Historical Tour of Building 3

March 5, 2001

BUHM SOON PARK: Today is March 5, 2001. I am Buhm Soon Park, Junior Fellow of NIH History Office. I am in Building 3, one of the oldest buildings at NIH. This building was established in 1938 and since then this building has become a home for many distinguished scientists, mainly from the NHLBI, the National Heart, Lung, and Blood Institute.

Today and tomorrow, I am going to meet scientists in this building to record their past memories and capture their current research activities, especially because the laboratories in this building will move to a new space in Building 50, a newly constructed science building, in April 2001.

I'm going to start with Dr. Stadtman -- Dr. Earl Stadtman -- and then I will meet Dr. Boon Chock, the Chief of the Laboratory of Biochemistry, and I will meet Dr. Ann Ginsberg. This afternoon, I will meet Dr. Teresa Stadtman and Dr. Rodney Levine and I will finish with Dr. Sue Goo Rhee, the Chief of the Laboratory of Science.

Tomorrow, I will meet the people in the Laboratory of Cellular Biology starting with Dr. Edward Korn and then I will meet Dr. Evan Eisenberg, Dr. Richard Hendler, and Dr. John Hammer, and other principal investigators. Thank you.

Thank you very much, Dr. Stadtman, for having an interview with me. Could you say a little bit about your educational background and the reason of why you came to NIH and when you came here and the people you interacted with at that time?

EARL STADTMAN: I did my undergraduate work at the University of California in Berkeley and I took a degree in Soil Science. The reason, as I told you before, is because I had done a lot of gardening work—this was during the Depression years—and very often people would ask me, what can I add to my soil to make things grow better? So, I thought that if I learned how to analyze soils, I could set up a soil testing laboratory and make some money. What I found out was that you cannot do that; that you cannot, on the basis of a chemical analysis alone, determine what kind of fertilizer would have to be added.

But during that time, I worked as a technician to the mad Dr. [Horace Albert]Barker, who subsequently became my mentor. It was during that period that I learned a little bit of how to make and do science. Then during the war, I went on the Alcan Highway as a Soils major.

When I returned, I visited my old professor, Barker, and he offered me a job working on a new project that he had agreed to work on, which as the browning of dried apricots. I spent five years in the Food Technology Department studying the browning of dried apricots. After that, I decided to get a Ph.D. degree. I went to graduate school again at the University of California and I got a degree in Comparative Biochemistry and my mentor for this study was again H.A. Barker.

After that, I took a post-doctoral fellowship at the Massachusetts General Hospital, in Boston. Spent one year there working in the laboratory of Dr. Fritz Lippman. After that, I came to NIH. During the year

that I was in the laboratory of Fritz Lippman, my wife was also a student of Barker's and she, as a post-doctoral fellow, obtained a job working with [Christopher] Chris Anfinsen, who was then at Harvard.

When Chris was offered a position here at NIH in the newly started National Heart Institute, he wanted to bring my wife, Terry, here with him. In order to get her, he also had to offer me a job. So, we both came here in 1950 and have been here ever since.

PARK: 51 years.

EARL STADTMAN: When we arrived, we were rather disappointed to find that the laboratories that we were eventually going to occupy had not yet been built. The laboratories in the basement of this building at that time was just a big gaping hole; there were no laboratories there when we arrived.

Fortunately, in the building at that time, on the first floor of this building, Arthur Kornberg had a group, including Leon Heppel and [Bernard] Bernie Horacker, and he had a laboratory that wasn't being used much so he offered it to Terry and me and to Chris Anfinsen to work in that laboratory while our laboratories in the basement were being constructed.

Now during that period, Kornberg had a Luncheon Journal Club Series and he invited Terry and me to join in their Journal Club Series. At that time, [Herbert] Herb Tabor who, as you probably know, has been at NIH longer than any of us, was invited to join in those Journal Clubs. So, I had an opportunity to meet Herb Tabor as well.

In this first year, it was rather hectic because we had to sort of take turns working in the small laboratory that was provided by Arthur Kornberg. But in the laboratory at that time were what turned out to be a very large group of distinguished scientists. James Shannon, for which the building is named over here, Building 1, was then the Director of the Heart Institute and he had on board --

PARK: You mean Scientific Director of the Heart Institute?

EARL STADTMAN: He was Scientific Director of the Heart Institute, as it was called in those days. He had a number of senior people working with him, including Robert Berliner, [Seymour Steven] Steve Brody, Sidney Udenfriend, Jack Orloff, Robert Bowman, and then of course Chris Anfinsen and Terry and me were all a part of the Heart Institute.

On this floor at that time, two other people had offices, but they were not doing any research. One was Luther Terry, who subsequently became the Surgeon General, and the other was Nathan Shock, who became head of the Laboratory on Aging over in Baltimore.

In fact, in the following year, [Bernard] Bernie Witkop and Evan Horning and Wayne Kiley all joined the Heart Institute. It turns out that out of the 19 people who were in the laboratory at that time—in this building at that time—15 of them became members of the National Academy of Sciences.

That's extraordinary when you think that on the average only about one out of 25 or maybe 50 people become elected to the National Academy. During that time, or subsequent to that time, members of the Building 3 group, including Arthur Kornberg and his group, three received Nobel Prizes. One was Chris Anfinsen, one was Arthur Kornberg, and the other was [Julius] Julie Axelrod.

They were all here at that time. In the subsequent three or four years before we moved to Building 10, temporarily—our group at least—the laboratory was joined by an even larger group of distinguished scientists. Many of them came here on sabbatical to work in Arthur Kornberg's laboratory or with one of the other senior people in the laboratory.

I guess I didn't mention that Jack Orloff was also here at that time. In any case, something like 42 rather distinguished scientists joined the laboratory during those four years and of those 42, 28 became members of the National Academy of Sciences.

