Murayama, Makio 2001

Dr. Makio Murayama Oral History 2001

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Dr. Makio Murayama

November 15, 2001

The time is 11:15. Dr. Valerie Williams from the NIH History Office will be interviewing Dr. Murayama on the historical aspects of sickle-cell disease from the period 1949 to 2001.

Williams: Thank you for meeting with me today. I appreciate your time, the time you'll spend with me for this interview. I'd like to start off just finding out a little bit about you. How did you get started doing research? How did you sort of get into doing research?

Murayama: Before I got into my Ph.D. program, I was working as a hospital blood chemist to earn a living, because during the war years -- that's 1942 on till 1948 -- I worked as a blood chemist for the Children's Hospital, Michigan, in Detroit, and the Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, and then Children's Pediatric Service, Bellevue Hospital, New York, for three years.

Williams: This was prior to your Ph.D.

Murayama: Yes, and I was asked to do this research. There's war on, and you can't -- the doctor said, "I can't find anybody. I know you're working full time here, but by any chance, could you," and he explained to me what was wanted. Well, I could squeeze that in, running tests to determine blood urea, nitrogen, every other day or something like that. And then this was the day of the sulfa drugs, and blood level of sulfa drugs, and then came the diazine. We found one era after another because the bugs developed resistance and we kept on leapfrogging. And then came the antibiotics. Antibiotics changed everything, we thought that all you have to do is just dole out penicillin and go home and get a good night's sleep. Oh, wow, what do you know. Patients running up and around. Well, that didn't last very long.

Williams: So that's how it started.

Murayama: So, working around the hospital, watching the doctors fumble, physicians still fumbling.What's the big deal? Do you see any real cure for sickle-cell anemia, cure for cancer? See what I mean?

Williams: I do.

Murayama: What shall I say? Working at the bedside and trying to study for my degree, there was always crossover between the laboratory bench and the bedside for me.

Williams: Tell me now a little bit about your first research project. I guess that would be what you worked on as a graduate student then?

Murayama: Yeah, graduate student. I was trying to get away from what we used to call the wonder drugs, and so I was trying to . . . In order to get away from it, I have to find out about the mechanism of host resistance against infection.

Williams: Okay, did you have a working hypothesis about that at the time?

Murayama: Yes. Today it's right up there. It has to do with the mechanism of anthrax acting on rat. Rat is absolutely immune to anthrax, and sheep and guinea pigs, they all die of infection. And, you know, the origin of the term anthrax, where it comes from? Why is it called anthrax?

Williams: I don't know.

Murayama: You know what an anthrocite is?

Williams: No, I don't. Anthrocite?

Murayama: Anthrocite is a true, pitch-black coa

l.

Williams: Really?

Murayama: Yes, and the black blood that was oozing from animals, a farmer would see this black, tarry mess oozing out of sheep and that's how the name anthrax came. And it's common knowledge amongst the farmers in the olden days that rat will eat the black, tarry stuff with impunity. Now, the question is, how come rat is completely immune to anthrax. And my experimental animal that's readily available to me, which -- I bought these animals out of my own pocket, by the way.

Williams: Did you?

Murayama: I wanted to determine the difference in the enzyme activity. In those days, everything, it still is, the energy source is ATP triphosphate. Okay. What happens to ATPs of white blood cells obtained from guinea pig versus the white blood cells of a rat? Now, here's an interesting situation. The back side of the [?] is very sensitive to pneumococcus in the guinea pig, so you need two to look into the ATP's influence of the anthrax antigen and pneumococcus antigen against these host white cell. You see, the immune system being able to ward off the invading bacteria only could be won by the battle which the white cells put up. And white cells . . . In the rat, ATP of the rat -- I'm talking about the white blood cells - would be activated by anthrax antigen. This was kind of a secret for a long time for reasons not known, but I didn't know that my mentor at the University of Michigan, Dr. Nungaster, was the scientific advisor to Fort Detrick. That was the biological warfare center.

Williams: Right.

Murayama: You came at the appropriate time for me to tell you this story.

Williams: Yes. This is great timing.

Murayama: Nobody, but nobody, has heard this before.

