

GORTLER: I take it that there was never any question in your mind that you were going to some university, considering your background. Were there any professors or teachers before you ever entered the university that were particularly influential? Do you remember anyone from Alexandria or Japan?

NAKANISHI: You mean teachers of science. No. Because of the war in Japan, there was no continuous flow of thought. As I mentioned, I don't think I was exaggerating too much when I thought that I was never going to live through the war. I remember the same thing when I got engaged to my current wife. I thought, "Okay we're engaged now, but probably we'll never marry." I remember that sort of thing going in my mind. My wife was against the war and she was much more mature and calmer than me. She said, "Eventually this war is going to end with Japan being beaten," but I was far more simple-minded than that.

GORTLER: You've pretty much told me about Nagoya. That was also a rather disrupted experience until the war ended.

NAKANISHI: Yes.

GORTLER: Then, I suppose the two that influenced you most were Egami and Hirata after that.

NAKANISHI: Yes.

GORTLER: Did you have any conception of what being a chemist was like? I mean, you sort of accidently became a chemistry student, but at what point did you have some feeling about what you might be doing?

NAKANISHI: Well, it's very difficult for you to understand because postwar Japan was very chaotic. We didn't have enough food to eat; the Americans were there, and it was very chaotic. I may be jumping ahead again, but just to give you an example of what it was like, there were no reagents, no spectroscopy, no journals, and no food. And with the bombing, we had to re-erect here and there. No heating. We had to work under those circumstances, so what a professional chemist would be, I had no

idea. I was still young also, twenty-three, twenty-two, and had just gone through the war.

I remember that there was an American cultural center--every major city had set one up--and that was where Chemical Abstracts came. I went to that place once a week on a bicycle and stayed there from afternoon through the night copying by hand of course, to keep up with what was going on. Paper chromatography was introduced around this time. I think it was 1948-1949. I was one of the first people to do it. Most knowledge came from absorbing through Chemical Abstracts and from books which came from the States. Nothing like what you people in America would have thought.

GORTLER: I was going to ask about your textbooks, but you had very few. Even your training in physical-organic chemistry was done without textbooks.

NAKANISHI: Japan had a very strong tradition in natural product chemistry because, like many other countries, the organic chemist who went to work in Europe went to work in a natural products chemistry lab. I think most of the organic chemistry which was flourishing was natural product chemistry. Physical organic is relatively new compared to natural products, and the great European names in organic chemistry at that time were mostly natural products chemists.

In the early years, in the 1870s and later, young Japanese organic chemists were sent abroad to Europe. At the same time, professors were invited from Europe (mostly England and Germany) to start the University of Tokyo. The basic organic chemistry in Japan was split into three faculties and it still is so today. In other words, we don't have a Department of Chemistry. We have the Faculty of Science, the Faculty of Agriculture, and the Faculty of Pharmacy. And organic chemistry, practically the same material, is taught in all three faculties. We still have the same distinction, although there is tremendous overlap. There is a little difference in emphasis, of course, in agrochemistry, pharmacology, and so on. But not much.

GORTLER: They still maintain the same system of having a single professor of organic chemistry?

NAKANISHI: No. There are many more in the Faculty of Agriculture and the Department of Agrochemistry. Each faculty has at least two or three professors in organic chemistry. And then each professor, or each group, has their own assistant professor and two assistants. So the number of faculty in one chemistry department, for example, within the faculty of Science or Pharmacy, is enormous.

There are three pioneers in the various faculties. These were all people who were sent to Europe around 1910. The one in Chemistry, in the Faculty of Science where I come from, was Professor Toshiyuki Majima. In Agrochemistry it was Umetaro Suzuki, and in the Faculty of Pharmacy it was Yasuhiko Asahina, among others.

All three of them were natural product chemists. Even in the prewar years, the tradition in Japanese organic chemistry was that it was quite strong in natural product chemistry, and much weaker in synthetic and physical organic chemistry. Right after the war, people were trying to reconstruct the framework again for research. Natural product chemistry recovered from the war damage the quickest. We were trying to get information, any scrap of information from America in particular, because we were completely isolated during the war. In that sense, the American Cultural Center was a big help.

GORTLER: You were married in 1947. What was your wife's background? Was she a student at the University as well?

NAKANISHI: She was a lab assistant in the analytical group at Nagoya University. It was rather unusual for this type of thing to happen. It was not an arranged marriage, of course.

GORTLER: I suspect that disrupted the family some.

NAKANISHI: Not too much.

GORTLER: What has her role been in your career?

NAKANISHI: Well, I was a straight A student. I was very serious. I'm not saying that I'm not now. I was simple-minded and I still am. But, as a human, I was much dryer...no fun, you see. But my wife is the opposite. She's very relaxed. As I told you, she had much more pragmatic views about the war. She reads a lot. And she was a lab assistant in the University because unless she was employed she would have been drafted into a factory. So that's why she was a lab assistant. She's so much more mature than I am. And then she knew much more about literature and art. She's now a semiprofessional artist in several areas. So that has changed my character a great deal. And I think maybe I've moved away from being a dry person. [laughter]

GORTLER: I've heard you talk, and your talks were never dry at all. As long as we're on your family, you have two children. How were they influenced by the fact that you are a scientist?

NAKANISHI: My daughter is now thirty-four years old. Well, it's jumping the years a little bit. I went to Sendai, Tohoku University in 1963 and then stayed there until I came to Columbia. But, my daughter was entering middle school around 1965, and that summer she lost total interest in the Japanese school system. She didn't enjoy it. So without us thinking that we would be coming to this country, we sent her to Palo Alto, where I had friends--Carl Djerassi and the Packards. Martin Packard was, at that time, the Vice President of the Varian Company. So we sent our daughter to Palo Alto and they took care of her. She went to Gunn High School. She first stayed with the Packards and then with the Crostens. Loran Crosten was head of the Music Department. But when she was coming back for college, we came to Columbia, so she had to get to college.

Anyhow, my daughter with a background like that has a personality very much like mine. And what it means is, I think, I'm ambitious and my daughter is too, in a sense. She's now married to Fred Alt, who is a professor in the Biochemistry Department at Columbia. He's thirty-six. I hate to say this from my own mouth but he is supposed to be one of the best molecular biologists of his generation. So, my daughter is becoming like my wife, but my wife is more relaxed. Since Fred is a hard worker, my daughter takes care of all the home stuff.

GORTLER: Your daughter's name is?

NAKANISHI: Keiko, but we call her Kay.

GORTLER: And your wife's name?

NAKANISHI: Yasuko. And my son, when we came to this country in 1969, of course, spoke no English. I mean just average, whatever any other Japanese early middle school kid would have, so he had great difficulty at first. But in three or four years he was okay. He belongs to my wife's side in personality. He is more easy going.

GORTLER: And your son's name is?

NAKANISHI: Jun. He is twenty-nine years old and still lives with us.

[END OF TAPE, SIDE 1]

GORTLER: How were you supported as a graduate student?

NAKANISHI: By the government. I was married in 1947, two weeks after I got my bachelor's degree. It was the postwar years and it was very difficult to support ourselves. My wife worked and we had a very trying time. I mean, we still remember digging up potatoes from the fields that farmers had already harvested. That's the way we survived. It was like that all over Japan.

GORTLER: In fact, your earliest research problems were in natural products. You did some work on actinomycin.

NAKANISHI: Yes, in retrospect it was an impossible task to work on the structure of actinomycin in those years. I had no idea. I was just doing hydrogenation, trying to find out how many moles of hydrogen it could absorb. But if you look at the structure of actinomycin now you'll see that it's almost impossible. It was done by the old classical method.

GORTLER: You had no spectroscopy?

NAKANISHI: No spectroscopy, no. No.

GORTLER: I noticed that your third paper was on xanthopterin from silkworms (1). You've come back to the silkworm on a number of occasions. Is it just because it's a major source of natural products or because it's so prevalent in Japan?

NAKANISHI: No, it is just a coincidence. Xanthopterin was my third paper. We started getting into that field because we started collaborating with Dr. H. Kikkawa, a geneticist who is retired now. He was a well-known geneticist in the classical sense. He was the head of the Sericultural Station in Okazaki, near Nagoya. Hirata started collaborating with Professor Kikkawa. The silkworm was used as a favorite animal for genetic studies. I got more and more involved in the project. When I went for the Garioa exam and passed, I was asked to give a few places where I wanted to work. So the two names I knew at that time were Louis Fieser at Harvard, and George Beadle at Caltech. The latter of course, because I was working in genetics at that time.

GORTLER: That's right, he's not a chemist but a geneticist.

NAKANISHI: Yes, a geneticist who got the Nobel Prize later. He became the Chancellor of the University of Chicago. It's interesting how I decided to go to Harvard and not to Caltech. I was in an organic group of course, but I think what went through my mind was that if I go to Harvard I could go to the West Coast without paying out of my own pocket. I could go to the East and then visit Caltech on my return. If I ended up in Beadle's place and I wanted to go to the East Coast, even for tourist-related reasons, I would have to pay myself. And I think that's one reason I went to Harvard. As a result, I became an organic chemist. But otherwise I could have been something else.

GORTLER: I see. It is interesting how those things influence one's life at any given time. When you went to Harvard you essentially did not have the equivalent of a Ph.D?

NAKANISHI: No. I had at that time two-and-a-half years of graduate training. I was, however, a so-called post-graduate student. Can I go into my Harvard years now?

GORTLER: Yes, I'd like you to tell me as much about Harvard as you can.

NAKANISHI: I had lots of interesting experiences at Harvard. First of all, we went by an American military plane.

GORTLER: Your wife came with you?

NAKANISHI: No. That I regret, but in 1950, it was still a trying time. And it was just two months after we had a baby, our daughter, Kay. So it was almost inconceivable moneywise to bring her. It was totally out of the question. On the military plane we were served a chicken leg and I remember how excited I was just to see a chicken leg. The food situation was like that in Japan. Then we were sent, after a brief stay at the International House in Berkeley, as a group (that Garioa group) to Rensselaer Polytechnic Institute (RPI) for a so-called orientation course. We learned about American jokes, history, geography, and so on, and what democracy meant. They were a bunch of good teachers. The man who taught us American colloquial language was an author. His name was Smith. He was quite a well-known author. He died recently. He was a teacher at Bennington. People like that.

All of these people who were the Fulbright or Garioa students now comprise a big proportion of the ruling, top management in Japan. In every field there are lots of our contemporaries. Many presidents of universities and ministers, numerous professors, bureaucrats, and artists have come out of

that program. It was a very elite, select group who came to this country after the war, and I am extremely grateful for this program. It has contributed enormously to postwar recovery as well as to my professional training.

GORTLER: About how many were there at that time?

NAKANISHI: I can't give you the exact numbers, but in my group I think there were thirty or forty. After returning to Japan they all did very well, of course, because very few people had gone to the States at that time, the early 1950s. The tenure was for one year. I went to Harvard in any case, and I remember seeing Fieser the first time on a weekend afternoon the day I arrived in Boston. He used to carry his dirty towel and was still experimenting. It was in 1950, so he must have been in his early fifties. I think he must have been rather suspicious or had no idea about Japanese chemistry. He left me alone for about a month or so. I was pretty hard-working. I always used to work until one o'clock, two in the morning and practically all weekends.

GORTLER: Did he assign you a problem there?

NAKANISHI: Yes, he did. There were two remarkable things. I did a Friedel-Crafts reaction on naphthalene and that gives you a carbonyl group. From my training in Japan, I had learned to detect the carbonyl function by making a carbonyl derivative and then carrying out an elemental analysis. But my lab mate was Costa Anagnostopoulos. He was a graduate student at Harvard. Since then he's been at Monsanto and was responsible for making the artificial turf. He has been very successful and he's very high in management now. He is one of the senior vice presidents. Anyhow, he told me, "You know, Koji, we should take an infrared spectrum of this." I had no idea what an infrared was.

GORTLER: At that time I think they had a single-beam instrument at Harvard.

NAKANISHI: It turned out that the second commercial double-beam instrument had just been acquired by Harvard. It was a Baird instrument. He took me to the IR room, inserted my sample and set the instrument. I watched the pen moving down and up to record a a sharp peak at 5.9 microns (approximately 1695 cm^{-1}). That was my first exposure to spectroscopy. I still have that first IR chart. Somehow it must have clicked because I got very interested in it. I started collecting data. I also got a small group within the Fieser group and we used to get together once in a while and discuss infrared and UV among ourselves.

GORTLER: Was Peter Yates there yet?

NAKANISHI: Peter Yates? Yes, he was there but he belonged to Woodward's group.

GORTLER: Oh yes, that's right. He was not on the faculty yet. Who were some of the other people in the Fieser group?