So, Building 3 has had really an extraordinary tradition.

PARK: Do you recall the name of the laboratory?

EARL STADTMAN: Some of those people that I referred to work with Arthur Kornberg, who was in this building at that time. Some work with other senior people, for example, Martha Vaughan and [Daniel] Dan Steinberg joined the group at that time—during that period. Again, they became members of the National Academy of Sciences. But I have a list here—you can look it over later—of all of the people who had come and spent some time in the laboratory in those early years.

As you know, over time the Heart Institute became the Heart and Lung Institute and [then] the Heart, Lung and Blood Institute, as it now stands. But it had its origin in Building 3. I don't recall whether it was '54 or '55 that we moved into Building 10. It was just after Building 10 was completed.

After one year there, I requested to come back to Building 3 because I didn't have as much room in Building 10 as I wanted and besides, some of the organisms that I was growing produced some nasty smells, which the people in the Clinical Center objected to.

So, in any case, we returned to Building 3. I later became head of the Laboratory of Biochemistry, a position which I held up until about four or five years ago and then I retired from that slot and Boon Chock took over. I think you're going to talk to Boon Chock and his people later.

PARK: When was the Laboratory of Biochemistry was created?

EARL STADTMAN: I don't remember the exact date, but it was sometime, I think, in the late 1950s.

PARK: And then you became the Chief of --

EARL STADTMAN: I became Chief of the Laboratory of Biochemistry; it was created at that time. When they made me a chief of the laboratory, I selected the term biochemistry so that was how the biochemistry got started.

PARK: Could you describe your scientific work since 1950?

EARL STADTMAN: Well, it's been extremely various. You may know, I started out working in the area of fatty acid metabolism, which of course was a very interesting field from the standpoint of the Heart Institute. Following up on work which I had initiated as a graduate student and then continued to work on in Fritz Lippman's laboratory in Boston led to the demonstration that organism that I had used to study fatty acid synthesis in Berkeley.

In fact, he synthesized acetylcholine. So, my earlier studies in this laboratory in this building dealt with the role of co-enzyme A and a number of basic reactions, such as the conversion of one CoA derivative to another CoA derivative by CoA transfer reactions.

Then I became interested in three-carbon metabolism and for many years worked in that area, propionic acid metabolism, primarily, which led me into an interest in Vitamin B_{12} co-enzyme and its functions.

Thereafter, I took advantage of the so-called soil enrichment technique, where you isolate organisms from the soil that are specialists during particular reactions. We isolated organisms that could grow on one-carbon compounds, organisms that could decompose heterocyclic compounds, such as riboflavin and nicotinic acid.

I had taken a sabbatical and went to Germany for six months and worked with Theodore Lennen (ph.), who later got the Nobel Prize, as you probably know. There, I continued work on the propionic acid fermentation leading to the B_{12} co-enzyme function.

After six months, I went to the Pasteur Institute in Paris, where I worked with George Colon. The research there dealt with the regulation of branch metabolic pathways. We made the observation that there was a mechanism of so-called feedback control and in the case of multiple end products of a single precursor compound.

We looked at the aspartate metabolism specifically because it is a precursor for the biosynthesis of lysine and methionine and also of leucine. In the course of those studies, we demonstrated that there's a feedback control of each of the three different pathways by different end products of the pathway.

When I returned to NIH, I accepted a young post-doc and he came and he—by the name of [Clifford A.] Woolfolk—and he asked if he could continue working on the aspartic acid branch pathway study, which he had read about from our publications.

I told him that no, he couldn't do that because that was George Colon's problem but if he wanted to work on branch metabolism, he should find another enzyme that is unique. After a week or so, he came back to me and among several suggestions was the glutamine synthetase.

So, I had him work on glutamine synthetase as an enzyme which had—it turns out there were seven different end products of glutamine metabolism and he found, in fact, that there were seven different mechanisms for inhibiting the activity of that enzyme.

This led to a very complicated mechanism of control—one of the first cyclic controls, in fact, I think now still the only one, in which you regulate the activity of an enzyme by converting the enzyme to an adenylated form, reaction with ANP adduct to the protein.

Subsequent to that, we spent maybe 20 or 30 years working on glutamine synthetase because of its unique and extraordinary properties. Finally, coming now to date, an interest in cellular regulation. I realize that one of the unanswered questions in this field was what regulates the turnover of proteins. Different enzymes turned over at different rates in the cell and that the nutritional conditions also determine which proteins are going to be turned over and which are going to be up-regulated and so on.

So, we then turned our attention to that study and made the interesting observation that a regulation involved the oxidative inactivation of those enzymes that were going to be down-regulated and that this, in turn, made those enzymes highly susceptible to degradation by proteolytic systems in the cell.

That led to the discovery on my reading that it had been demonstrated by other people that many proteins accumulate as catalytically less active or inactive forms during aging. I proposed that this aging process involved oxidative damage to the proteins. That study now has blossomed and continues to be one of the major interests in this laboratory.

PARK: Could you comment on the size of your laboratory?

EARL STADTMAN: The laboratory as a whole has numbered around, over the many years, has numbered about 30 people—30 to 40 people, depending upon visiting scientists and that sort of thing. But those are distributed among five different sections. So, on the average, each section has four or five positions; mostly post-doctoral positions and technician positions. But that's been the average number of people in the Laboratory of Biochemistry for many years.

PARK: Could you talk about the relationship between the sections? Are they pretty much independent or do they collaborate?

EARL STADTMAN: They are independent. I usually sit down with them when they first arrive and discuss a number of projects that we're interested in and they select one of the several topics that I discuss and then pursue that pretty much on their own, only seeking advice now and then from me.