Williams: It is absolutely amazing to me that you were investigating this question that has so much relevance today. It speaks about the timelessness of research, I think.

Murayama: I tried to get the paper published, but I don't remember those experiences. I think that the manuscript was turned down. Well, anyway, that was the beginning, and I did other work. I was assisting clinicians at Bellevue, in Detroit Children's Hospital, Michigan, the University of Michigan, and I got to know my mentor as a chemist. He needed my help for something. And one day he said, "You haven't got your Ph.D. yet, have you? You've got to get your Ph.D." We sat down and worked out what to do, and I ended up getting a Ph.D. and an NIH fellowship.

Williams: I see. So that's the connection. So it was an NIH fellowship. Did you start off at the Laboratory of Physical Biology? Is that where you went initially?

Murayama: Yes. I was with the Laboratory of Physical Biology. After I got my degree in Ann Arbor, Michigan, then I did my postdoctoral work under Linus Pauling at Cal Tech.

Williams: Okay.

Murayama: I was interested in sickle cell anemia, working in the Department of Pediatrics from time to time and doctors were coming in saying, "We have a sickle cell anemia patient in crisis. Can you help us?" I don't know anything about it. So I'd get on the phone and call up all the hematologists at Harvard University, all over the country, about it

.

Williams: I don't have your CV. What year?

Murayama: That was between '45 and '48.

Williams: This was just prior to Pauling's paper. Let's see what was going on. I have my time line here; '45 through '48. So, actually, Sherman had done his studies about the oxygenated red cells. What was the big question then? Do you remember what was the central question about sickle cell disease during that time?

Murayama: Well, first, Pauling had shown that this was a molecular disease. Remember?

Williams: Right.

Murayama: And my friend Itano [Harvey] was a postdoctoral student under Pauling, and Pauling told him what to do to separate out the normal and S hemoglobin by using a gadget called an *electrophoresis* apparatus. It was very simple to show that the A hemoglobin moved slower than the A hemoglobin in this gadget. And Pauling coined the phrase molecular disease. And then I went to learn more about the physical chemistry of hemoglobin, both the normal and sickle cell hemoglobin, and then I discovered that negative temperature coefficient of chelation of deoxy-S hemoglobin, which, by the way, I started to suspect that the hydrophobic bonds must be involved in the process of sickling. Then this notion was not completely confirmed but partially confirmed when Ingram found that the beta-6 was valine instead of glutamic acid in human S hemoglobin. That was Ingram and Hunt.

Williams: Hunt, right. And before we go there, I'm going to back up a little bit, you were working in the laboratory. Who were your collaborators in the laboratory that you were working with?

Murayama: Ed Caltay [sp.]

Williams: Where was that?

Murayama: Well, I was at Cal Tech on my own. That was -- I received a postdoctoral fellowship under Linus Pauling. He didn't quite tell me where the money came from, but I had two years of wonderful time at Cal Tech. And this is the year that Linus Pauling received his Nobel Prize. I got there in July, and a couple of months later he got a phone call from Stockholm, and, well, we had no idea what a great deal of excitement and joy that was. And I don't know how it came about. I think it was he meant to be a joke or something, you know.

Williams: Was he completely surprised, do you think?

Murayama: I think he had many years of disappointment, because he's done so many things. The alpha helix was one of the many things. And other great works of Pauling's prior to that in mathematics, what shall I say, atomic chemistry calculations were way beyond people other than Einstein could understand it. Einstein worked at Cal Tech in the '30s. But, anyway, I was working on what is known as the sulfhydryl group.

Williams: The sulfhydryl group as in cystine.

Murayama: That's right. This was the method of determination was electrochemistry, amperometric titration, which was not very popular. It's very tedious. So I decided to put together an automatic gadget so that when I'm out of the lab, the gadget will automatically crank out the data. I ended up getting a patent on that. This took place before I got to Cal Tech. And so while I was in Cal Tech, I built the gadget and cranked out data on it, and the thing to do was to change the temperature, raise the temperature, and the number of titratable sulfhydryl group increased. Reduce the temperature down to zero, and it decreased in half, when 50 percent was titratable, indicating that some sort of architectural change took place and that 50 percent of the sulfhydryl groups got muzzled, became unavailable to the ion. Mercaptan [sp.] means capturing mercury. After you titrate mercaptan [sp.], the mercaptyl [sp.] group was chloride, and in capturing it increased this temperature because the space that's available to mercuric iron increased, whereas at the lower temperature, got squeezed out, so to speak, or muzzled. So, in the course of amperometric titration at zero degrees and at 38 degrees, I discovered the negative temperature caused the titration of S hemoglobin.