NAKANISHI: I'll tell you in a minute.

I got into spectroscopy that way. And then, two and a half years later I went back to Japan. When I went back to Japan, I had collected enough data. So I wrote an introductory article on what infrared spectroscopy was and what its implication in organic chemistry meant. This was quite an eye-opener for practically all the Japanese organic chemists and I soon became flooded with requests to write more articles. So I started a monthly series in a Japanese chemical magazine. At the end of that, I compiled this and came up with a book which turned out to be very successful.

Just to finish this part of the story, in 1960 there was the first IUPAC Natural Product Symposium in Australia. I happened to be having breakfast with Carl Djerassi and Derek Barton at the same table. These two people, of course, are great names. At that time the great names in natural products were these two and R. B. Woodward. I had my infrared book with me in Japanese, so I very timidly brought it from under the table and showed it to these two people. I asked, "What do you think if I published this thing in English?" Both of them said, "Why don't you try it. It seems like a good book." So I went back and did the translation with a friend of mine--by dictation. We did it in a week and published it (2). And that was quite a big hit. That made my name, at least, in applied infrared spectroscopy. Lots of people got to know my name so I profited a great deal, professionally as well as financially.

GORTLER: Was it published in Japan in English as well as here? How was it published here?

NAKANISHI: Yes. In the U.S. it was published by Holden-Day. Why did I do it with Holden-Day? Because Carl Djerassi had just got involved with this new company. It was through his advice. I think it also helped Holden-Day in the early days. It was quite a hit.

I told you that Fieser left me alone for about a month after giving me a project. The project was on alkylated naphthoquinones, a project on antimalaria drugs. I did a series of Hooker oxidations. It's an oxidation in which the side chains switched from top to bottom, top to bottom. As you keep on doing it the side chains become shortened, one by one. Hooker, incidentally, was quite a magician. Fieser also had posthumously compiled Hooker's papers and had published a monograph. I had to analyze the products, so I said, "Why don't I do it with paper chromatography?" I did the paper chromatography and came out with a beautiful series of spots, depending on the length of the side chain. Apparently no one had done that at Harvard before. So when Fieser came down after a month, he said, "What's going on, Koji?" I showed him the results and he was astounded. I think my evaluation went up then.

GORTLER: I imagine it did.

NAKANISHI: Then I started attending Paul Bartlett's lectures, just sitting in. He started mentioning S_N1, S_N2, E1, E2.

GORTLER: Was this your first introduction to those concepts?

NAKANISHI: I had never heard about those words. So I had to study. I worked hard in the lab and started reading books on the so-called electronic theory too, you see. When I went back to Japan in 1952, not many people knew about electronic theory so I profited tremendously because I had my early stay in the States. I was far ahead of the average Japanese organic chemist, in English, spectroscopy, and electronic theory. With that I went into natural product chemistry. I had a good head start.

Fieser had a stuffed bat in his office. He didn't tell me what it was about for a year. You see Fieser was a very nationalistic person. And he is, of course, responsible for making the napalm bomb. When I joined him at Harvard, he was fully involved in the antimalarial research and also cortisone.

GORTLER: Was he working with the Merck people?

NAKANISHI: Yes. A fierce competition with Woodward. The introduction of oxygen at the 11 position of the steroid nucleus.

I was supported by the Garioa Foundation for the first year and then later Fieser subsidized me, which was very kind of him. From the second year on he fully supported me. I remember going to buy baby clothes and shipping home the baby clothes every once in a while. They were impossible to get in Japan in those days.

After a year he asked me if I knew what this stuffed bat was, and of course I had no idea. It turns out that when it's taken to high elevation, the cold temperature and the low pressure causes the bat to hibernate. They are taken up in a big bomb, which we called the Molotov breadbasket in Japan. It's a big bomb, a parent bomb which when dropped opens up and many tiny bombs come out. So, the idea was to take these bats with time bombs placed under their wings into the high skies of Tokyo, and the bats will hibernate. When they're dropped on top of Tokyo, they would start flapping their wings because they would wake up from hibernation. The flapping of their wings in turn starts the time bombs. And, as is the nature of these bats, they have a habit of going under the roofs. As you know, Tokyo housing was mostly wooden in those days, and the bats would start fires all over Tokyo.

It's like a Kamikaze bat and that was Fieser's idea. He had some support from the military and the last test was done someplace in New Mexico. The trial was successful, but unfortunately or fortunately it was done near a hangar, a military hangar where there were many planes inside. And it blew up the whole thing. So that upset the military and this whole thing was discontinued. Fieser told me about it. He wrote about this episode in one of his books.

Anyhow, at Harvard it was an absolute revelation because I came from prewar and then postwar Japan where chemistry was almost dead. All of a sudden I come to the center of modern organic chemistry. It must have been an amazing era. Just at random I mean, Woodward was there as a young associate professor, Gilbert Stork was a young electron-pushing assistant professor.

GORTLER: I think Breslow must have been there.

NAKANISHI: Ron Breslow was an undergraduate working for Stork. There were Franz Sondheimer, Peter Yates, Jerry Meinwald, Harold Conroy, Ernie Wenkert, Dick Hill, Guy Ourrison, Dick Turner, Alex Nickon, David Ginsburg, Huang Wei-Yuan, Dick Holmes, Fred Greene, Leon Mandel, Flash Georgian, Al Burgstahler, Mike Cava, Jim Hendrickson, Gene van Tamelen, David Taub, G. Singh, W. Nolland, Dan Koshland, P. Rylander, K. C. Tsou, Al Cotton, John Babcock, Costa Anagnostopoulos, Sam Levine and others. It's an amazing collection. Derek Barton and G. Wilkinson were also there around this time.

GORTLER: That's right. In fact, the Bartlett group during that period had people who ended up going out and becoming important members of the chemical community.

Don Cram preceded you so he was no longer there.

NAKANISHI: Cram was in Fieser's group, but I understand he didn't get along with Fieser and he had just left with his Ph.D.

GORTLER: Unfortunately, I think he came across a letter of recommendation or nonrecommendation which Fieser had written. [laughter] That was part of it.

Did you have much contact with Woodward? I don't know if he was teaching at that time or not?

NAKANISHI: Well, I went to attend his graduate course on the biogenesis of alkaloids. This was when he was elucidating the structure of morphine based on his biogenetic hypothesis. He came out with the proper structure, and there was a fierce competition going on between him and Robert Robinson.

GORTLER: Was he running his Thursday night seminars?

NAKANISHI: Yes, that's right.

GORTLER: When you came back to Japan, you continued your work with Hirata.

NAKANISHI: Yes. When I returned to Japan I became an assistant. During my absence, Hirata had become a full professor and formed his own organic chemistry group while Egami remained a biochemist and enzymologist. So I became Hirata's assistant and then a half a year later, assistant professor. That's around 1953-54.

GORTLER: What were your responsibilities as assistant professor? You continued to do research with Hirata and then what?

NAKANISHI: After I returned from Harvard, Hirata went to Harvard and spent a year with Fieser. And so, I helped Hirata in starting the Nagoya group. My early knowledge about the electronic theory and so-called "modern organic chemistry" and spectroscopy was of tremendous help in the early days. The Hirata school has since produced many organic chemists including T. Goto, H. Kakisawa, M. Ohashi, K. Yamada, Y. Kishi, M. Isobe, and others.

GORTLER: How soon were you able to get modern instrumentation, such as a new IR and a UV?

NAKANISHI: We were one of the first to get a new IR and that was around 1953-54. It was a Hilger single-beam machine.

GORTLER: Many of the people you've mentioned here were members of Woodward's group.

NAKANISHI: Most of them were in Woodward's group, but also from Bartlett and Stork.

GORTLER: Who else was in Fieser's group at the time?

NAKANISHI: Ourrison, Alex Nickon, K. C. Tsou, Dick Turner, David Ginsburg, (as a visitor), and Hans Heymann were there. There was another guy, Huang Wei-Yuan. He's now the Director of the Organic Institute in Shanghai and is one of the most influential Chinese organic chemists.

GORTLER: You have been interested in all types of spectroscopy and used it in many, many ways. Do you consider it primarily a tool, or are you interested in spectroscopy as spectroscopy? Are you a gadgeteer?

NAKANISHI: I'm not a gadgeteer. I would like to be a spectroscopist but for that I have to have a much sounder physical background and I don't. So I simply like to use them. For that I seem to have a knack.

GORTLER: Who developed all these techniques for doing spectroscopy on a microgram level?

NAKANISHI: I think if you're forced to do it, you do it. It's hardly a technique; it's just a knack of how to handle the samples. Like most people, if you're confronted, you will do it.

GORTLER: You moved to Tokyo in 1958?

NAKANISHI: Kyoiku, which is Tokyo University of Education, in English words.

GORTLER: What prompted your move? Did a professorship open up?

NAKANISHI: Oh yes, that's it. I think, as I told you, I had a good start, you see.

GORTLER: You were advanced by Japanese standards?

NAKANISHI: Yes, above average.

[END OF TAPE, SIDE 2]

GORTLER: You received the Award in Pure Chemistry in 1954.

NAKANISHI: In 1954. Yes, that's right. I remember this was for structure elucidation using a combination of various spectroscopic methods. When I was young I was pretty good in that area. At the first Japanese Natural Products Symposium held in Nagoya in 1957, Professor Sugiyama came to me and said, "We have an opening. Would you like to come?" That was to be a professor at Tokyo Kyoiku University. At that time I was thirty-two years old, which in Japan in those days was extremely young for such a position. I think when I became a professor at thirty-two, I was the youngest of the professors in Japan. I don't know whether that move was wise or not, but in any case, I went there and started my own group.

GORTLER: Did you have people working with you at Nagoya?

NAKANISHI: I did. But then finally I shifted the whole group to Kyoiku.

GORTLER: What were the students like at Tokyo? You said this was a teachers college.

NAKANISHI: Yes, but a teachers college in Japan is different from a teachers college here. Lots of teachers come out of it, but lots of research is done also. Tokyo Kyoiku University has now been terminated and has become the Tsukuba University. It's a model university the government set up. It's a showplace now. They set up a university city in the middle of nowhere in the northeast of Tokyo. That's also the site of the Science Expo 1985. Now it has become like the North Carolina Research Triangle area. It's the largest research area in Japan with the highest density of Ph.D.'s. All major government research labs have moved to Tsukuba and centered around the University. Recently many private company labs, both Japanese and foreign, have moved to Tsukuba as well and a highway has been built from Tokyo to Tsukuba.

GORTLER: When were you first introduced to NMR?

NAKANISHI: I think the very first NMR spectrum I saw was in 1958. It still came in a strip chart in which the needle scratched the paper as the five-cm-wide recording paper rolled along.

GORTLER: Almost like taking an electrocardiogram.

NAKANISHI: Yes. One of the first samples that I remember was pristimerin. It was a compound which had been studied a great deal by Alan Johnson at Nottingham. It was a tiny strip chart with a very crude NMR but I could read seven methyl singlets and I remember how excited I was. Almost as shocked as when I saw the carbonyl bond in my first IR in 1950. Again, this time I could count the methyl groups and it turned out this compound has six angular methyl groups and the other one was a methyl ester.

The next generation updated NMR was when we received by mail a 60-MHz (60 Megacycle) spectrum of monascorubrin measured at Varian. Monascorubrin is the yellow-orange pigment of the Chinese wine commonly served in Chinatown restaurants. That was in the late 1950s.

GORTLER: When did the university that you were associated with finally have an instrument? Did you ever have one at Tokyo, or not until you moved to Sendai?

NAKANISHI: No, not until I moved to Sendai in 1963.

GORTLER: Before we get into that move, were you consulting at this time?

NAKANISHI: Well, in Japan you're not supposed to consult. We were government officers, and we still are. It's getting a little bit more lenient, but at that time, I think the idea or notion of consulting did not exist. But I had close connections because of my association with Syntex and Varian.

GORTLER: You had obviously already met Carl Djerassi.

NAKANISHI: Yes, because he had already visited Japan earlier. This was while I was still in Nagoya. And I remember, he came here with Alex Zaffaroni, who started the ALZA Company. This was, I suppose, in the mid-1950s. I was working on the structure of monascorubrin, the wine pigment I mentioned, trying to figure out the structure. I remember going to Carl Djerassi's hotel in Nagoya. I think it must have been around 9:30 at night, and I dragged him out into the hall and we had almost an hour and a half discussion on the spectroscopic data and so on.

GORTLER: The little article from American Men and Women of Science says that you started to consult for Syntex and then it said Zoecon in 1965, but I think Zoecon came later. Isn't that Djerassi's company?

NAKANISHI: Yes.

GORTLER: All along you were working on a fairly wide variety of natural products. What, at any given time, determined your choice of problems or the choice of materials you would work on?