I have encouraged people in the laboratory to interact with one another. As a matter of fact, when I was the post-doctoral fellow in Fritz Lippman's laboratory in Boston, he took Terry and me out to dinner one night just before we left and he told me something which I remember very clearly. And that was

that he thought the most important thing in running a laboratory was creating an atmosphere. A familial type of atmosphere where everybody interacts with everyone.

So, when I became head of the section and then head of biochemistry, I have tried to generate that kind of an atmosphere because I think it's very critical to give people a sense of independence but you watch carefully what they're doing. When they come up with an experimental result, well then we sit down and discuss it at some length and I can make suggestions for further investigations and that there may be somebody in the laboratory who's better-equipped to do this or that and they should contact them.

As a consequence, we have had very close interactions, not only within the laboratory but also outside of the laboratory; many social events, parties and what not, which I find are very important in securing the kind of interaction that you want to maintain within a laboratory.

PARK: In connection with social interactions within the lab, could you comment on your famous Journal Clubs or the daily news meetings or whatever it is that—

EARL STADTMAN: This was all, of course, started with our experience with Arthur Kornberg and his group. I felt it was such a useful and important thing in helping people to keep abreast of the current literature. If we had—we started out having one day a week—every day a week we would meet for a Journal Club.

Each person in the laboratory, in turn, was responsible for reading something in the current journals and give us a brief summary of what they found out. In that way, because each person's interest was a little different from another person, you get a broad range of exposure to other recent developments that otherwise you wouldn't become aware of.

In the meantime, we have changed a little bit the program. We meet now three times a week—the Journal Club—and then we have one session each week in which a member of the laboratory describes what he is doing and gives a report of—each person in turn, he has a full hour to discuss what he has been doing. That way all of the members of the laboratory learn what another person in the laboratory is doing. This, again, is very important because they learn that this person has a technique that they could take advantage of, so they interact in that way.

Then each Friday we invite an external person to come to the laboratory and give a seminar on some topic.

PARK: So, for those Journal Club Meetings and the Seminar Meeting, everyone in this building, not only—

EARL STADTMAN: No, no, everybody in this laboratory.

PARK: In this laboratory.

EARL STADTMAN: In the Laboratory of Biochemistry. What has evolved, as you probably know, is that Sue Goo Rhee came as a post-doctoral fellow and then after a number of years here, I requested that he be made a lab chief and he was made a laboratory chief and occupies a space on the first floor and his group continued to participate in our meetings. But Ed Korn, in the meantime, has become a member of this building and his group is very distinct from ours and they have their own meetings, various kinds, but they do not participate in our Journal Clubs.

PARK: Before moving to your laboratories, could you say a couple of words that you want to give for young fellows, young students or fellows, coming to NIH to build their own career?

EARL STADTMAN: I think that the NIH is a wonderful place for young people to come to because unlike most academic environments, when they come here they can devote full time to their research and if they're, I should say lucky, they might get a mentor who is good and if that's the case then they have a pretty good assurance of achievement.

I personally am very proud of the people who have come through and have worked directly with me in the laboratory. I think that once I mentioned to you that a number of them have become members of the National Academy and many of them are heads of departments in various universities and research organizations throughout the United States and also in Europe. So, I think it's been a good training field for many people and I think that's pretty much true NIH-over that mentorship is very good. On the whole, opportunities are very great for young people.

PARK: You also have two Nobel Laureates among those who stayed with you.

EARL STADTMAN: Yes, there were two that got the Nobel Prize. One was Michael Brown, the other was [Stanley] Stan Prusiner, who curiously were here at the same time working in the laboratory but on entirely different problems.

PARK: Thank you very much.

PARK: Good morning, Ms. Merry Peters. Could you talk about your job here in Dr. Stadtman's lab and when you came here?

MARY PETERS: I came here in November of 1984, which is quite a few years ago now. I started out in Dr. Terry Stadtman's office. I was her secretary for nine years and Delores Andrews was Dr. Earl Stadtman's secretary and she retired six years ago, and I moved upstairs to work for Earl Stadtman.

PARK: Could you say a little bit about your job in terms of coordinating between the lab chief and the other parts of the lab; the post-doctoral fellows and the—

MARY PETERS: Dr. Stadtman, both of them, they run it on a—I call it an informal basis. Everybody goes by first name and everybody feels free to ask anybody what they need and what they need to talk about. So, people come and go and they come in and talk to Dr. Stadtman without formal appointments or anything.

If he's in, he lets them come in and talk for a while. And they all do; all of his post-docs come in and talk to him frequently and he'll go and talk to them in their labs. My impression is that everybody—it's like a family atmosphere; very friendly here. We all get along well and we all feel comfortable. People seem to be happy, all of them. Over the years, I've seen a lot come and go and they all seem to be happy and they do great work and it's very productive, they're dedicated, and they all have only praise. I've only heard good things about working for both of the Dr. Stadtman's. How they feel like it's a privilege and they enjoy it and they take away a lot with them when they go.

PARK: How about yourself? Do you enjoy working here?

MARY PETERS: I enjoy working here. Like I said, I've been here 16 years, either downstairs or up here, and I have no plans to go anywhere else. I enjoy it. I enjoy the people. I enjoy the work. I feel like it's important and what they're doing has meaning and so it makes it a lot better than just pushing papers. I see that the papers I do have a reason and a significance and a purpose, so I enjoy working here.

PARK: Thank you very much.

MARY PETERS: You're welcome.

EARL STADTMAN: This is Barbara Berlett and she has set up all of the instruments and she is in charge of operating the laboratory and carrying out most of the experimental work that I am directly involved in. She will now give you a briefing of what some of these instruments are all about.