Williams: You discovered that, I believe, that was '57. I don't have your CV in front of me, so I apologize. You were still a postdoc at this time?

Murayama: I was at Cal Tech '54 to '56, and then I sent in the manuscript from Cal Tech. It's published.

Williams: Later.

Murayama: A little bit later.

Williams: Okay. So you did the work while you were at Cal Tech.

Murayama: Yes.

Williams: But in '57, officially you were at NIH

Murayama: No. I came here in October '58.

Williams: Okay.

Murayama: After Cal Tech, I went to the University Pennsylvania.

Williams: I see. So your research at Cal Tech was this titration, amperometric titration of sulfhydryl groups. Is that correct?

Murayama: The physical chemistry of S hemoglobin, the main thing. And amperometric titration was one aspect of the physical chemistry investigation into sickle cell hemoglobin.

Williams: Okay. And this was to better understand the structure?

Murayama: Yes.

Williams: So these were in the realm of structural characteristics.

Murayama: Yes, hoping that I'll figure out the mechanism of sickling on red cells. And what happens is that the sickle cell hemolysate gels upon deoxygenation warmed up in my hand. I was holding the test tube actually like this, and the only thing I had was a beaker full of ice chips. And I put in an ice chip and then shake, and, lo and behold, turned into liquid.

Williams: I read that.

Murayama: I must be out of my mind. I discovered something. And I started to, well, this is quite contrary to what you expect. If I wanted to make jello so jello will set, I put the ice back.

Williams: You don't put things in ice to make them melt, to make them liquefy

.

Murayama: Yes. And then I didn't know much about hydrophobic bonding then and learned a lot because of it, because it was on my mind day and night.

Williams: Was it?

Murayama: Well, you know, this is it; I did a lot of searching in the laboratory, in the library.

Williams: When I first read, I guess the '62 paper, your 1962 paper. This was the June 1962 paper from *Nature*, actually the one that described it, and I was so amazed here about that phenomenon because I didn't read the '57 paper.

Murayama: Is that one in *Nature*?

Williams: This is the one in *Nature*. That's correct. So, the JBC paper I guess is where you first reported it.

Murayama: Yes. I suppose it was confirmed by this optical dispersion. This was a tremendous excitement. This was -- I couldn't get home. I was starting an experiment. That's one of the other nights that I didn't have time to come home for dinner. This was done in Building 4 basement. There was a gadget there that occupied a whole room in those days.I suppose I did a lot of thinking, and there are lots of smart guys around, you know.

Williams: Who did you talk to?

Murayama: [?] thought it was very interesting, and then it was consistent with the temperature coefficient.

Williams: But you found this and you weren't working with anyone else. You were doing these experiments.

Murayama: I worked by myself.

Williams: Yeah, this is by you.

Murayama: Like everything else, I do everything alone. I had to find these people for the blood specimen. Nobody's done this type of optical dispersion before. It was fun.

Williams: I can imagine that was just exciting.

Murayama: You know the difference is so bizarre. You don't even have to do any statistical work.

Williams: And how many times did you do it over? I mean, obviously, the first time you did it, you probably thought maybe I did something wrong.

Murayama: Yes. So sample and do it over.

Williams: And finally you realized.

Murayama: Just like the first time, it could be the wrong time, but the second time around...

Williams: This is true. So it is with science.

Murayama: A tremendous amount of time.

Williams: Trial and error. So you have this exciting conclusion. Perhaps you can tell me. I know that you did a lot of this work by yourself, but you were speaking with Pauling about this. Were there any other people that you worked with or, maybe not collaborators, but I guess colleagues?