NAKANISHI: Well, in those days of natural products chemistry, it was still, "Get something interesting and do the structures." Since a great proportion of the Japanese organic chemists were doing that type of work, I went into that field without too much thinking of what to work on except that I had some interest in bioactive materials from my early training.

In addition to that I had a tendency that was maybe somewhat different from others. I wanted to come out with new applications of spectroscopic methods. One of my very early lectures given at the Japan Chemical Society meeting was "Structure Determination with Physical Constants." A title like that nowadays is nothing but no one had used the name of "Physical Constants" when I first gave this lecture.

My interest in bioactive compounds comes from Hirata because when I was at Nagoya, in the mid-to-late-1950s, he was already starting to work on luciferin. Luciferin is the Cypridina bioluminescent factor which, in those years, was a tremendously challenging problem. What is the structure of the compound which leads to bioluminescence? He had also started to work on the isolation of tetradotoxin. Also, I started working on the diapose hormone of silkworm. This is still not solved and is being continued by Professor T. Goto at Nagoya University. It's one of the most difficult isolation problems. A massive effort has gone into this. Professor Hasegawa of the Department of Agriculture started this project when he was young; he's already retired and it's still continuing.

In any event, because I was in a lab like that I had an

interest in bioactive products, much stronger than other people. But, in addition, I was trying to devise new spectroscopic methods which have general applicability.

GORTLER: Then in 1963 you went to Tohoku University in Sendai. Again, why did you move there?

NAKANISHI: Well, because Tohuku University was probably, as a chair of organic chemistry, the most prestigious in Japan in those years. There were two chairs in organic chemistry. One was held by Professor Tetsu Nozoe who is now eighty-two years old. He's the one who discovered tropolone. He encountered tropolone when he was a professor in Taiwan during the war. He came out with the seven-membered aromatic structure for hinokitiol which didn't make sense. After the war ended, he repatriated and returned to Sendai, where he got his degree.

Professor Majima, whom I told you before was one of the three pioneers who started organic chemistry in Japan, was at Sendai. (Tetsu Nozoe had received his degree with Majima earlier.) From Sendai, Majima went to Taiwan and after the war he came back to Sendai. Then, he published this work all in a bunch in Japanese in Proceedings of the Japan Academy. That is when Michael Dewar had proposed the seven-membered ring and Erdtman, in Sweden, had also come out with the same structure.

Anyhow, another chair became vacant with the retirement of Professor S. Fujise. Unfortunately, soon after his retirement, Professor Fujise died.

Then Nozoe approached me and asked me whether I'd like to come. He likes to joke. He says it was like throwing bait into the pond in which there's some very hungry fish. And the moment he threw in the bait, I grabbed it. [laughter] That's why I moved.

GORTLER: Had you started working on the ginkgolides before that, or did you begin that work after you moved to Tohoku and you inherited the project from Fujise?

NAKANISHI: That's right. I inherited the problem.

GORTLER: I don't know what to ask you about that work. It was extremely impressive. In the article I looked at, you had, in a very deliberate fashion, shown how the spectroscopy had shown you the way (3).

NAKANISHI: Well, it's one of my favorite works. As far as I'm concerned, it's the last so-called structural study which was done in a classical manner. Many derivatives were made. The team led by M. Maruyama (currently professor at Miyagi Kyoiku University), made about fifty derivatives and it was an extremely tough structure to solve. We had gram quantities of ginkgolides. The ginkgolides are extracted from the root bark of the "fossil tree" Ginkgo biloba. They are huge trees and of course cannot be uprooted at random. There was a timely typhoon in Sendai which destroyed many gingko trees so we went out into the city and started peeling the root barks. We were able to carry out an immense number of reactions, photochemistry and everything. The NMR of each derivative was meticulously measured in detail. So, it was a combination of spectroscopy and "classical" wet chemistry because of the many derivatives and all of the chemistry carried out by Maruyama, A. Terahara, Y. Nakadaira, and others. It was nice chemistry.

GORTLER: Yes, it was. The structure was unique and it seemed to be a very delicate molecule because of all the lactone rings.

NAKANISHI: No, it's rock stable. You can dump it into concentrated nitric acid and evaporate it off; nothing happens.

GORTLER: But your problem was when you shined light on it, it rearranged. That is, it was extremely photosensitive.

I don't know if that was the beginning of a new approach, a coordinated effort where you brought to bear the work of a lot of people...

NAKANISHI: May I interrupt you before that? It's about the nuclear Overhauser effect (NOE). Can I mention that now?

GORTLER: Yes, absolutely. It's one of the important developments in this work.

NAKANISHI: I told you that we had no NMR when I was in Tokyo. But when I moved to Sendai, with some help from the Varian Company, we got an NMR instrument as well as some financial help. Financial help in the sense that we got my so-called first non-Japanese postdoctoral fellow, who was M. C. Woods.

I had met him when I was giving a UNESCO course in Kuala Lumpur, Malaysia. He decided that my place might be an interesting place to come to learn spectroscopy. He was partly paid by the Varian Company. At the same time, we employed a young technical high school graduate by the name of Iwao Miura.

Now, Mervin Woods, whom we called Vyn, was an absolutely uncompromising scientist who liked to dig into details. This upset me and made me frustrated very often because, on the contrary, I'm very sloppy about details. But he would never budge. He would not compromise. The ginkgolides contain three lactone rings. In addition, the skeleton contains several quaternary carbons, so that there is not much connectivity among the protons. In fact, the original NMR spectrum of ginkgolide is so simple that it's hardly of any use.

Then, what we did out of desperation was to reduce the lactones. From the three lactones, you get a hexa-ol. Plus, there were three other hydroxyls, so you get a nona-ol. Then, we left this product to dry in an oven. This was left in the hands of an undergraduate and, in the meantime, we all went out in the fields and played baseball. The oven was defective so it scorched the sample and this undergraduate was shocked to find that he had burned all the precious compound given him by Vyn and his seniors. But we noticed that on the roof of this oven we had beautifully sublimed crystals. The whole cage structure of the ginkgolides had recycled to the original skeleton, except the three lactone carbonyls had all been reduced to methylene groups ("Ginkgolide A-triether").

Now this gave us much more connectivity. The proton spectrum became much more complex because we had introduced six more hydrogens and started connecting the isolated systems. So, Vyn and Miura started a tremendously detailed and stepwise decoupling experiment, including treatment with lithium aluminum deuteride instead of lithium aluminum hydride. When the t-butyl group was irradiated they found that the integrated intensity of some protons had increased. This can happen if someone is not careful. At that time, NOE was unheard of in NMR. So ordinarily people would have taken it for a faulty integrator.

But Vyn repeated this experiment over and over again, and confirmed that there was a 20-30% increment on some of the protons. He started suspecting that this is a real thing, a new phenomenon in NMR. Then he noticed that there was a paper published by Overhauser in ESR called an NOE effect. Just about that time the first paper by Anet and Bourn came out in 1965 on the NOE of acrylic acid (4). We were discovering it at the same time, in a very complex natural product, by accident. But Anet probably had something specific in mind because he did it on a very simple compound. That was the first paper on NOE. After that, all of a sudden the ginkgolide structure, because of the NOE's, fell into place and we got the structure.

That is when we tested them for all sorts of physiological activity, but no activity was found. However, just four days ago, I got a telephone call from Upjohn--from John Pike--and he says that a French group had given some papers at an international meeting stating that the ginkgolides are platelet activating factors (PAF). The ginkgolide extract is the best selling crude extract in France. Since then I have received

three more inquiries. It may be interesting, so we're going to send him some samples now. Our research on the ginkgolides was an extensive effort, headed by Dr. Maruyama.

GORTLER: So you had someone who was essentially directing that project for you at that point?

NAKANISHI: Yes. He was my assistant at that time, and coordinated the ginkgolide team.

GORTLER: You were having things like high-resolution mass spectrometry done elsewhere and Takeda Pharmaceuticals was doing extractions for you, so it seems to me that you were beginning to do what might be considered, "Big Science." You're planning strategy at this point.

NAKANISHI: Well, yes. I suppose I gradually started getting into biologically active compounds and trying to look for these in particular, for a purpose, instead of just going for a plant and isolating something. The Takeda Company, which is the largest pharmaceutical company in Japan, had been very kind to me. When I started as a young professor at Tokyo Kyoiku University, two senior scientists, Drs. Y. Abe and I. Tanaka, came and said, "We would like to support your work." This continued throughout my years in Sendai and even for a while after I came to Columbia, they would pay for my trips back to Japan so that I could visit them.

So we started looking for biologically active plant constituents from Southeast Asia and cancerostatic or cancer-curing constituents. This was a team project carried out mainly by Takeda, on expeditions to Malaysia, Indonesia, Taiwan, and other places. I'm hardly a botanist, but I used to go myself to botanic gardens. I'm shocked to see how I behaved with my total absolute lack of knowledge in botany. Anyhow, I managed to camouflage myself, I suppose. Can I tell you how we found the ecdysones?

GORTLER: Yes. However, before you start that, in one or two places you mention the way compounds taste to humans. In the case of the worm antifeedants, you said that they tasted "hot" to humans. That's sort of nineteenth-century chemistry where one tastes the compound. Was that common among Japanese natural product chemists?

NAKANISHI: No, it wasn't. However, I think it is safe to say that bitter or hot-tasting extracts have biological activity in most cases, an outstanding exception being the ginkgolides, which are extremely bitter. With their PAF activity the ginkgolides

also now belong to bioactive compounds.

We went to all these Southeast Asian countries and collected plants and extracts and brought them back. For one of the compounds, we went to central Taiwan with Dr. H. W. Hsu, into rather deep mountians. We collected the leaf from a plant which is used locally in Taiwan, quite popularly, as an herb for curing cancer and many other diseases. We came back and carried out some isolations which were partly done still in the old-fashioned way; in other words, not solely based on bioassay. The extractions were monitored by assays. Once in awhile we wandered off and, if we found something interesting, we would do a structure determination. So we were still working both ways.

GORTLER: There are millions of compounds. When you're looking for anticancer reagents, how do you go into the field and do this?

NAKANISHI: By folklore. That's why we went to villages and asked the people what they've been using.

GORTLER: Do they know what they're using? Not the compounds, but do they know they are in fact treating a cancer-type disease? What were they in fact treating?

NAKANISHI: That's a good question. Well, yes in a sense they knew. Cancer is well known. Or it was some infection. Then we would collect these biologically active plants and they would be assayed at Takeda, especially for anticancer activity. When we extracted the Podocarpus makaii, a tree used for curing cancer, we got a tremendous mixture of white steroidal material. When tested, there was no activity.

[END OF TAPE, SIDE 3]

NAKANISHI: We had isolated this grand quantity of a fairly water-soluble compound (5). It was done by M. Koreeda, who is now a professor at the University of Michigan. He was an undergraduate at that time. Through his two years of master's work and three additional years for the Ph.D., he worked on the separation and structures of these steroids. He had gotten one structure by the end of his master's year. This was around 1966. We thought before publishing it we should check whether it's a known compound or not. So we went through the literature and it turns out that just half a year before, a very similar structure, differing only by having one additional hydroxyl group in the side chain, had been published by a German group (Huber, Karlson) and this was what is now called alpha-ecdysone. They had done the x-ray also. This was by Huber, the first x-ray done on a

molecule with no heavy atoms (6).

GORTLER: The name Butenandt also appears. This is not the same Butenandt that won a Nobel prize in 1939.

NAKANISHI: Oh, it is the same Butenandt. He's still alive. He must be in his eighties. He got his Nobel prize when he was thirty-six.

GORTLER: But they had isolated from the...

NAKANISHI: Bombyx mori, the silkworm. The ecdysone structure elucidation was the culmination of many years of work started by Butenandt and Karlson. I remember attending two talks given several years apart by Butenandt in which the ecdysone molecule slowly discloses itself as a steroid. They were exciting lectures.

GORTLER: Yes, the ecdysone was isolated from something like a thousand pounds of silkworm.

NAKANISHI: Yes, that's right. I have the exact amount somewhere.

GORTLER: I have it written here. It's 25 milligrams from 500 kilograms of silkworms. It was in one of your papers.

NAKANISHI: There's only a difference of one hydroxyl group. Before that I had no idea about insect physiology whatsoever. I mean, whether they molted or not, I didn't know anything about these things, you see. And, ecdysone, of course, no one had heard about it. So we sent it to Takeda and two other places including Dennis Horn at CSIRO, Melbourne. Dennis Horn, one year later, isolated the crustacean ecdysone from crayfish waste. One ton of crayfish waste gave him one milligram of ecdysone mixture. That's a fantastic achievement. Anyhow, I sent some of our compound to him, and he sent us a cable, "It's more active than ecdysone!" All of a sudden the excitement started. When we had the structure, I don't know what we would have done if we had patented it. The moment the ecdysone structure was published by the German group, pharmaceutical companies started synthesizing it, Schering and Syntex. A milligram was costing about $100 in those days and we had in our hands about 3 grams of this compound which is ten times more active. That got me involved in insect physiology. I may have been able to have an NMR instrument in exchange for some of the ecdysone powder.