BARBARA BERLETT: I'll start with this one right here. This is a spectrophotometer. It's one of the top-of-the-line, made by Varian. I can show you a picture. We use it to identify different products that we've create when we oxidize proteins or amino acids. By the spectrum you get, you can identify what you have. That's what this is used for. You can do kinetic reactions, where it will show you a rate of a change of a product, either a loss or an increase. So, it's very important in our lab.

I've been here since 1980. I've been in this room with Earl directly since 1984 and those are my notebooks. They go all the way up to 100 now. Some of the other equipment that we use, this is our newest piece. This is an EPR [electron paramagnetic resonance spectroscope].

I have three HPLCs here. HPLC is high-pressure liquid chromatography, which is a technique used to separate compounds using different columns and different properties of the compound. I have three of them. They have different kinds of detectors on them. This one here, like I mentioned, had the electrochemical detection, which measured potential of compounds.

I also have, over here, this first one here has a fluorescence detector, which you can derivatize your sample with compounds which will make them fluorescent. This is an example of some of the peaks that you'll get from the different fluorescent compounds.

And on the last one, which is over here, it just has a UV [ultra-violet]-detector. It has what they call a diode-ray detector, which measures light emitting at certain wavelengths. We use these routinely in most of our oxidase studies when we're trying to pick up compounds that are produced via oxidation.

We also have here a Speed Vac, these are routine things, and a centrifuge for drying compounds, processing them in order to look at them either with the spectrophotometer or the various detectors and HPLC.

MICHAEL POSTON: My name is Michael Poston. This is the anaerobic room in Building 3. This room is essentially just a carbon steel line box but it's a standard laboratory. There's nothing unusual about the room itself except that the atmosphere contains no oxygen. At the moment, the room is open and we're able to go in and out the doors. But we're in the process of preparing to close it up. We have two fellows visiting from Japan who will be utilizing the laboratory.

This happens to be the first time that it's been utilized in a couple of years, so we've had to do some playing around to make sure that everything works. Everything seems to be fine. The emergency system works. We're ready to go.

This room has been used over a period from—it was built in 1965 and put into formal operation in 1966. It's been used primarily to purify and characterize enzymes that are subject to oxygen damage of one sort or another. We've been very fortunate because this is the only large facility like this in the world. There are some that will do some of the things but we can utilize major equipment, such as centrifuges, large columns, other gadgetry that fits into this space.

As I say, it's just a standard laboratory and we're in the process now of setting it up for a particular set of experiments. It's been used probably by about 50 or 60 different individuals over a period of the years that it's been in operation. Some of them have many hours in this room. Because it's a hazardous environment, whenever anybody is in here, he has to wear a mask that provides breathing air and a

vacuum line to take away exhaled air, and monitors of one sort or another. And there's always somebody outside; a monitor watching those inside. We have been fortunate. There have never been any problems but there's always that fear because this is a hazardous environment so we've been very careful about that and we hope that as the building ages and finally is put to rest that we will continue being equally safe and successful in that.

One of the things I'd like to demonstrate for you is part of the emergency system. If something happens to the individual inside, the person monitoring them on the outside has an emergency button and that causes all kinds of things to happen: Bells to go off, fans to start, doors to fly open, one thing and another. In order to make sure everything is fine for the individuals who are in here, we test each of these components before we close them in.

So, I'm going to show you the testing of one of the doors. It's dramatic but it's mostly noise and a door flying to and fro. I'll show you that over here. This is an emergency door normally closed during operation. It has a pneumatic control. When I press this button, the door will fly shut, if everything goes right. This is the way it is when it's normally operated. But if an emergency should occur, the door should fly open when you press the button outside and this is what happens.

By the time the fans have turned on and the person can walk into the room, enough air has flowed through the door here and the one in the back so that the atmosphere is completely normal within 20 seconds. It will support life just as soon as the person can walk through these doors into it. So, it's a fairly well-controlled atmosphere. Normally, of course, we want that door closed tight and we don't want any oxygen coming through it.

This is the personnel door in which people come from the outside into normal atmosphere here. This door is normally closed every time it's used. Then the individual who is coming to work in the room will don a mask like this. Since there is no air running through there at the moment, it gets to be a little close. But what happens is the individual wears this, receives breathing air during his or her time in the room. It contains a compressed air line and a vacuum line plus communication and a signal so we constantly monitor the oxygen that's apparent in the mask, so we know what the person is breathing. Occasionally, depending on the shape of the face, certain people have a tendency, particularly at the temples, to aspire nitrogen from the atmosphere here. And will dilute out the oxygen in the mask. And we learned that the hard way when the first time we used this we had a long, skinny-faced fellow who put it on and he was getting a little woozy.

So, we decided we'd better monitor that and we have an oxygen monitor in here now. This is what normally would be observed by a person outside. If you look through that window, I'll show you how a person inside looks like.

Of course, by the time I would have come this far I will already be wearing the mask but there's a limit to what I'll do for science. So here we are. Now I can do something, I can do something like function as a regular laboratory individual.

We are now on the outside of the anaerobic laboratory. This is where the monitor normally functions, and these are the controls that he would be observing. There is an oxygen analyzer. There's a temperature recorder, hydrogen analyzer, monitor of the mask -- the oxygen levels in the breathing

mask. This one right here is the one that would be operating. And various other controls which turn on and off.

PARK: Thank you very much, Dr. Poston. Could you tell us when you came to NIH and in what position?

MICHAEL POSTON: I was hired originally as the laboratory technician for Earl Stadtman. I came here—I had a master's degree. I came and started work July 3rd in 1961. After I'd been here for a while and realized that I did know something, that my education had amounted to something, I began taking courses in one thing and another. And then --

PARK: Where?