Murayama: Yeah. Well, most of the work done at NIH, people, nobody was interested in sickle cell hemoglobin in those days.

Williams: Really?

Murayama: I did all this work after Nixon went to the, got himself in front of the microphone and said, "This is a neglected disease. Nothing has been done." Well, it so happens that by the time he said that, all that stuff in this book has been published, and, subsequently, no major important finding came out NIH or anywhere. There are a lot of other fine refinements. But the hydrophobic interaction of S hemoglobin, and that's it. What I do is muzzle the binding site, hydrophobic binding site, with a bit of urea. The patient stays out of the hospital. I never said that this is a cure. This is to extend the survival time. I found it hard to get anybody to work with me. I went from door to door and talked to many, many physicians in hematology, but you can see that my clinical co-worker is Dr. Robert Nalbandian and he's from Grand Rapids, Michigan, the backwoods of Michigan. That's where I finally found somebody who got excited about hydrophobic interaction, the sickling.

Williams: I guess I'm not surprised to hear that, but there was a lot of activity during that time on sickle cell. Who were some of the researchers? You had Pauling, Harris, Neel. I'm just trying to think of some of the major researchers.

Murayama: Neel got interested in the genetics of it and then tried to locate the origin of S gene. He was from the University of Michigan. And, well, he was very friendly and nice, but he said, you know, "Makio, the work you're doing is very interesting, but it's all 'hifalutin' chemistry, which I don't understand." There were people interested in what I was doing, but I had to go around trying to convince them. "Look, I'm doing the chemistry part. I need clinical co-workers." So Nalbandian was the one that I finally got hold of.

Williams: Even though sickle cell started out in the clinics, I mean, it was basically uncovered through clinicians that noticed.

Murayama: The hospital chemist, people came and asked me. That's how I got interested in it.

Williams: Right, yes. And so now here you are taking it on, working on this issue, you find this amazing result, and it's really hard to believe that clinicians, who were initially interested in this disease, were seeing patients, were trying to move forward with this finding.

Murayama: Something happened along the way. I really don't know. There are many parents of sickle cell anemia patients and organized a Sickle Cell Anemia Association, this and that, and, well, to show you the point. So I lost contact with Harvard.

Williams: Oh, you did?

Murayama: I used to go over there on a weekly basis and get S hemoglobin samples and the old man . . .

Williams: Smith?

Murayama: No. Roland Scott.

Williams: Right. Roland Scott.

Murayama: Roland Scott went to work the Department of Pediatrics in Michigan and in Bellevue, and my boss, who knew Dr. Roland Scott asks, “Are you going to NIH?” Roland Scott, Harvard University is too far away from where you are. My boss was interested in what’s known as the acid-based Down’s of newborn infants. Newborn, premature infants and newborns who possessed anoxia and working on the mechanism of the infants’ resistance against hypoxia. Well, Roland Scott was interested, and he said whatever you need, you know, sickle cell, blah-blah-blah, and he was really nice. But as soon as my science paper appeared, the whole department took me off. They never asked me to come and give a seminar. They know that I’ ve been going there on a weekly basis. I didn’t send an NIH messenger.

Williams: You went personally to pick up the hemoglobin.

Murayama: I personally picked up the blood and make sure that it was picked up from Scott, because being a hospital chemist; I’ve criticized other biochemists for not getting in close touch with the clinicians. So I knew, at least I didn’t want to do the same mistake that I’d been criticizing other people for. Well, I really don’t know. I didn’t do anything. See, somebody at Harvard proofread my manuscript. It was a Hungarian fellow working with Dr. Scott’s assistant. But anyway, I hadn’t been able to get samples, so Nalbandian got a sample and then took it to the Greyhound bus station, and I go to Greyhound bus station and pick it up here.

Williams: He went to a Greyhound bus station in Michigan and sent it here?

Murayama: Yes.

Williams: That’s something, because no one here would collaborate or was interested.

Murayama: Well, I knew that they’re a small group of investigators in the center, NIH, getting sickle cell blood from Harvard, but for some reason, they decided not to, decided to keep me out, I guess.