GORTLER: It reminds me of the story of the chemist from Penn State, Russell Marker, who started Syntex. He came walking in with a couple of kilograms of progesterone at one point which was then selling for $80 per gram. He synthesized progesterone from diosgenin. I noticed someplace that you had synthesized one of the ecdysones from diosgenin. Is that something that Djerassi had recommended to you?

NAKANISHI: No, that was an idea that first came out when we were chatting in a bar with Dr. K. Morita of the Takeda Company.

GORTLER: In the early days Syntex was making everything from diosgenin. What's the value of these ecdysones?

NAKANISHI: It is a molting hormone of all insects and crustaceans. Physiology-wise it is an extremely important hormone.

GORTLER: What is the interest of the pharmaceutical firms?

NAKANISHI: They synthesized it because of its activity and challenging polyhydroxylated structure. But in terms of agro-chemistry, for example, the interest is limited. It has a steroid skeleton which means you have to find its effect on humans before it can be used. Also, it's too expensive, especially to use it as an agrochemical to spray on big fields. A method was discovered by Takeda to use ecdysteroids for synchronizing the molting of silkworms. However, it has not taken off in a big way because of the difficulty in applying the compound to the insects within a short crucial period. But in the test tube, you can do all kinds of fantastic experiments with it such as controlling the metamorphosis of insects and crustaceans.

Professor T. Takemoto, Department of Pharmacy at Tohoku University, had also discovered ecdysone from a weed at the same time as us. He gave ecdysone pills to his wife and he told me it cured her rheumatoid pain. (He didn't tell me she molted!)

The compound we had was ten times more active than the alpha-ecdysone. So that led us into insect physiology and my interest still continues there.

GORTLER: In 1969 you moved to Columbia. What prompted you to do that? Was it an offer you could not refuse?

NAKANISHI: Well, it's funny. It's almost like a made-up story but I can tell it if you are interested. The way it went is the following. My group was very big, and at that time I was getting some NIH grants also. Mine was probably the most well-funded organic group in Japan. In addition to federal and NIH support, I had some money from Syntex and so on. My group at the largest time was close to fifty. It was an enormous group. There was no particular reason for me to leave. But I suppose, somehow inherently, I wasn't comfortable with the Japanese system. Although I was the leader of one of the largest groups, I didn't like the so-called hierarchy. There was not enough freedom in academe. It was too democratic in Japan. Everything had to be discussed, at the department and higher levels. We had so many committee meetings. Endless! I hate committees and that must have been in my mind.

We had a sports day in my group and it started at 8 o'clock. There was volleyball, basketball and then baseball. I started doing all of this. And, in the third game, it was baseball. I was batting and then suddenly I twisted and got a severe slipped disc; extremely severe. I went flat on the ground, face down. I didn't know what was happening. I couldn't move and someone touched the tip of my fingers. It immediately came to my spine. My house was very close, only four or five minutes walking. So they put me on a stretcher and they took me to my home.

My wife called the hospital and I was supposed to be hospitalized. Again, we marched about fifty minutes to the hospital, people walking like a funeral, with all my group following. I was put in the hospital but the nurses didn't give a damn; they rolled me over and so on. I was groaning all the time. My wife had notified a few of my friends. The doctor told me I should be hospitalized for three or four months. I didn't like that idea at all. By that time a friend of mine in Tokyo, the late Mr. S. Homma, president of the JASCO Company, immediately sent the company's chiropractor who came to the hospital. And while the nurses were out my son kept guard at the entrance of my room and this chiropractor jumped on my bed and started massaging me. After about five minutes, even though aching and wobbly, I could stand up with the help of two nurses. I said, this is nonsense, I'm going to leave. So I told the doctor, "Tonight I am going to have a very important long-distance call so I have to leave today."

And then that night, by chance, it turned out I did get a long-distance call from Manchester. They were looking for someone to succeed Arthur Birch at Manchester (England) and asked whether I would like to succeed him. I said I would certainly like to think it over. So I was at home, sort of resting from my back, with the chiropractor living in together with us. Shortly afterwards, I went to Manchester and on the way back, I discussed with Gilbert Stork, Carl Djerassi and others what I should do.

Then, on my second visit to Manchester, because I couldn't make up my mind, Gilbert started giving me the idea, why don't

you come to Columbia. Then I started getting offers from other places--Switzerland, Canada, California and here (Columbia). I restricted it to Manchester and Columbia; those were the final two choices. I procrastinated for about a year. Going between Manchester and Columbia, I couldn't make up my mind. The reason was, if I go to Manchester, I thought it would be a buffer. In Japan, I was top of the group. I had an assistant professor, two assistants and a huge hierarchy. The English system was somewhat like that but here (U.S.) you're isolated. It is only the professor and the postdocs and graduate students. No buffer. So I was more inclined toward Manchester. I started going to many palm-readers because my wife believes in this art. Everyone said I should go towards Manchester's direction, not towards (from Japan) the East. They all said I should go towards the West, which meant Manchester.

GORTLER: But in the Japanese system, you don't have the opportunity for as much interaction with other people at your level. I mean, here you have a Gilbert Stork, a Ron Breslow, etc.

NAKANISHI: Yes, we don't have that. But I was comparing the American system with the English system. It went on for about a year and then finally the Department said, "You have to make up your mind. This cannot linger on."

GORTLER: Which department?

NAKANISHI: The Chemistry Department in Japan.

GORTLER: Oh, I see, because they knew you were...

NAKANISHI: Yes, they knew that I was going to leave in any case. Then the graduate students had to make up their mind. You see, it was going to be a sort of minor migration. They had to either live in England or come to New York. And I said tomorrow. It was the night before and we were all discussing the move in my home. 12 o'clock, one o'clock... I called Manchester, just to make one trivial thing clear. I had almost 95% decided to go to Manchester and find my own house. But there was one minor problem about accommodations for one of the graduate students I was taking. That was still not clear. So I wanted to check this but when I phoned Manchester, the head of the Department was out. A friend of mine, John Bu'Loch answered and took the question. He said, "Probably, we can do that. There seems to be no problem. But we have to defer the answer until the department head returns from his trip."

Then a few minutes later there was a call from Gilbert and Ron Breslow, on the same line. They started bombarding me with quick language, you see, and now it's about two o'clock in Japan. I told them, "Give me some time. I'll call you back in about an hour because I cannot make up my mind." About an hour later, I'm still discussing it with my graduate students--should I go to New York? All the pros and cons. I couldn't make up my mind and an hour later I called them here (Columbia). Gilbert and Ron had both gone out for lunch and the secretary answered. What I meant to say was that I'd go to New York to check once more, but she misinterpreted this. She must have given the message that I'd decided to come to New York. So when Ron Breslow and Gilbert Stork came back from lunch, they pick up the phone and said, "Hey, great Koji, you've finally decided. Welcome to Columbia." [laughter]

GORTLER: And you didn't have the courage to tell them?

NAKANISHI: Well, no, I could tell them, but I never regretted that decision, of course. This is just an extra episode, but the thing was, basically, I felt myself getting more and more shielded and remote from chemistry in Japan. There were too many committee meetings, and I was losing grip of what was going on. I think I wanted a more challenging thing.

Also, before I even thought about it seriously, when I got this call from Manchester, I discussed this with five or six senior Japanese professors whom I respect. Everyone of them said I should leave. They all were saying it in a positive sense. They all knew, I think, that I didn't exactly fit into the Japanese system because of my background. I mean, I'm not a typical Japanese. But I think they also wanted to find how a Japanese chemist who was educated in Japan would survive outside. And if someone was going to do it, I was one of the chemists who had the least language barrier and also custom barrier too. So everyone said you should go, then come back later to Japan. Everyone said you should take this offer. At that time it was Manchester.

GORTLER: At the same time, you took on another position. That is, you became the director of research of the International Center for Insect Physiology and Ecology (ICIPE). Was there any connection between the two?

NAKANISHI: No. When I came to this country, to Columbia, it was the beginning days of the ICIPE at Nairobi. The person who started that whole idea is Carl Djerassi, who wrote an article in Science which said, "Wouldn't it be nice if one set up, in a developing country, a center of excellence for research with international support."

GORTLER: So one of the goals was really to train people in those countries.

NAKANISHI: Yes. But importantly, at the same time carry out basic research which would be done much more efficiently on site. Tom Odhiambo responded to that. He's still Director of the Institute. He started visiting this country, the American Academy and various academies. Carl asked me whether I would be interested, since I had some experience in going to Southeast Asia and various places and I was a natural products chemist to start with.

GORTLER: And you'd also gotten very interested in these insects.

NAKANISHI: Exactly, and ecdysone. So I got involved and that's how I became director of research.

GORTLER: What did that involve?

NAKANISHI: The name Director of Research is misleading. It means sort of a group leader. It's not the director of research; it was a title according to the British name.

GORTLER: Tom Odhiambo was the Director of the Institute?

NAKANISHI: Yes. I was like a group leader of the organic group. It was myself and Jerry Meinwald. He was also a director of research.

GORTLER: I thought he took over after you gave it up.

NAKANISHI: No, we were contemporaries. I may have joined slightly earlier, but at the same time.

GORTLER: I see. I remember hearing him talk about some of his ant work.

NAKANISHI: The other people were Carroll Williams, John Pringle, J. de Wilde, D. Schneider, D. S. Smith, M. Luscher, T. O. Browning, R. Galun, and A. R. Moller.

GORTLER: You began to consult for Syntex before you came here.

NAKANISHI: While I was still at Sendai.

GORTLER: And your contact there was Djerassi. You'd already met Zaffaroni as well.

NAKANISHI: Yes, those two. Carl has helped me a great deal starting with infrared and insects.

GORTLER: And CD (circular dichroism) as well.

NAKANISHI: Yes, that's right. I should have mentioned that too. Carl Djerassi started a renaissance in optical rotation when, in the mid-1950s, he started publishing papers on optical rotatory dispersion (ORD). CD was started on the other hand, simultaneously by the French group, Legrand and Veluz, at Roussel. By the late 1950s, Carl had published about thirty papers on ORD. So I looked through them thoroughly and compiled them into a review article. At the same time I translated Carl Djerassi's optical rotatory dispersion book into Japanese. This goes back to the late 1950s.

I was closely connected with Japan Spectroscopic Company (JASCO), which started out as the largest infrared maker, and has now branched out into other fields. It is currently the largest CD maker in the world. I was involved with the company from the very beginning because of my interest in infrared. When they started making the CD instruments, at a fairly early stage I got a CD instrument into Sendai. I gave a CD problem to N. Harada, who happens to be a classmate of Koreeda who was working on ecdysone. Both were undergraduates. I gave this CD project to Harada, and asked him to come out with some simple method in which we can determine the absolute chirality of alpha-glycols. For Harada it turned out to be a very appropriate project. He is very mathematically inclined, he understands MO's but, as an organic chemist he can also design and carry out his own synthesis and derivatizations. So, it was just a very fortunate combination of my interests and Harada's talents. He is one of the foremost leaders in CD now.

GORTLER: I see you've just published a book with him on this method (7).

NAKANISHI: Yes, that's our CD book. I frequently meet with Harada in Japan and once in a while, we collaborate. We discuss problems, but he is doing his own CD, and I'm doing my own CD at Columbia.

GORTLER: In 1970, just after you came here, you published the structure of the fluorescent Y-base from yeast phenylalanine t-RNA, and I know you consider that and some of your related work very important (8). Can you tell me a little bit about it and why you think it's important?

NAKANISHI: That is another one of my favorite stories. When I first came to Columbia, during one of my visits, Charley Cantor said, "Koji, if you are a structure determination man, you should take up this Y-base structure." Charlie used to be in chemistry, but he is now the department head of Human Genetics at our Medical School. So that's how I got interested. He put me in contact with some of the medical school people, and they are still there. One is Bernie Weinstein, who now heads the Cancer Institute. I just saw his name in the Columbia Record yesterday. We started collaborating with his group. They prepared the t-RNA and we did the isolation and structure.

What I liked about the project was that the compound was very unstable. The Y-base is only stable from pH 3 to about 8, and the total amount that we had was only 0.3 milligrams. Because of it's fluorescence, many people in the t-RNA field were interested because they wanted to use it as a fluorescence tag and for many other things. It is still the only nucleic acid base which has a tricyclic skeleton. We managed to derive the structure by combined spectroscopy and lots of model syntheses. Not many people believed it when we published the structure, but we have synthesized it since.