MICHAEL POSTON: At the University of Maryland, for the most part. Some of it with the NIH Graduate School. But toward the end of the '60s, I resigned and went back to the University of North Dakota, where I had got my master's degree, and was able to take my research and most of my credits from Maryland with me and completed my year's residency there. And finished my Ph.D. there. Much of the research in my thesis had begun here. Then I was without a job and terrified and I recall writing over 400 letters and the panic. Finally, I called up Dr. Stadtman and I said, do you have any suggestions?

And he said, he'd think about it. Then he called me back in about two or three days and he offered me a position, which amounted to essentially laboratory manager. I was to be an independent researcher, but I was also to have responsibility for running the joint. That meant all the little nitty gritty details. He was able to be above that and do his thing and it worked very well. I continued in that job until he stepped down as Laboratory Chief and continued with it under Dr. Chock.

So, most of my experience has been sort of in mid-level management, if you will, of the laboratory. Some original research and an awful lot of tracking down why something else didn't work.

PARK: So, you were also responsible for running the instruments here?

MICHAEL POSTON: In part, the instruments. Certainly, coordinating their repairs and their lifecycles, making recommendations on what we buy and what we don't. As time went on, of course, instrumentation became a whole different matter. When we started off, we had relatively simple stuff.

PARK: Such as?

MICHAEL POSTON: We had fraction collectors and columns and spectrophotometers and things of that sort. But they became more elaborate and more sophisticated. After a while I would say, oh, yes, that's very nice and bow to the person who actually was running it. I had no way of dealing with it. But I still had to do with the coordinating all the things that went on to a degree.

PARK: Also, you were responsible for bringing animals for experiments or culturing of cells?

MICHAEL POSTON: We did a lot of culturing of cells, yes. Culturing of cells is one of those things, in this laboratory, where it is the primary source of our enzyme material. Some people look at bacteria as really exotic little beasts and they want to study them that way. Our tendency was to look at them more as bags of enzyme and we got them as source material. But yes, we also used animals for various things, mostly however individual researchers went out of their way to get their own animals. I was not responsible for that. Nor would I want to be because that has become a very complex business of animal care and making sure that they have all the things. All the various advocacy groups have to be satisfied. I want no part of it.

PARK: From your experience as a kind of mid-level manager of the lab—

MICHAEL POSTON: Low mid-level.

PARK: What are the peculiar aspects of NIH as a working place or the life as an NIH scientist?

MICHAEL POSTON: You have two kinds of scientists here. You have the core cadre of individuals who are permanent staff with whom the others interact. And then you have the training fellows who come in for varying levels, from a few weeks to a few years.

As far as the training fellows are concerned, I think—not having been one—I think that they're coddled, carried very well because there were people like me who were there to provide the support supplies, make sure that they had what they needed. That's not true for the staff, not that I didn't work with them too. But each of them has responsibilities for things and for their fellows. Any staff member who comes in here with fellows and doesn't take care of the fellows isn't going to have fellows very long because that word gets out.

It's a real phenomenon. It's a good place to work in that there was plenty of support. The support has decreased with time. Shops and other extraneous things of that sort have decreased and been a real problem.

Everything was better in the '60s. Isn't that what they always say? No, I can't say specifically because the attrition on these things was gradual. Some things were an enormous improvement. Ordering went from a hassle of the first magnitude to something that was relatively simple.

There were rules and regulations which caused us agony but that's a matter of bureaucracy. The program was simple. I think that the person who had the biggest effect on the laboratory of the people who actually were involved with ordering and that kind of stuff was Ed Becker—Ted Becker—when he came in as big cheese in Building 1. He made tremendous strides in assisting the laboratory personnel. He really understood what the laboratory—

MICHAEL POSTON: What position was he?

PARK: He was Deputy Director for Supplies or something like that. I can never keep track of the names. But he was our savior as far as that was concerned. There were the other kinds of problems to creep up. We'd like to have instruments made and it used to be a snap to get things mended or made and then it became more of a hassle. Sometimes they contracted them out, sometimes they didn't. Sometimes we tried it ourselves and were unsuccessful. It all varied.

PARK: You have been in NIH for about 40 years.

MICHAEL POSTON: Close to 40 years, yes.

PARK: Do you recall any exciting moments?

MICHAEL POSTON: The most exciting moment I had personally was the fire that was in this laboratory. I had a gas chromatographic system operated with a hydrogen flame and the hydrogen tank had run dry and we were without gas. So, I brought in a new tank and it still had the cap on. I went to take the cap off and as I was doing so, the pressure valve or something in there let loose and there was hydrogen spurting out. I was terrified. That's explosive stuff and I didn't want to be around. So, I immediately ran down the hall, hit the fire alarm. The building was evacuated. The fire department came very promptly and we're all standing out there in the middle of a snowstorm. Big flakes of snow on our shoulders, wearing epaulets and that sort of thing. The Fire Marshall comes up and says, show us what the problem is.

I didn't want to come back into this building at all, but I did and when I came up, the door was closed and there was an enormous jet of fire coming out of either side of that thing. It had, probably from static electricity, it had caught fire. This is the best thing that could happen because it was consuming the hydrogen rather than exploding. It singed the ceiling and melted some of the electrical, the plastic

panels, and singed the back of some of my books. But other than that, and the soot and the water all over the floor, it was a minor event, but it scared the pants right off me.

PARK: When did it happen?

MICHAEL POSTON: It was in about—I'm guessing—about '78, '79, something of that sort. I was old enough to know better and young enough to do it anyway.

PARK: Could you comment on the renovation of this building?

MICHAEL POSTON: Renovation doesn't exist. In my time, I came here in '61 and our labs were laboratories in the basement level and Terry Stadtman had the labs that are now part of our conference room in the library and there wasn't much else than a few here and there. But they were labs, they were just standard laboratories. The main Heart offices, the Institute offices, were on the first floor. Very elegant offices. Lovely, nicely painted, everything was nice. But there were three laboratories on that floor.