Williams: I was just in looking at all the people who have been involved with it, seeing your name as a single author on something that was what I wanted to ask about. But let me go back a little bit. Who else was in the Laboratory of Physical Biology with you at the time?

Murayama: Well, others were not interested in physical chemistry of S hemoglobin, like Dr. John Buck. This is the nephew of the very famous writer, Pearl Buck. But he was interested in the sex life of the firefly. That’s okay. But he became the section chief and a lab chief, and as a lab chief, it was his prerogative to take away my lab assistant’s slot. And Victor Cohen came in and interviewed me and came to Building 6, and, “Dr. Buck, do you want to talk to Victor Cohen?” Victor Cohen thought that, as a taxpayer, he felt the fact that some money is going to the study of sex life of firefly and not available for the study of human disease, sickle cell anemia.

Williams: Okay. That needed some explanation.

Murayama: I’m sure you understand these things do happen.

Williams: Oh, of course. Let me go back to my questions here. So you observed this finding, this temperature dependence, gelation, which is somewhat inconsistent with what you thought.

Murayama: It’s called a negative temperature coefficient of gelation.

Williams: Right.

Murayama: Think of the jello in the refrigerator.

Williams: Right of course.

Murayama: Put this thing in the refrigerator and it'll become, turn liquid.

Williams: What were some of the significant findings in the time that led you to your initial hypothesis? I mean, now you're working toward the molecular mechanism of sickled red cells, how this chemical difference between normal hemoglobin and sickle hemoglobin, you're working toward an understanding about how this chemical difference occurs.

Murayama: It was a confirmation in the physical, that there are other means, the interpretation of optical dispersion of the A and S difference that's consistent, and then that the normal glutamic acid in beta-6 is changed by the hydrophobic group. And then, just about this time, the titration of sulfhydryl titration of horse hemoglobin paper came out. Now, horse hemoglobin was being used by Max Perutz in the study of the structure of hemoglobin molecules. There was a conference held by National Academy of Sciences in Washington, and I was asked to come and present my paper on titration of horse hemoglobin at zero degrees and 38 degrees. And when I presented my slide, Max Perutz got up and said, "Makio, will you come to Cambridge?" And I said, "Thank you very much." I was happy. As soon as I find a permanent post in USA. And that was a wonderful time because I got my job that afternoon. I was approached by the scientific director of the Heart and Lung Institute, and Hans Stetten was another one that offered me a job. And in the Cancer Institute, NCI, there were three jobs I got offered.

Williams: At your presentation?

Murayama: And then what do I do? Go to Cambridge. I forgot who but somebody said, "Makio, let me have your address. I'll send you forms to fill in, and then we'll get you a special fellowship from National Cancer Institute to go to Cambridge." So I was a special fellow from NCI to my work at Cambridge University.

Williams: You became an overnight sensation.

Murayama: Well, it's just being at the right place at the right time.

Williams: So your initial results were met with a lot of skepticism? People were saying, "How can this be?" even before you actually were able to provide some sort of explanation of your findings?

Murayama: No. Nobody did anything like that.

Murayama: And Nalbandian got excited. And if he could figure that out, he'd get additional information on it, and we might be able to at least prevent sickle cell crisis; in other words, prevent blood cells from sickling, which means automatically that sickle cell crisis can be prevented. And in vitro I tried. I told him what happened. Nalbandian got a lady chemist to work in his lab and perform in vitro study of sickling in a different concentration of urea.

Williams: Right. I was going to say, Nalbandian comes to mind in my time chart in about 1970, when he started doing work with the urea therapy.

Murayama: That's right.

Williams: So that's a little bit later. But before that . . . So you were working So, were you working with Perutz when you were there? Or how did that situation work out?

Murayama: I went to Cambridge in spring of, Valentine's Day of '58, and it was no big deal. For some reason, everything took about only a week to set up the lab, and, "Whatever you need, let me know," says Max. And he would through the lab. And then we shared a centrifuge. We shared different equipment, so we'll be shoulder to shoulder many times in the course of a day. And then four o'clock, of course, the traditional afternoon tea, which he must attend. And then you talked everything over. It's a wonderful tradition.

Williams: Yes, it is.