GORTLER: It can be synthesized now so people can use it?

NAKANISHI: Yes. With the 0.3 milligrams, we determined not only the structure, but also the absolute configuration. We did an ozonolysis on about 10 micrograms of the Y-base, isolated the side-chain moiety with the chiral center, and determined from it's CD the absolute configuration of this fragment. I think it's still remarkable by current day standards.

GORTLER: That is absolutely remarkable. I keep thinking, when I hear you talk about your work on microgram quantities, that in most cases you can't even see the sample.

NAKANISHI: No, you can't see the sample.

GORTLER: Is it all a mirage? Are you always certain that what you're doing is real?

NAKANISHI: Well, in this case the compound was fluorescent. Once in a while we do a painstaking measurement on the weighing balance. But, in most cases, the amount is estimated from the UV once we know the chromophore. This Y-base is, biochemically, an important compound.

GORTLER: As a result of some of the work in Nigeria, you isolated and characterized a number of antifeedants. Can you tell me a little bit about that work?

NAKANISHI: Yes, when we first went to ICIPE, the Insect Institute in Nairobi, except for my group, the others were biologists. And the chemists and biologists work on a totally different time scale. Chemists are much more impatient and if they want to accelerate the reaction, they can raise the temperature, add some catalyst, etc. The biologists, on the other hand, have to wait until the animal grows.

So we thought that although it's good to collaborate, we should also do something on our own. Then, without knowing too much of the literature, we started looking for biologically active compounds, as usual through folklore.

An Indian lady came and said, "We use this Indian neem tree to repel bugs from my garden." (Later it turned out to be a well-known concoction.) So we started working on this neem tree. We extracted berries, smeared the extract on a coffee leaf and then put a coffee bug on it. We found that to our amazement, it underwent dramatic morphological changes. We then took the neem tree extract and the same weight of pure ecdysone was applied to another coffee leaf, but the neem tree extract was much more active.

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NAKANISHI: It had a stronger effect than the pure molting hormone. So we called this "super-hormone" and we started to go after it. But then we lost track of the "super-hormone", and instead we isolated what is now called azadirachtin (9). The structure of that was not out yet. A good portion of the basic chemistry was published by David Morgan. And since the whole structure was not out yet, we decided to do the structure determination. Meanwhile, we forgot about the super-hormone. It turned out that azadirachtin is still the most potent insect antifeedant found in nature.

GORTLER: It has a fairly complicated structure.

NAKANISHI: Very complex. There is no practical value to synthesizing it. But the neem tree itself, the twigs are used by the Indians to brush their teeth, and they never have tooth decay. Also, the leaves are used by locals as a very common remedy against malaria. It's been tested over the years, so we know it's nontoxic. The berries are a favorite fruit for the birds. So it is nontoxic, you see. It is a fast-growing tree. For example, the U.S. Department of Agriculture is trying to grow this tree in a fast way. You don't have to isolate the azadirachtin itself. Just spray the sap. Some field tests have been carried out in West Africa with positive effects.

Now we think that this azadirachtin has also turned out to have a very potent ecdysone-like effect. If it's a very potent molting hormone, of course, it will deter the insects from eating it because such a compound will derange the insect life cycle. It's as if you had a heavy lump of testosterone and you're forced to eat it. Of course, at some stage, I think you would start spitting it out. The super-hormone, I think, was the azadirachtin mixed in an appropriate condition so that it was not enough to repel the insects. Maybe there were also attractants so they ate it but at the same time, took enough azadirachtin. I don't fully understand, but I have some suspicion.

When I was at ICIPE, Isao Kubo joined the Institute as one of the research scientists dispatched from Japan. He has a tremendous instinct for natural products. He is now a professor at Berkeley. He managed to learn the Swahili language. Unlike me, he has an accurate instinct about directions in the rain forests and is an adventurer. He went to all sorts of wild places alone or with his technicians. He's been caught plucking fruit trees when all of a sudden, he heard a growl and then noticed a leopard on a branch several feet away on the same tree. Another time he was up in a tree and all of a sudden he noticed that he was surrounded by a herd of water buffalos, one of most ferocious of African animals. So he was stranded in the tree for several hours. He learned the Swahili language, and he went to various local doctors, the so-called witch doctors.

GORTLER: Where was he a student when he first came?

NAKANISHI: He came from Osaka City University from the lab of Professor T. Kubota. The Japanese government sends one person every year. So he spent two years at ICIPE and then, since he had so many compounds by that time, on the way back he said he would stop by Columbia and spend a month or so. This one month extended to about three or four years. So it was mostly with Kubo that we did the systematic antifeedant work on African plants. He is continuing the studies at Berkeley, where he is now an entomology professor. It's much more appropriate for him to do it and so I have discontinued these studies.

GORTLER: And he did all of those compounds?

NAKANISHI: Except azadirachtin, but all the others, like warburganal (10).

GORTLER: And all the related compounds. And they're so much simpler. Now, is it possible to use those as insecticides?

NAKANISHI: Well, I don't know. The reason is, for example, warburganal is one of the most potent antifeedants. On the other hand, upon injection, it causes strong hemolysis. I was once giving a talk at the entomology department in Hawaii and I said this probably won't be practical because of its very strong hemolytic properties. Then a toxicology professor from the audience asked whether I knew that the pyrethroids, also upon injection, are very potent hemolytic compounds. Of course the pyrethroids and the synthetic compounds derived from them are the most important insecticides right now. So, in that respect, there may be some hope for warburganal.

GORTLER: Was that also taken from the neem tree?

NAKANISHI: No. Warburganal is from another tree called Warburgia ugandensis.

GORTLER: Certainly one of the most exciting areas that you've been working in is the chemistry of vision. This was a further shift into biochemical mechanisms. Can you tell me a little bit about the origin of that problem and the chemistry of the retinals?

NAKANISHI: During the early days, I think it was around 1974 or so, there were two young biologists in the biology department. One was Tom Ebrey and the other one was Barry Honig. Tom Ebrey was assistant professor and Barry Honig was a research associate.

GORTLER: Both were here at Columbia at that time?

NAKANISHI: Yes. They are close friends and they were both working in vision. I forgot why it was, but I wandered into the biology department and these two said, "Why don't you come and drop into our place and have a look." And that was the first time I went into a dark room where they were dealing with these rhodopsins.

Barry, a physical chemist who had worked on retinals with Martin Karplus, had a particular retinal molecule which he wanted an organic chemist to synthesize. So he said, "Why don't you synthesize it?" I had no idea what this all meant, but I put a Chinese graduate student, Wan Kit Chan, on the problem. The first molecule we synthesized was 14-methyl-11-cis-retinal. Tom Ebrey did the binding. It gave us the expected interesting results. Before us, I think, hardly any organic chemist was in the retinal field, doing synthesis.

The initial success led us to the idea to make specific tailored retinal analogs and bind them to rhodopsin. The rhodopsin analogs may furnish some new data from different angles. Before that, some work had been done, but fragmentary, not in a systematic way. So we increasingly got involved in this field. In due time, Tom left for Illinois, Barry left for Jerusalem and then after that Barry went to Illinois and now he's back at Columbia. Barry is now a biochemistry professor and Tom's still at Illinois, but we continued our collaboration. In the visual pigment we have 11-cis-retinal as the chromophoric form when it's bound to rhodopsin, and when the light hits this, the 11-cis double bond becomes the all-trans double bond. That is the primary photochemical event. All the rest is relaxation through thermal relaxation.

In a very simplistic manner we wondered what happens if you make a pigment in which the crucial 11,12 double bond is hydrogenated? Then there would be no photochemistry. We thought we might be able to make a nonfunctioning pigment. So we made that. Then, to our amazement, it bound to rhodopsin, made the rhodopsin analog but the wavelength had shifted tremendously. One of the central problems in vision chemistry or vision science is that the retinal, when it's in the visual pigment, is a protonated Schiff base linked to lysine. In the rod cells responsible for black and white vision, the pigment absorbs at 500 nm. When it's in the cone cell of various animals the maxima range from 440 nm all the way up to about 620 nm. There is a tremendous wavelength variation, although the chromophore is the same protonated Schiff base of 11-cis-retinal. However, when you make the protonated Schiff base <u>in vitro</u>, between retinal and butylamine it only absorbs at 440 nm. So there's a big discrepancy, a big shift; one is 440 <u>in vitro</u>. In the animal, depending on the protein environment, it goes from 440 all the way up to 620.

If you can rationalize this on a structural basis, it adds a little bit more to our understanding about what goes on in the eye. Barry got interested in the tremendous shift observed with the 11,12-dihydro pigment. We, on the other hand, thought that if 11,12-dihydro causes a big shift, why not make the other series. So we made three other dihydro series, the so-called dihydroretinal series. We came out with a table on wavelength shifts and that led us and Barry to the external point charge model which explains why, depending on the protein environment, the chromophore absorption maxima are different from the <u>in vitro</u>

value of 440 nm. This external point charge model, I think, is generally accepted. However, until more structural details become known, it cannot be proved or disproved (11). This was the first model based on experimental facts to explain the important wavelength variations. Numerous hypotheses or theories had been published before and are still being published. The point-charge model at least gives some answer to one of the central problems.

GORTLER: Are you still making retinals?

NAKANISHI: Oh, yes. Since then we have gone into bacteriorhodopsin in purple membrane (12) and more recently, we have worked on another so-called sensory rhodopsin in purple membrane with John Spudich. In November of 1984 we published a paper together with Ken Foster on the photoreceptor of the green algae called Chalamydomonas (13). This may turn out to be an economic substitute for studying vision-related rhodopsins. About one-third of my group is involved in retinal-containing sensory pigments. We are directing our major efforts to collaborative studies with Laura Eisenstein of the Physics Department at Urbana on difference Fourier transform infrared studies. This technique has great potential and Laura's group has excellent techniques and experience. I've started to do some retinal related studies in Japan at the Suntory Institute also. They are very well equipped and in some areas they can do things which we cannot do here.

GORTLER: I did want to come back and talk for a few minutes about the Suntory Institute. I also wanted to ask you about your work on the red tide, dinoflagellate. The brevotoxin was certainly impressive, but in a sense, to me it was kind of scary because you couldn't tell very much from your own work and it was in fact the x-ray work that gave you the structure. It reminded me of a story I heard--you mentioned Harold Conroy a few minutes ago--when I was a graduate student. Conroy left organic chemistry for just that reason, that the x-ray crystallographers could do all the structures.

NAKANISHI: That is a rather peculiar story. But, I'm still pleased with that work, because for twenty years the red tide toxin had been known. There are even chapters and a whole book on dinoflagellate toxin, including this particular brevotoxin. All the early work was done on impure mixtures. Finally, one of my earliest Ph.D. students (from Japan), Dr. Lin, senior author of this paper (14) who was at the University of Texas in Galveston and involved in this project for many years, contacted me and asked, "Could you purify this and work out the structure?" I gave it to a Polish postdoc by the name of Jerzy Golik and, in about a month and a half, he got it pure. It shows, if we collaborate interdisciplinarily, how efficiently science can

advance. Much quicker than trying to do it on your own. I'd like to continue this aspect a little later.

GORTLER: I think that is really an important part of what you're doing.

NAKANISHI: And this, somehow, changed my philosophy and I'm changing even more rapidly these days. I'll come back to this in a moment.

I personally am not interested in x-ray, although no doubt it is by far the most efficient and in many cases the only method for doing structural studies. Advancement in science depends on new concepts or new methodology which has general applicability. From the viewpoint of an organic chemist engaged in isolation and structural studies, I try to devise new methods, or introduce a twist in the application of physical methods during the course of structure determination. The ultimate structure is, of course, important, but also important is the methodology development which can be applied to general cases. In that sense, I like the challenge I get from working on submilligram quantities of noncrystalline compounds. You're forced to come out with new methods.

GORTLER: And obviously the students learn from that.

NAKANISHI: Yes, and of course it's a challenge to devise new spectroscopic methods. As far as I'm concerned, there is nothing new or exciting in a paper with a 500 MHz routine spectrum. Anyone who has the money and the opportunity can produce that. The more important point is the <u>way</u> in which that particular method was used and that the audience gets excitement out of attending or reading that paper. That's my main point. For that reason, I tend to avoid x-ray, even when we can do it.