Two were controlled-temperature laboratories, where we grew bacteria, and one was a cold room. Occasionally, I would have to harvest bacteria in one of those warm rooms and the interesting thing to us, as soon as I started that I could hear doors slam up and down the hall. The stuff was pretty stinky, and they didn't like it. They were delighted when they were able to move over to Building 31. Once they were gone, then we began to renovate those offices as laboratory space. All that meant was putting in benches and shelves.

There was no physical change to the building. So, we really haven't renovated the structure. The structure is old and decrepit. We had a few risers had to be replaced over the years, the plumbing, and there's been innumerable additions to wiring, cabling and this sort of thing, such that you couldn't bring anything new into the building.

We'd maxed out electrical usage. We'd maxed out everything. There was no room for pipes, much less anything else. The only thing that's holding the building up now, I think, is the paint. But that's an old joke which doesn't really count. We've done some painting and we've done some renovation of the lights and put some tile down on the floors, which improved matters. The corridors were dark as the inside as a mine pit but they're quite bright and pleasant now. And that helped but it certainly didn't really improve the laboratory much.

PARK: I was just going to ask if you could tell us a little on tape about some of the—you were talking about the roosters and the cats.

MICHAEL POSTON: You want to know about life in Building 3, as I knew it. When I came, this building had some of the Arthritis Institute and some of the Heart Institute. There were various people around. Dr. John Karastaze (ph.) had the pilot plant area in the sub-basement.

And some of Evan Horning's labs were on the basement level. On this level, Jay O'Davis, who was a renal physiologist, had a lot of the labs here. Harriet Maling had three of four labs at the far end of the hall. Roy Vagelos had the rooms next door. He was part of Stadtman's group.

Upstairs, that nebulous region above here—we never went up there—but that was the surgery branch and the animal people were in the upper floors. One of the things that, as time went on, there were changes in personnel. Davies left, Stadtman inherited his space.

What is now the library and conference room was a smaller room then and the room next to it was part of the animal care facility. We had cats and chickens and other small beasties in there. The hens loved to lay eggs and they would generally do it sometime between 12 and 1, right in the middle of our seminars. So, somebody may very well have laid an egg as a seminarian but he had a competitor next door as the hen laid the egg and cackled. Later, the surgery people were bringing in larger animals, not just dogs; they didn't use dogs much after about the mid-'60s.

But they brought in all kinds of things. They had mini-pigs. One time we came out of the seminar and discovered that they had done a cesarean section on a pregnant sow and she was displayed for God and everyone to see there in that lab.

Many is the time I've gotten onto the elevator only to discover I was sharing it with a calf and who knew what else. So, there were lots of interesting things. When I first came, the laboratory was part of the enzyme section of the Laboratory of Cellular Physiology.

Chris Anfinsen was the head of that. Chris Anfinsen never worked in this building, that I was aware of—I certainly was never aware of it—but he was over here all the time. We had a dishwasher. We thought he was the neatest looking man you had ever seen. And he had come in and stopped at the elevator to go up to see whoever was on the upper floors and Kay wouldn't look at him and she thought he was the absolute cat's pajamas.

We had others. We had a dishwasher who had a little problem with alcohol. And she didn't always come up to snuff. We had some problems with her occasionally. And a mailman who used to take naps on the mailbags down in the back entry. And we had a man who kind of served the building as the receiver of dry ice and kept track of things. He had a desk out in the back platform, right next to the autoclaves. Hotter than the engines of hell down there. He wrote poetry, the world's worst poetry; dreadful stuff.

Finally, I'd like to ask you -- do you have any more questions?

PARK: I have one question. I just wanted to go back to something you had said earlier. You were talking about NIH Graduate Programs. Could you talk a little about that?

MICHAEL POSTON: The graduate program is part of a formal educational program that was set up by the Foundation for Advancement of Education in the Sciences or some such thing of that sort. It was the originally, I understand, although I don't know this for sure, I understand that it was originally started as a branch of the USDA Graduate School and then became independent by the FAES. Many of the people who are really top-notch scientists, people like Louis Cohen, who taught one of the most exciting organic chemistry courses I ever took, taught these courses. There were a lot of other droners, but he made organic chemistry come to life. There were marvelous educational advantages to this. The problem was, for educational purposes, these credits did not transfer to other institutions and that sometimes created some hassles.

PARK: Finally, I'd like to ask you to comment on Dr. Earl Stadtman's managerial style.

MICHAEL POSTON: I will tell you this, whatever else you may say about him, he's fair. I've never found him to be unfair. He's been sorely tried on a few occasions with people who have presented him with problems. But he's been very fair and very helpful as he saw himself able to be so.

He's the kind of person who lays out projects. He may lay out a dozen and you, as the incoming fellow, will look at this and say, that one looks kind of interesting. And if you were lucky, and usually you were because there was some thought given to these projects, you progressed from that and went on to an interesting career. One or two years here and then who knew, the sky was the limit. But sometimes they didn't work out and so you could go to Earl and say, I've got a problem. This isn't going anywhere. He'd come up with another one. Sometimes fellows had to go through two or three of these.

But once it clicked, it was wonderful. When Earl was bored with a project, you never saw him. But let him be interested, he'd come in two or three times a day and say, what's new or what's going on. He'd just throw the fear of God into you if you were just….

He was an involved person. Not hands-on in that he was actually working in the laboratory himself very much, although he loved to do it. But he'd get trapped at his desk writing. But he certainly was hands-on, or he had his hands on the reins. He knew where things were going, and he directed. Sometimes the direction was very subtle, but he directed. And I think, on the whole, the 200 men and women who came through here have been well-trained. They came well-trained. He didn't take dolts.