Murayama: He told me that, but I didn't quite catch on, that many things Perutz would say like that. And he was fascinated by the crystals of horse hemoglobin that I prepared. "For some reason, Makio, your crystals look so beautiful." I put them in my x-ray diffraction meter and so beautiful. And he wanted to know what I did. I described it. It was nothing extraordinary. But apparently there's something I left out in my story. So the next day, he followed me, watched everything I did. That I didn't get.

Williams: I think preparing crystals is more of an art than a science.

Murayama: That's right.

Williams: I think so.

Murayama: But anyway, I put the second mercury crystal in order to orient the stack of x-ray diffraction from different phase. Phase orientation requires two points, mercury one and mercury two. So we had two lines to orient to get the whole three-dimension, the proper orientation. Consequently, a few weeks after I left Cavendish laboratory, Perutz got me three-dimensional stuff.

Williams: So the work in Cavendish was good?

Murayama: I helped in permitting Perutz to get the 3D structure of horse hemoglobin.

Williams: That's what I was going to ask. Basically, that's what it sounded like.

In terms of your own research, though, what came out of that time period in terms of your discoveries or what you were working on?

Murayama: Well, I needed a 3D structure, and he promised me that he'll send me the coordinates, mathematical X, Y, and Z coordinates, from which I was making plans, talking to, well, anyway, with people who were in charge of the finance in the institute. I knew this would take a lot of money. And people in the shop were all ready, and I had a drawing of components, and this is the type of atomic scale model that was available at Cal Tech. At the NIH, sure, we can make anything, especially the drawing. I was able to get the 3D structure. Once 3D was made, the question of how did they stack together.

Williams: So you determined at some point that there's hydrophobic interactions occurring when you have the residue instead of the glutamic acid, and you come up with an intracyclization theory?

Murayama: Yes. No one has proven me wrong yet, but I don't know that it really does exist. It's a hypothesis. It's like many other hypotheses still out there. At the time, it was an exciting big deal, but after so many years, it's still there, hasn't been proven wrong, yet, on the other hand, no one has been able to confirm it either.

Williams: Was it the first mechanism that was proposed?

Murayama: Yes.

Williams: That's what I thought. I didn't see anything before your paper, so I wrote in my notes that this was the first molecular mechanism for how the red cells sickle as a result of this chemical difference. And prior to your paper, I did not see anything else, so I just wanted to be sure.

Murayama: The molecular orientation in the sickle cell fiber. What I did was I knew from the work of Linus Pauling a long time ago that the oxyhemoglobin is diamagnetic, but the oxygenated hemoglobin is paramagnetic. So deoxygenated hemoglobin must be magnetic if, in its course of sickling, they all stack together the same way, it's oriented in the magnetic field.

Williams: South, along the axis, perpendicular. This is '65. I guess I don't have that paper.

Murayama: I did this arrangement in my basement lab because I had to hacksaw off part of the microscope, and I used my own microscope. You can't deface government property. I said, "Okay, okay." I hacked my microscope.

Williams: That's very novel there.

Murayama: Laboratory jack.

Williams: Right, the laboratory jack. So, were there any other researchers that you were aware of who were, again, trying to find out how this chemical difference alters the hemoglobin molecule, which then affects the red cell?

Murayama: Everybody was working on, talked about it, and that's Perutz's group imaging. That includes John Hunt, Ingram, Francis Crick.

Williams: From a mechanistic point of view were looking at it structurally, like what do we see differently, what are some of the different structural features.

Murayama: Not so sure. A lot of people I talked to, they were interested. I couldn't get interest. Maybe it was my fault. I couldn't get them excited except Nalbandian.

Williams: It is such a critical question. As I go back, I think that's such a key question. I mean, it's *the* question. And I guess people were working on different aspects of it. But the mechanism, if you understood that mechanism, it seemed to me you could really be on the path toward treatment

.

Murayama: That's right.

Williams: And you clearly stated that in your paper that was what you were trying to do, to develop an understanding. So I just wanted to find out if there were others who were trying to look at it in a similar manner, mechanistically.

Murayama: Nalbandian came along with me.

Williams: And this, of course, was before funding came. This was before 1971 that you sort of went out with a lot of your information, '66, '65, '64.