So we started fiddling around with brevotoxin, but we had a total of only about 10 milligrams. We performed an NMR and so on. Nothing came out. Finally, when we were measuring the NMR in acetonitrile, it suddenly crystallized. By that time, we had half given up because we were doing periodate oxidations. We had the palytoxin structure in mind, which had been mostly elucidated by periodate oxidation, ozonolysis, and NMR. It is the largest marine toxin known. It's got a fantastic long structure and a molecular weight of close to 1400. We were following the palytoxin precedence for no clear reason. We sent the crystal to Jon Clardy at Cornell. In looking at the structure they came up with, I'm glad that we did not pursue our work, because it's impossible or senseless to do that by NMR. However, I'll come back to this point in a moment.

After two or three months, he called me and he said it's the

most bizarre structure. It's like a stiff ladder. It has eleven ether rings, all trans-fused. So that was the story of that. He didn't want to go into the absolute configuration by putting in a heavy atom. He didn't want to spoil the story. On the other hand, it was a good challenge for us to use our CD method. So we did that portion, which is a twist of the CD method.

GORTLER: And that gave you the absolute configuration?

NAKANISHI: Yes. The isolation was also not so difficult. It just turns out that we have been in the field of isolation for many years and had the experience. On the other hand, the biologists and biochemists have been publishing paper after paper on the mode of action of this toxin based on work on the impure mixtures. This had been going on for the last twenty years.

Since then we are working on the structure of brevotoxin-A. Its skeleton is different from that of brevotoxin-B. Brevotoxin-A has a molecular formula of $C_{49}H_{70}O_{13}$. It does not crystallize. Now we have a little bit more since we have succeeded in cultivating the toxin in our lab, but when we did the major structure determination, we only had 3 milligrams or so. It has 70 protons and is not crystalline. We did the most extensive COSY or 2D-NMR proton studies.

We haven't published this yet. One of my colleagues, Mike Tempesta at the University of Missouri, gave a talk at the Hawaii meeting this past December. We have the gross structure. I think it shows what can be done by modern NMR. The NMR spectrum was taken at Suntory, on a 350-MHz instrument. In a 2-ppm region there were 60 protons, all overlapping. We could clarify most of them, except for four protons, by a combination of various new pulse sequences. That's what you can do. Also, in this case we were forced to do the NMR studies because we could not crystallize the compound. We have tried to make x-ray suitable crystals for Jon Clardy, but so far without success. He's a good friend of mine, so we always have fun talking about the x-ray versus the non-x-ray approach. Brevotoxin-A is forcing us to use this COSY method to the extreme because it does not crystallize.

GORTLER: I'm afraid I'm not familiar with the COSY method.

NAKANISHI: It's one of the new two-dimensional NMR methods.

GORTLER: Yes, that was one of the things I noted here. I said that it seemed that the determination of structure had reached another milestone. There were first the classical chemical

methods that we talked about before, and then the classical spectroscopic methods. And now it's gotten down to x-ray, except, of course, you always need crystals. And if you don't have those...

NAKANISHI: Exactly. For example, if you want to study how some antibiotic binds to DNA, it cannot be done by x-ray. We were the first to totally elucidate how benzpyrene binds to DNA. And that was also done by NMR. This was done with Bernie Weinstein and his group. We determined the absolute stereochemistry as well as the full structure, and showed how benzpyrene binds to DNA and RNA. We had less than a milligram of these compounds, and they were, of course, totally noncrystalline (15).

GORTLER: As I was reading the brevotoxin paper I wondered whether the brevotoxins could be used as antidotes for the saxitoxins, since they do opposite things.

NAKANISHI: Maybe. There's not enough pure brevotoxin yet. I can tell you, we are just starting a massive culture now. At the recent biochemistry meeting in 1983, there was one morning session on the brevotoxins, so once the supply becomes sufficient, I think there is going to be some interest.

But once you get the new structure, that used to be the end of the organic chemist's role. But my concept has changed these days. Once you have a compound in the pure state then structure determination becomes relatively easy. But the next thing that organic chemists can do is to go into the mode of action--why does it work? For example, this brevotoxin is a new neurotoxin and we want to find out why it is a neurotoxin. This is an interdisciplinary problem. We cannot work by ourselves. It is impossible. So we are going to get together with two neurobiologists, one from France, the other from Harvard. We are starting to collaborate with these two to isolate and find out more about its mode of action.

Another thing we started doing this year was to start this massive culture. Now we want to go into the biosynthetic mechanism, which is more like traditional organic chemistry. But now, with difficulty, I would like to go into the difficult area of studying action as well.

Now I mentioned this isolation business. I can quote two examples without going into too much detail. These are unpublished, but we have just elucidated one challenging structure and may be close to another. One is collaborative with Ken Custin, a bioinorganic chemist at Brandeis. It is tunichrome, the vanadium sequestering pigment of the sea squirt Ascidia nigra. Sea squirts are common marine animals that are sessile and stick to rocks, etc. The blood contains vanadium, sometimes up to 0.1M. It uses vanadium, but the vanadium

biochemistry is not understood. Vanadium was recently found in human blood also, and its biochemistry is also hardly understood. The vanadium in the sea water is vanadium (V). In the blood cell of this animal it's supposed to be vanadium (III) and the blood is green. People have been trying to isolate and identify this vanadium chelating compound for almost seventy years because they noticed that once you cut the heart and bleed it, the pH is 1.2 and a precipitate is obtained with barium hydroxide. It's written in textbooks and in Encyclopedia Britannica that this lives in sulfuric acid.

Ken Custin found, a few years ago, that both of these conclusions were incorrect. It was not sulfuric acid, it was vanadic acid. Vanadium also precipitates with barium hydroxide. The moment the blood cells are exposed, the vanadium becomes vanadic acid. It's oxidized. So the conclusion was all wrong. The intact blood cells are at pH 7. This isolation has been a great challenge for us, but, finally we've been able to do it. The isolation was done by a good German postdoc by the name of Reimar Bruening. He is a senior person, and he's one of the best isolation chemists I have had. He has shown that from the very moment that you slit the heart open, the isolation must be done under specially purified argon, in the dark. And everything else, including the packing of the HPLC column, centrifugation, everything, has to be done under argon, in the dark. And, after five years, we finally have the structure now.

Now we have the structure, and we are going next week to Ken Custin's lab. We're writing the paper this weekend (16). From here on we want to go into the mode of action. It may be a new reduction-oxidation system.

The other challenging isolation project we have been involved in is the crustacean molting inhibitor. Again, many institutes all over the world have been trying to isolate this and in this case, the difficulty has been to set up a reliable bioassay system. This study is carried out at the Suntory Institute, with a little bit of help from my group here at Columbia. The work is done by Dr. Yoko Naya at Suntory. She is coming here next week.

[END OF TAPE, SIDE 5]

GORTLER: What will you be discussing with people at Wood's Hole?

NAKANISHI: The physiology of crustaceans and the mode of action of the molting inhibitor. This is, after all, an ecdysone biosynthesis inhibitor. The question is, what is the mode of action? There are many things we can do. It's not just determining the structure. I may be exaggerating a little, but

the structure of the molting inhibitor, when it's clarified, will be a starting point of another new project which organic chemists should go into.

I can generalize a little bit now. When I left Japan, I was working on ginkgolides. The first bioorganic studies we did were made when I left Japan. I like this work. It's a minor thing, but it has made some impact in the physiology of reproduction. For our first bioorganic studies on factors which are directly involved in the function of life, we isolated and determined the structure of the meiosis-inducing substance in the starfish (17). This turned out to be 2-methyladenine, a very simple compound which we subsequently made. This has played an extremely important physiological role. As a result of this work and subsequent studies on its mode of action, Dr. H. Kanatani received the Vatican Gold Medal. Unfortunately, he passed away two years ago.

About three or four years ago I changed my strategy, my broad directions. The meiosis-inducing hormone, MIS, was the first of the substances in this direction. I told you a little earlier that structure determinations have become routine. Usually they are not exciting any more. Particularly when you compare the stories going on in biochemistry and molecular biology, they're dry and not exciting. So, if I put it in the extreme, my feeling is that in about ten years from now, organic chemistry except, perhaps, for the field of synthesis, per se, may disappear. It will be totally amalgamated or incorporated into other fields, but becoming even more important in a totally nondisciplinary manner.

As far as natural products are concerned, I think what I'm saying is probably true. I don't say this for physical organic or some other fields, but in my field it's safe to say so in the sense that structure determination is becoming routine. It's only organic chemists who can, together with biologists, biomedical people and biochemists, start to understand how things work on a structural basis, instead of hand waving. I feel this rather strongly, when I look at what's going on in the rhodopsin field. We started making these analogs, and at least for organic chemists it makes things much more clearly focused. As a result, we are collaborating with about twenty groups now, just in that field. That is, in a sense, another structural determination. To put it succinctly, we want to elucidate, on a structural basis, the factors which are involved in the maintenance of lives of animals and plants. That also involves receptor studies and membrane studies. For example, in the bacteriorhodopsin, how does a proton go through a membrane? That is, of course, one of the most central problems to be addressed in the biological sciences. There's a limited number of things that we can do, but at least we can contribute as organic chemists.

As a result, we have switched to the so-called dynamic natural products and I am interacting even more with other people. Fortunately, living in New York is a big advantage. I

publish papers in this field, so I do get various phone calls from people telling me, "We have this compound. We would like you to collaborate with us." It's getting increasingly biomedical also. I don't know what it's going to lead to. I was just together with Professor Simeon Pollack of Albert Einstein Medical School. We haven't started this project, but will start shortly. He is working on how iron is transported within the red blood cells. It's not known. And it seems to be isolated.

Another professor with whom I began collaborating about a month ago is Professor Vincent Butler from P and S (Columbia Physicians and Surgeons). When humans have heart trouble, we take Digitalis purpurea (foxglove), cardiac glycosides or toad venom for treatment. These all belong to a particular group of compounds, cardiac glycosides or bufadienolides -- "bufo" comes from toad. The toads secrete a particular poison, which is non-toxic to them, toxic to most animals, but for humans, it's given for a heart treatment. All are steroid saponins.

There's a growing hypothesis that maybe we humans are secreting a cardiotonic substance. However, it has not been isolated and is not known whether such compounds exist. So we have started looking into human bile to find whether there is an inherent cardiotonic hormone for humans. This is very recent.

Another thing we started doing is, what are the factors which cause cells to differentiate themselves? What turns a cell into forming hands or heads, etc.? This is being carried out at Suntory by Dr. Y. Ohta with plant cell cultures. You see, these are all tiny chemicals, we think. This is what I call dynamic natural products, which we can certainly not do ourselves. It's becoming more nondisciplinary. That's why I say my field, natural products, will disappear, but it's going to play an even more important role. That's why I'm changing. It's undergoing a transition now. But the basis for this is to be able to do isolation and structure determination on submilligram quantities that may be noncrystalline.

GORTLER: Essentially, you've been preparing yourself for this for a very long time.

NAKANISHI: Yes. And I've got this somewhat scattered, broad interest in the biological fields, you see. I cannot go into molecular biology because that's far too competitive. It's also become too much a technical area. But I think we can fulfill lots of needs. However, I am dangerously spread out.

GORTLER: How do you juggle all the projects? [Laughter] Do you in fact have lieutenants that look after various projects?

NAKANISHI: Well, presently there is Dr. Fadila Derguini, who has been with me for six years, and Reimar Bruening, another senior person who has been here for four years. I'm trying to get jobs for them both. No, I don't have a continuous lieutenant.

GORTLER: In 1979 you became director of the Suntory Institute in Osaka. What is Suntory and do they give you freedom to choose your problems?

NAKANISHI: Suntory in Japan is the largest whiskey company and has also branched out in many other areas. Worldwide, it's very successful because the Japanese are heavy drinkers. It doesn't export too much, but the home consumption of whiskey is so great that, in its best years, the Suntory brand has sold more than twice the amount of the second leading best-selling bottle in the world. So they make quite a profit. Keizo Saji is the president of this company. In fact, I was just meeting with him last night. He's an organic chemist and he's a natural product chemist. He comes from Osaka University and he got his degree with Professor Munio Kotake. Kotake is deceased now, but he also comes from the Majima school at Sendai. (Remember, I mentioned Majima and then Nozoe.)

Saji wanted to go into teaching and research, but his elder brother died so he had to inherit his family business. He was forced to become the president of the Suntory Company. But he's always had a nostalgic feeling for basic science. He was the first one to give money in postwar Japan to Osaka City University to buy the first infrared spectrometer to come into Japan. When they opened the office in New York, he got the Audubon Society award because of his bird sanctuary. He's an essayist and he's quite a person.

GORTLER: He wasn't one of these scholars, these fellows that you talked about, the Garioa Fellows?