They came, they were well-trained, and they left better trained. If Earl gave them nothing else, he showed them how to design an experiment. He's perhaps the most thorough designer of an experiment. There may be 30 tubes in a thing. Twenty-eight of them may be controls but they're two critical ones. The other thing he always said was, never repeat an experiment. He didn't mean don't replicate your work, but he meant, don't repeat it precisely. Do something but add a tube or two. Do something else so that you will advance it a little bit more. Don't leave the experiment just lying there and doing it a second and third and fourth time all by itself. Add something new so you'll make progress. And it worked.

A very clever man and very quiet. Very hard to hear him when he was—if he wasn't really engaged in what he was saying, he was a very soft-spoken man. And in seminar, we had some other people who were soft-spoken.

[Martin] Marty Flavin, who you may have heard about, he worked in this lab for a while and then with Ed Korn. They were in seminars together. Neither one would raise their voice if they could avoid it. And Marty would be giving a seminar and Earl might be making a comment and after while it was like a tennis match. You'd look at one and then you'd look at the other and you'd look back. You weren't hearing what they were saying, you were reading their lips.

One other incident that may give you an idea of how science has changed in the 40 years I've been here. In about 1963, the concept of messenger RNA first came out and we had enormous discussions about this. One day Don Martin, who was an MD fellow of Roy Vagelos, was scheduled for Journal Club and he had selected three very short notes out of *Nature*, and they all dealt with messenger RNA. The discussion went on and it was very controversial, and it was a lot of argument. Well, they didn't do this, but they could've done that. Back and forth, trying to tear it apart. The hour, hour and a half, went by, Earl says, we'll continue this tomorrow.

Don had expected to be done with his rotation in one day. He came back the next day and we went through it again and it continued, and it was abrasive. We were—I wasn't—Earl and some of his senior fellows were really tearing this apart and working very hard at it. At 2 o'clock or so he says, we'll continue this tomorrow. So, Don did it again. We continued the next day and Thursday it went on, it seemed, for hours. Finally, Earl said, well, I guess he's right.

At that point, we had torn it apart, put up all the objections we possibly could and then looked in the data that they published to prove one way or another had they met these things. They had. So we accepted from that point messenger RNA as a functional entity and went on with it very happily.

And from then on, we just said, “messenger RNA” with whatever else the topic was. That was a '63. My son was born in 1975. And in 1983, when he was in third grade, he came home one day and at the dinner table he told me how it all worked, and he was right. We went from cutting edge, really disputed data to twenty years later, it being taught in elementary school as a concept that they could just learn; they didn't have to worry about anything. But I can think of no other instance where something as abstruse as messenger RNA could become dinner table conversation for an 8-year-old.

PARK: Great story. Do you have anything else to say?

MICHAEL POSTON: It was always a privilege to work here. Exasperating sometimes but always a privilege. I recognize that people who were researchers at NIH were in a privileged area because of our funding, our ways of being responsible for this.

It didn't make much difference where you were, you were doing interesting work. And we had the support, at least in this laboratory, we always had the support of the people above us and they certainly had support from the people above them. So that we were a privileged lot. And while we may have moaned and groaned about various things, in our innermost heart, we recognized that. When I retired,

in '99, after nearly 40 years of this nonsense, what I didn't miss was the bureaucratic side of it and the hassle.

But occasionally, I still find myself planning experiments and that doesn't help much.

PARK: Thank you very much.

PARK: This is Dr. [Thressa] Terry Stadtman's lab and thank you very much for giving us a demonstration of your experiment.

THRESSA STADTMAN: As you probably know, the emphasis of my laboratory is on selenium biochemistry. Recently, we have been studying what turns out to be the kind of universal donor of selenium for making selenic proteins and for putting selenium into nucleic acids.

Dr. [Gerard M.] Lacourciere who you will be talking to later, and I, and also his two young Japanese visitors who are spending weeks in the lab, are dealing now with really the very forefront of this problem, which is how do you deliver the selenium to make this important product, selenophosphate, which then will be used as the biochemical currency for putting it into proteins?

So these delivery proteins are beginning to tell us how cells, how you and I, how bacteria, get the selenium from normally occurring compounds, from waters and inorganic compounds in water. And they make some kind of intermediates on these proteins that we're trying to figure out what they are.

And they deliver the selenium then, it looks like, from one enzyme to another through some sort of a lipid membrane, probably. And we're trying to learn something about this chemistry. So, one of these enzymes, which I will show you a little bit about what we do, is one of these delivery proteins that I'm purifying from a strictly anaerobic organism that makes its living making methane.

And these are so highly anaerobic, these bacteria, that they're designed for handling these exquisitely oxygen-sensitive compounds. Also, this one that I deal with makes a lot of selenium-containing essential proteins. So, this currency that we're dealing with is elevated in amounts and also, these delivery proteins.

So, I'm purifying what I believe is one of these delivery proteins. The assay for this may involve -- I have a fraction that I've purified quite a bit. I'm going to add some of this enzyme with one of these fancy little delivery proteins to a reaction mixture.

Then I have to run this reaction under really very oxygen-free samples. I have a tank here of argon, which is free of oxygen. Then I'm going to bubble this pergolas sample for a while so that any oxygen in the gas phase is removed and from the liquid.

Then I'm going to put a stopper in this tube and then so this now is an oxygen-free system and I would set up several of these in order to measure how much of this enzyme is present in a sample.

And another one might have double the amount of the enzyme that I would put in. And then I would also go through the same procedure so that before I carry out the real reaction, incubation we call it, in which the enzyme is going to have time to work.