Murayama: Nineteen seventy-two was Nixon's mention.

Williams: Right. That opened up a lot of funding, a lot of attention to sickle cell. How did that change things in terms of the atmosphere among sickle cell researchers?

Murayama: I think it became a political disease.

Williams: A disease?

Murayama: Political disease. The political groups from Building 2, when John Buck organized it, he didn't ask me to join that group.

Williams: That's interesting. What aspect were they looking at?

Murayama: Hard to say, he remains very friendly, but he doesn't want to talk about the lab work because we were all friends. I'd see them in the cafeteria, just talk about personnel, personality, your friends from Cal Tech, blah-blah-blah.

Williams: Right.

Murayama: And, anyway, the funding probably helped sickle cell anemia research, permitted a lot of people to publish a lot of papers, but the result is, how much does this help the patient, is the main question. And I have the advantage of work in the hospital laboratory. I always had my main focus on the patient and the family.

Williams: Well, that was certainly one of the criticisms, which the disease started off in the clinics, moved into the basic research domain, and really stayed there for some time. People became more interested in understanding sickle cell disease and that led to a lot of research on hemoglobin, protein structure, and function, and somehow the focus toward treatment got lost. Would you agree with that?

Murayama: I agree with that. This is the universal law of the preponderance of the means over the end.

Williams: Fascination with process instead of the goal. And so, in a sense, at least with you doing molecular mechanism study or theory, hypothesis, you in many ways influenced, then, the urea therapy that came along. Would you agree with that?

Murayama: Yes, I hope so. I left out mentioning the hydroxy urea from the beginning. Hydroxy urea, methyl urea, all toxic. And hydroxy urea has been known for over a hundred years as carcinogenic.

Williams: Hydroxy urea is a slightly different mechanism. It increases the synthesis of fetal hemoglobin. Urea, though, was based on sort of decreasing the aggregation, if you will, of the molecule, polymerization of the molecule. And there were a number of things that could have been tried, but the toxicity was really a problem with the urea. Is that a correct statement?

Murayama: No toxicity with the urea.

Williams: No toxicity?

Murayama: Look up in the *Textbook of Toxicology.* Urea is one of the least toxic substances known. Even water, you can get too much—there is a name for it. Anyway, you get waterlogging and you have to administer diuretics to get rid of the excess water. Urea is nontoxic.

Williams: Right. So now we move into urea therapy. How did you and Nalbandian Nalbandian begin this work together? Did he know you from earlier days in Michigan?

Murayama: Yes.I worked as a hospital chemist at Harbor Hospital in Detroit, and then my former ex-boss told Nalbandian, “You know, there’s somebody you ought to look up. You ought to call up Makio.” Now, Dr. Nalbandian had had a question in his mind and wanted to talk to my former boss, who was a physicist, and he had a very interesting question. And the problem with Nalbandian was he always talked to the professor of physical chemistry, a mathematician, and so on, got so far away from the clinic, from the patient, that the *Ivory Tower* professor went over the head of the problem and then came down low enough to the clinical level. We sat down and talked it over, and Nalbandian went back. I forgot the exact problem. It was very important then…anyway, worked on it and the solution was so simple, Nalbandian thought that I’m the guy that can solve it. Anyway, he kept on calling me every day for years.

Williams: That’s how the collaboration started.

Murayama: And you have to remember, I must have looked and looked and looked in Bethesda, all the clinicians we have in Bethesda, and I have to go out and talk to somebody in Grand Rapids, backwoods of Michigan.

Williams: That’s very interesting. But it certainly was a question I had because, like I said, in looking at the papers that you published and the work that you did, one of my main questions was, who were your collaborators? Who did you work with? I know later on, with the urea therapy, I did see Nalbandian. But prior to that, I didn’t see very many. And I didn’t have your CV in front of me, so I couldn’t verify it, but I didn’t notice it from the literature.

Murayama: I’ll get you a copy of my CV.

Williams: That will be helpful. My goal was to get to 1970, so we're pretty much at 1970 in your review of the history, so I think we can continue this later if that's okay.

Murayama: Yes.