NAKANISHI: No. I just came to know Saji recently. Soon after the war, Suntory started a foundation called the Institute of Food Science, the name reflecting the postwar shortage in food. The foundation is nonprofit. This went on for twenty years and then the past director of this Institute was about to retire. One of my high school friends is on the board of directors of the Suntory Company. He came to New York, (he's also an organic chemist) and he asked me whether I'd be interested in becoming the director. So it gave me a good foot in Japan, too. When the previous director retired, Saji decided to give a quantum jump to this Institute. Before that they didn't even have a decent NMR, but now it's probably one of the best equipped laboratories in the world. Not only that, it functions smoothly. He said yes to practically everything I asked him to do. And that's how we started this postdoc system.

GORTLER: What is the postdoc system that you started at Suntory?

NAKANISHI: In Japan, strangely enough, no formal postdoc system exists. Practically every professor in the science field has asked for a postdoc system. And, not only within Japan, but these days there are quite a few who are interested in coming to Japan from other countries too. I'm speaking of developed countries, so that it would be a mutual exchange. Practically all the Japanese postdoc students who have come to this country or have gone to Europe have been paid by the respective governments and not by the Japanese government. Terribly backward, in this case.

First of all, the major Japanese universities are Federal universities, national universities controlled under the auspices of the Ministry of Education. And the Ministry of Education has not a single person who has had the experience of research. They all are liberal arts graduates from economics, literature, philosophy, law and so on. Incredible. Not a single person who has had the experience of doing scientific research. It's almost impossible to convince these people that the postdoc or any other system is better than the existing one.

Our system now goes back to the last century. It is basically the German system. The Germans changed their system after the war but the Japanese have loyally stuck to the nineteenth century German system. That's why it's so hierarchical. The Germans are not like that any more. Maybe one hundred years ago it was better because in those days, when Japanese science started, we used to invite various foreign chemists. Japanese chemistry was started by foreign chemists, not by the the Japanese. And then after that, Japanese students were sent abroad at government expense and then they came back and that's how it started. About three years ago, they appointed the first professor in a science field who was a non-Japanese. This person comes from Nottingham and he is now at the University of Kyoto. Kyoto does many more advanced things than the University of Tokyo. The University of Tokyo is such a big body. It's the most influential. Because the Ministry of Education has no science bureaucrats, they tend to rely strongly on committees. And most of the committees, because of the geography and because of the reputation, are controlled by the University of Tokyo people.

Now, if a University of Tokyo person is rather mediocre, and there are some mediocre professors there, of course, and he suddenly becomes the head of a committee, he becomes very influential. This is a very comfortable position. In the hierarchy system coming from the University of Tokyo and being head of a committee, he becomes very influential.

A system like that will not undergo a drastic change because it's comfortable for the professor. I'm not necessarily speaking just about the University of Tokyo. This is true in general. Because to sit on the top of a big group in which you have an assistant professor and two assistants, all paid by federal money--you don't have to pay anything and all the graduate students are paid. It's a very comfortable thing. I think that is one reason that I started to feel uncomfortable. I started to feel that I was getting spoiled, and I was spending too much time on committees. Changes are extremely slow in the feudal bureaucratic Japanese system. Despite the fact that the professors have been asking for postdocs and crying about the situation for years, not a step has been taken. It's very disturbing. Several years ago the Japan Society for the Promotion of Science was set up. This makes more sense. I mean, scientists are involved and they know a little bit about what's going on in contrast to the Ministry of Education, which controls most of the research budget in Japanese universities, despite their total lack of experience about research.

GORTLER: Is the Japan Society also government sponsored?

NAKANISHI: It is a government organ. It's called JSPS. For example, they started, several years back, inviting foreign professors in an exchange program. This has been extremely popular and I think it's a great thing they are doing. They invite professors from abroad, paying them first class air tickets, with the understanding that if they want to bring their spouses, they can do it at their own expense, by paying the economy fare. The per diem is very generous. It's a rather tough schedule. Maybe three lectures a week and covering all the universities in Japan. But practically every professor who has been through this (and lots of organic chemists have gone through this) have enjoyed it. They return with a good feeling and of course a better understanding. It's a tremendous program. It is a nice, positive thing.

JSPS has started, on a very small basis, an internal postdoc system. But to my surprise, practically all the people who got postdoc support have been remaining with their mentors. In Japan there is an overproduction, in some fields of science, of doctorates, Ph.D.s. So, they have nowhere to go. Japan being Japan, even after they get their Ph.D.s, if they have a wealthy family they are still supported by their parents. This is just an oriental custom, you see, even if they are mature and grown-up. So these people survive, or they are supported by their spouse or whatever. These are called "over-doctors". The internal postdoc money is all spent on maintaining these "over-doctors" together with their mentors within the system, so there's no exchange of blood.

So, it was sort of an adventure, a gamble, but we started this formal postdoc system in Suntory. It's now in its fifth or sixth year. It first started by getting approval of the company and the president was very positive about this. He even said, "If it becomes necessary, let's employ someone on a permanent basis." Once he said that, everything was fine. The first group of postdocs were postdocs who applied here at Columbia. I said, "It's full now, but what about going to Japan?" As a result, we've been getting really first quality postdocs all the time. There have been quite a few.

GORTLER: Are these people applying to you or are some of them now applying directly to Suntory?

NAKANISHI: Increasingly they are applying directly to Suntory. There are four ex-Suntory people who are in academia now. One is at Tohoku University, another applied to American universities directly from Suntory and he is an assistant professor now. Another one is an associate professor at National Taiwan. Another one is the deputy director of the Shanghai Institute of Materia Medica. He came as a more senior person. And we have guys from Poland, China, and Taiwan, but mostly American. More recently, we had a postdoc from Ireland. This kind of thing is new for Japan.

Now the pros and cons of this. It's a new experience for Japan. In particular, you have different customs and a different language. When I said that we have had no formal postdoc system, it also meant that the accepting people, the Japanese people, had not been sufficiently exposed to the postdoc system.

Before that, maybe I should say a little bit about the Suntory Institute setup. It's a foundation and we call it SUNBOR, an acronym for the full name [Suntory Institute for Bioorganic Research]. The rough structure of SUNBOR is about twenty-seven permanent staff, of whom seventeen or so have degrees. Most of these are quite senior people. All are experienced, having had postdoc experience abroad, mostly in America and some in Europe. The other seven or eight have bachelor's or master's degrees, mostly from Osaka University or Kyoto University. Except for two, they are female scientists. They could stay permanently, but mostly (that's a big difference from this country) the females get married after five or six years and then quit. It's a pity for us. These females are probably the best group of scientists you can get in Japan now. They are well-trained in pharmacy, chemistry, etc., and are bright. They are extremely good.

The result of a nationwide questionnaire was out in the Japanese press recently as to what is the most popular company you would like to join. The questionnaire was sent to university

male and female graduates and Suntory came out on top in both categories. So we get extremely good people applying for the Suntory company and also for our Institute.

GORTLER: Are any of the senior staff women?

NAKANISHI: Oh, yes. The deputy director who is coming here next week is a woman. There is no discrimination; it's just the Japanese social setup. Professional women are becoming more common but still there is a large difference from this country. Women have their own world, and men have their own world. That is, we are not mixed up like in this country. Quite different. In addition to the staff I mentioned, we have the six postdocs.

I might just explain how the Japanese bureaucrats are in the Ministry of Education. I'm the only one who can attack the Ministry. Other people, including even Professor K. Fukui who received the Nobel prize, are hesitant because he, like most university professors, is a government official. Also, he is, in a sense, milder and more cultured than I am, but his feeling is as strong as mine. He says he cannot do this. We sympathize in many fields, but he says, "You can do the talking. I am not in the position to do this."

GORTLER: You cannot bite the hand that feeds you.

NAKANISHI: When they decided to overhaul this Institute, they wanted to change the name. So, I chose the word "bioorganic" research. I won't go into the details because it is in Chinese characters. Bioorganic Science, that's a more literal translation of the Institute name. But no such word was used in Japan before I started using this name. When I went to the Ministry of Education, they said there's no such word, you cannot use it. Because it doesn't exist in the dictionary, there's no precedence. So I had to fight for this.

GORTLER: Why did the Ministry of Education still have control?

NAKANISHI: Because ours is a foundation and it belongs to the Ministry of Education.

GORTLER: I see, even though it's funded by private funds.

NAKANISHI: Yes, it's a foundation. It is under the auspices of the Minister of Education. We have to send in our annual reports and so on. That's how it is.

GORTLER: There's no undergraduate education or anything of that sort going on there.

NAKANISHI: No, nothing like that. And then, finally they said yes. Of course, they totally objected when I said I want to use the name of Suntory. I thought it would do good for the Suntory Company, who was funding us. A good promotion. Of course, they objected. This I can understand better than using the name of bioorganic science.

But what upset me was, I went to this Minister of Education, who was a young clerk. I didn't say jerk. [laughter] He must have been in his mid-forties or something. When I got there I took out my name card. I went with one of the board of directors of Suntory Company. These people, particularly from a company like Suntory, who depend on selling drinks (liquor), have to maintain a good social image. So they are very courteous. This young clerk looks at my name card and I tell him I'm a professor at Columbia. This is the thing which upsets me most. I`m much more senior and he just looks at my name card and asks, "Do you have tenure at Columbia?" Without having any research experience, and probably only a superficial picture of the American academic system, what does this guy know about tenure? I almost blew up at him, but then this Director said, "Oh yes, of course." He calmed me down but, if I went there alone, I would have said, "To hell with you." This is the typical bureaucrats attitude. They want to show off. Well, at least this mid-forty clerk had heard of the term tenure.

Now we come back to the postdocs. That is, Suntory's setup with these six or so postdocs. A new experience in Japan means that the receiving party has not had experience in receiving postdocs. To start with, for example, we get a postdoc from Poland. Immediately after we get him, the local police come. SUNBOR is in a quiet residential place. We also got some postdocs from China. The police ask, "Why does this Institute have people from China, and now from Poland?" They start getting suspicious, but that's fine. But then I get upset and ask, "Why do you do this?" And they said, "Well, in case something happens, we have to protect them."

[END OF TAPE, SIDE 6]

NAKANISHI: In the USA academic circle, we do not hear much of Mafias. In Japan, the whole academe consists of various Mafia families. [laughter]

GORTLER: You were telling me about the local police and the receiving end.

NAKANISHI: That's one thing, but another one is more to do with the scientists. I noticed this quite recently. When the Japanese postdocs come to this country, it is quite different than when Americans come to do their postdoc. In Japan it is very paternal; it depends on the professors. They come for a postdoc to this country and when they go back to Japan to go job-hunting, they don't have to go to universities or companies to give talks on what they did. It depends on the professor's recommendation and the connection with the company. And particularly when it's an academic job. The personnel thing is absolutely hush-hush. It's top secret who is being considered. No one knows about it. It is the top secret of faculty meetings. Whereas in this country or in Europe, the moment someone gets a call, it's all out in the open. It's totally different in that sense. Sometimes power is applied, especially in the medical field. That's what I meant by a family of Mafias. It's like a chess game with pawns.

GORTLER: It occurs around here too. The "old boy" system. It also applied in England. Robinson could really control where his people went.

NAKANISHI: It's slowly changing, but still the Japanese postdocs who come to this country can simply concentrate on their work without minding too much. They don't have to bother about how much they can accomplish in terms of presenting an impressive interview talk. It's not their main concern.

Whereas Americans who come for a postdoc have to accomplish something to show at the interviews what they have done. I noticed this recently at Suntory. The American postdocs are assigned to the permanent, more senior, staff. The senior staff wants to train the postdocs. If the problem is very difficult and it doesn't give quick results, the Japanese senior person says, you do this and this, under these conditions and so on. Very explicit directions. The Japanese permanent staff are doing this to train the postdocs, with all best wishes, of course. They sincerely want to help them but do not grasp the difference in the concepts. The Americans have to get results. Not that quickly necessarily, but they have to get some impressive results. The Japanese, on the other hand, tend to give very difficult problems. They challenge so they can train the postdocs well. The Japanese have good intentions though.

GORTLER: Sort of cross purposes, in a sense.

NAKANISHI: I noticed this recently, quite recently.

GORTLER: So these are subtle, small things. But still, it shows you the difference in methods.

Do you have some control over the problems that are worked on there?

NAKANISHI: Yes, I discuss. That's what I do. I go there for a total of four visits, two weeks each, mostly during the winter and summer vacation. Nowadays it's becoming more and more discussion. I tend to carry out the whole discussion in English. The invited speakers, even if they are Japanese, are asked to give their talks and the discussion in English. I want the Japanese staff to be constantly lubricated in the usage of English. Not only in the receptive sense, i.e., just talking with postdocs, but when they go outside. Certainly when they're sent abroad to attend a conference, they should be able to not only present their own talks, but understand the discussions, ask questions and get involved in someone else's work. So this may be the only place that we have these outside speakers giving their talks in English. I find resistance to this, even at SUNBOR. Of course, it's essential for foreign postdocs, otherwise they won't understand.

At SUNBOR we are also the same as Columbia, moving more and more into nondisciplinary areas. So outside speakers who are not in organic chemistry are invited. Even in Japanese, their talks could be difficult to understand because of the technical jargon, or terms which we have not heard. It's like a power game. Not exactly like that, but I'm playing against some pressure to have the talks not in Japanese.

GORTLER: Are some of the people at SUNBOR doing your research? Or is there no one there that you collaborate with on problems.

NAKANISHI: We have about four groups there. I first started this Institute as a pair system. In other words, one senior staff and one junior staff. This junior staff could be a postdoc, or could be a predoctoral staff. With this pair system it is much more flexible, much more mobile. For interdisciplinary problems, pair A and pair B would get together and on another problem, pair A and pair C would get together, depending on their specialties. That is, in a sense, the system which they adopted at Du Pont, Bell Labs, and ICI. I visited these places and I am very impressed with the quality of basic work coming out.

More recently, we are forced to become more purpose-oriented. The pair system is basically maintained but it has been regrouped into four or five groups. One is tissue culture, one is bioactive compounds, one is marine, one is synthesis, and one is instrumental analysis. Within this, we still have the pair system. Although I am not involved in tissue culture, we

still discuss the future direction of this group, headed by Dr. Y. Ohta. Rather than just doing very basic science, it is becoming increasingly purpose-oriented. In synthesis, fortunately, we have one of the best synthetic chemists in that generation in Japan now. We had another excellent guy who is now at Tohoku University, so I discuss in broad terms what molecules they will work on. A general philosophical discussion. Of course, I cannot direct synthesis. In bioactive compounds and marines I am more directly involved. I am in touch, over the phone, every other day for about thirty, forty minutes with Japan. This comes anytime, usually at eleven o'clock at night. When I want to relax. [laughter]

I hope the postdoc system continues. So far it's been very good. I was worried about the job situation. The way it operates at Columbia, like any other place, is that people come here to Columbia to interview the graduate students. A company comes and they might interview say, ten to fifteen people. They go back and circulate the names with a recommendation. One or two are selected for a site visit. I talk with these interviewers and I mention the Suntory postdocs. I've managed to get five or six companies interested and they pay for the air fares. So the American postdocs at SUNBOR do have a fair chance comparable to those here, as far as interviews go.

GORTLER: Oh, I see. The companies group together and they all pay the single air fare and the postdoc comes here and visits them all.

NAKANISHI: That's right. And this year, it's even more challenging. It's a husband and wife team. They're touring right now. They'll go to Cyanamid, Monsanto, Rohm and Haas and others.

Another thing I would like to start is a sabbatical system at SUNBOR. It doesn't exist in the Japanese universities. On the other hand, professors can go for a trip anytime they want, but not for extended periods. Again, the Japanese professors have been asking for this for years, and it has never been realized. I've got the basic approval of the company now. All the permanent staff will have to go out every three or four years for a three-month period to a new field or whatever. Preferably not where a Japanese professor is found. Some will go and some are rather hesitant but this is the basic system.

GORTLER: So they will go to another country?

NAKANISHI: Yes. Basically another country in a different environment to learn a new thing. Or, if they are really in the first ranking, with an international reputation, then they can go to the library and simply discuss things and start writing

papers. But that stage has not arrived yet. So this is another new thing I will start at Suntory. The SUNBOR Institute is like an experiment. The system has attracted lots of interest in Japan and there's already two places which are starting to set up an institute like SUNBOR. Some are considering the possibility of starting this postdoc system also.

GORTLER: This is in Japan.

NAKANISHI: Yes. But it will be difficult. I know both countries so it's easier for me to do this. Anyhow, I think the postdoc system has attracted lots of attention. It has been written up in various places. So at least the scientific public is aware of it.

GORTLER: That's interesting. The postdoc system at Syntex is a little bit different, because the postdocs work at the company.

NAKANISHI: But that's okay. I'm not surprised about the American postdoc system, because the American companies are so far advanced.

GORTLER: You have said nothing about teaching so far. I don't know how much teaching you do here.

NAKANISHI: I do the same amount of teaching as all the other professors. Is that what you mean? At Columbia it is a two-semester system. One semester teaching a graduate course and one semester an undergraduate course. We alternate. We're trying to reduce our teaching load and we have been able to manage this somewhat starting this fall. We will have one semester full teaching at the undergraduate or graduate level and then the second semester, half a semester teaching.

GORTLER: This is a single course usually.

NAKANISHI: Yes. Our teaching load is about three contact hours or three lecture hours a week.

GORTLER: Do you feel that there's some separation between the kind of teaching you do there and the kind of teaching you do with your research group?

NAKANISHI: We don't do teaching in my research group.

GORTLER: Well, in the sense that you're teaching them to do research.

NAKANISHI: [laughter] That is just having fun. They teach me.

GORTLER: Do you resent the other aspect of it or do you find an interest in it?

NAKANISHI: Teaching?

GORTLER: Yes. Does it interfere with your doing research?

NAKANISHI: Basically, I don't like teaching. I became a professor, so I suppose I belong to the category of teachers. But I don't like teaching classes. Americans take teaching much more seriously and I fully admire these people. But somehow, I cannot. It may be my personality. I just like to be fully involved in research. Of course, by teaching you're forced to expand your knowledge. Preparing a course forces this, as you well know. For some, it does help a great deal. But basically I don't like it.

GORTLER: I couldn't end the interview without asking you about the magic. For those who know, you're almost as famous as a magician as you are as a chemist. When did that start? You obviously enjoy it. Tell me as much about it as you can.

NAKANISHI: I have a card trick. My own card trick. I developed it during my high school years, at which time we were working in factories, pounding on red-hot irons and things like that. No one has found out how it works. It's a pretty good trick.

In effect what I do is, I go to your home and you take out from your own deck a card and put it back. And you can shuffle it. And, I'll tell you what card you picked. It almost seems impossible. There is a very simple principle and I've only mentioned this to my wife. She says, "This is impossible. It can't work. It's so simple you have nothing to stand on to." But it's been working. And I've been practicing since I was twenty-three. It's almost forty years now. So it's quite refined.

When I started as a university student, I used to do this at parties. Friends applaud. They get mystified, and as a result I've built up my reputation. Then I started doing other, more routine things. Then, I was asked to perform.

GORTLER: You learned that trick from...

NAKANISHI: No, this is my own. And I don't think people have worked on this principle yet. Then I started adding more routine repertoires and was asked to perform at symposia, after lectures, parties, and so on. I lecture at other universities much more since I came to this country because in Japan the seminar system does not exist. This is another thing which should be adopted into the Japanese system. It's so simple. Just have this weekly seminar system. But it does not exist.

GORTLER: I see. So there's not as much interaction between chemists.

NAKANISHI: No, and here they have it and when I'm asked I perform. Since coming to Columbia, I do it every Christmas in front of the chemistry department. This is rather challenging. It's about 150 people. To make things worse, I don't have these so-called attractive assistants, you see. It is a senile male trying to catch the attention of these widespread people for a full forty minutes without a break. I may feel as if I'm enjoying it, but before I set up this thing, I get much more nervous than before a chemistry talk. But once I start doing it, then I start having fun. So now I perform here and there.

GORTLER: So, in a sense, it's relaxation or a hobby?

NAKANISHI: It's a hobby. I suppose this may have helped--it's psychologically very subtle, you see. It's not the sleight of hand things. Magic is much more psychological. This card trick, for example, is very psychological. You have to smooth it out and it may have helped me with dealing with people without my knowing it.

GORTLER: Do you have any other hobbies or diversions that you are involved in?

NAKANISHI: Well, I like chatting over drinks in a quiet bar with friends. I really enjoy it. I can go on and on.

GORTLER: [laughter] I'm surprised that you have been able to talk as long as you have.

NAKANISHI: I enjoy the drinking atmosphere, going to restaurants.

GORTLER: What is the biggest challenge for organic chemistry now? We pretty much talked about where you think your brand of organic chemistry is headed. What are the really big challenges that you see?

NAKANISHI: I think trying to understand the factors that control life on a structural basis is almost nonexistent. It's only a few hormones that have been structurally elucidated, but we do not know the mode of action. There's hardly any precedence for this. It is only very recently that even trying to solve such problems becomes thinkable because of the advance in various spectroscopic techniques, such as quick pico-second techniques, new isolation techniques, etc. Now we can start attacking these problems. Also, knowledge has become much more interdisciplinary. Organic chemists have acquired a much stronger interest in biology and, to a certain extent, the biologists have started to work on these problems as more structures become elucidated. So now we can start working together. At least we have an area in which we can speak the same language. And the advancements in technique are certainly helping.

For example, we can ask when you have an undifferentiated cell, why does this portion become the hand, why does an eye get formed? These are all controlled by chemical factors. This borderlines on molecular biology. But still, there are tiny, smaller molecules which induce this. And, we first have to find these molecules and then work out what happens later. I've just given one example. What are the factors which induce cells to differentiate? Biologists are getting interested in these differentiating factors from a biologist's viewpoint. There are hardly any organic chemists who have gone into this field yet. This is a very exciting area in which organic chemists can collaborate with biologists.

In the plant field there is even less collaboration. There's the so-called phytolexins. When plants are invaded by exogenous fungi, they start making defense substances. Lots of these are antifungal compounds, antibiotics and so on.

I attended the Gordon conference in agriculture last month in California. You have a plant, leaves spread out all over and you take one of the leaves, while it's on the plant and damage it. Soon after that a defense substance is secreted. These substances are called phytolexins. If you damage the area, as if it was chewed by an insect, for example, then a signal goes on and some antifeedant starts to form. Then the amazing thing is, in about an hour, the same substance is made throughout the plant. Nothing is known about these things. So it is very exciting. And these are small molecules.

There is another bioorganic problem in which I'm interested. To put it in very simple terms, you can grow undifferentiated plant cells called callus. Suppose you have a callus in a beaker and in a dialysis bag another callus. Somehow you can "tickle" this. Add some antibiotics, add a stress to this callus and then the cells become differentiated. In other words, the callus is undifferentiated and they become the leaves or buds or shoots. This is a dialysis bag, which means that only small molecules can go through the bag wall. After the callus in the dialysis bag starts differentiating, the callus in the beaker outside the dialysis bag starts differentiating too, which means the inducing molecules are small molecules. The structure of these are not known.

Most of the biomedical people, if they're involved in basic research, have observed some interesting and exciting phenomena. But most of the biomedical people don't realize they are chemical problems. We (the chemists) don't know that the problems exist. As I mentioned earlier, for example, it is not known how iron is absorbed and gets into hemoglobin. Now we can start arguing this on a chemical basis, and that's why we had this discussion with Professor Pollack. It turns out we had a three-hour discussion on this.

Vision is another example, but terribly complicated. It would have been totally impossible to attack this twenty years ago. It would be too frustrating a problem. It's still frustrating, but at least we think that somehow with lots of collaborative effort, current science will slowly clarify this.

GORTLER: Any advice for young people thinking about careers in science?

NAKANISHI: [laughter]

GORTLER: That's a bad question. It's the kind of thing I'll have to ask you on videotape, to inspire people.

NAKANISHI: If I can say one thing, it's to have your antennas stretched out and collect as much data as possible. Always have your antennas on the alert. Once you absorb something, don't just absorb and store it, but be imaginative and try to use it in your own research. Who cares whether a precedent is there or not. It's better not to follow precedents too much. Be imaginative, but imagination is something you have to train yourself to use. The first thing is to have lots of curiosity. Always be asking, "Why does this happen?" And keep good contacts.

One thing I gained from having drinks in bars with friends is that I was frequently going into what is curious in biology and nature. Lots of these friends are biologists and medical people. Sometimes some collaborative things have come out of this. At least, it keeps me prepared. I love listening to any person--animal behavior people or etiologists, for example. I tend to think there must be some chemical basis for behavior. I try to see things on a chemical basis as much as possible. And, if there's no chemical solution, and in most cases there's none, I would like to solve it as a natural product chemist.

GORTLER: At the very least there's this sort of cross-fertilization.

NAKANISHI: So to put it in simple words, the interest should be very interdisciplinary. You should have curiosity, an open mind, alert antenna, be imaginative and hard working.

GORTLER: [laughter] That's very nice. I have no other questions. Is there anything else that you'd like to add?

NAKANISHI: Yes! My wife says that the way I am spreading out, it's worse than a supermarket. [laughter] I am becoming aware of this and have to be very careful.

GORTLER: Thank you very much.

NAKANISHI: Thank you.

[END OF TAPE, SIDE 7]

NOTES

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