But first, I must get rid of all of this really poisonous oxygen. So, we've been looking, Dr. Lacourciere and the young Japanese visitors, have been looking at the bacterium *e. coli*, which we commonly use.

And they also have looked in the enzyme is present, one of these important ones, in our liver. I think they've looked at it from pig liver. So, we go to all of these sources and look for the best source of the enzyme and how we can get enough of it so we can really chemically characterize.

And what is this mysterious kind of selenium that is passing from one enzyme to another without going through the liquid. So, I've been consulting a German expert who is in this country briefly, how do we talk about this thing in the literature because they've used some funny names? So, he was advising me the other day what is the best kind of words to use that don't claim that we know chemically what's going on because it's going to take some very special studies to elucidate the real detailed chemistry of this process.

It's not really just inorganic element and it's not a reduced form. So that's a little bit of what we're trying to do and it's really on the forefront of this whole field now at the moment because if— the way we used to study this reaction in an *in vitro* system was to add a high amount of a substance called sodium selenite, which is extremely toxic. So, the amount that we had to put in would have killed us and the bacteria. So, these delivery proteins are able to deliver low amounts at a time directly where it's going to be used. So, this is how nature has solved this problem of the toxicity.

PARK: Could you say a little bit about medical implications of your research?

THRESSA STADTMAN: The medical applications of this are because one of the enzymes that can't be made unless we have this selenium phosphate, this currency for delivery, is a very important one that really was described accidentally only a few years ago in my lab by a young, visiting Japanese professor.

This enzyme is called thioredoxin reductase. You and I and mammals have this and it needs the selenium, which is put in via this delivery kind of protein. Without that, the enzyme is not active anymore. This determines—exquisitely controls—the amount of oxygen that is available and protects it from too much. You need a little. It's an exquisite kind of control. People are very interested in this because when control gets out of control, then we have transformed cells that are really cancer cells. So the first big amount of this enzyme we isolated was from a cancer cell line; in a human lung cancer.

So, for reasons that we don't understand yet, when some cells grow out of control and grow very fast, they make a lot of this particular enzyme, which is normally regulated very nicely. Which means that these cancer tissues grow very fast because the oxygen is kept away from them. They grow like anaerobic bacteria almost. So, this is part of the whole cancer production field. Of course, everybody working in the field of cancer prevention is interested in this thioredoxin reductase. It's important for us to make DNA because the precursors require the activity of this enzyme.

And so we don't even survive when we can't make DNA and it's involved, it turns out it's involved in regulation of making all kinds of other proteins that have to have just the right amount and not too much oxygen; just the right amount of some chemical that's destroyed by oxygen.

So it's so intricate, it's just amazing. Everything you do in these fields is astonishing. It's really astonishing that we, as organisms, survive because the control levels are so fine and so elegant. This is really what the whole chemist/biochemist/molecular biologists are looking at: How do we control these hundreds and hundreds of reactions? And now that the genomes are beginning, you have this big pattern and we can compare what the mouse is like us to a big extent. If we can locate one of these key ones in the mouse, then we know where to look in our genome.

And then we have to study the protein—it's a pattern for what the protein is going to be like is in the genome. So, there's all of this distance in between there, so it's amazing. Exciting every day when you work in these fields.

You have to do a lot of simple little assays like this to find how much the enzyme and how it really works. So, it's step by step by step.

PARK: Do you really feel the enzymes in the tube?

THRESSA STADTMAN: You get deeply interested in this whole thing. Actually, the enzyme that I'm purifying comes from a microorganism that I isolated from San Francisco Bay—the black mud in the bay—when I was a graduate student. Because at that time, my thesis problem was these organisms that can take carbon dioxide and reduce it to make methane and then they can also handle some other compounds. It's interesting and actually the word serendipity is very important in biochemistry because I got into this whole selenium business by just a very accidental thing.

One of the enzymes I was studying, I couldn't make very much of it and why couldn't I make more of it? It was stable under normal conditions. Turned out I wasn't giving this microorganism very much selenium and when I put in more, eureka, there it is. It works.

Then this discovery of the thioredoxin reductase, this nice, young Japanese professor and I, we were looking for a different kind of an enzyme with selenium in it. He isolated the pure form, determined that it was really selenium in this form that we knew should be there. But the particular co-factor, a cytochrome, was not on this protein so he discovered another co-factor, which was a flavin. So, what is this protein? We looked at the structure and we looked at the analysis and let's try this? Eureka, there we had it.

Friends of mine in selenium are in Sweden, who had studied this protein long before it was any hint that it was a seleno protein, called me one day and said, Terry, what a surprise. So, then everybody was surprised and jumped in and now many, many labs are studying this protein and its relationship to cancer and to heart disease and name it.

So that's the way these things happen.

PARK: Could you say a little bit about your Vitamin B_{12} work?

THRESSA STADTMAN: Earlier, before I got into this selenium field, we had been working on Vitamin B_{12}. Again, Vitamin B_{12} was important in some of these anaerobic bacteria, including these bacteria that make methane, because one of the intermediate steps, the intermediate that's going to eventually become methane, which is CH4, the gas, was sitting on a Vitamin B_{12} compound. And then that the next step, it was cleaved and reduced and became methane. So, we discovered three or four interesting enzymes in these methane bacteria. Then I had another one I'd also isolated originally from San Francisco black mud that was metabolizing various amino acids.

And it turns out these reactions also required this co-enzyme form of this beautiful red Vitamin B_{12}. So, a solution of that Vitamin B_{12}, if it's concentrated, would look like that; nice and red. So that was the early thing. One of those proteins that was involved in that kind of reaction actually turned out to be a selenal protein also. Life goals, research goals and accidental discoveries and then it circles and leads you back.

Now we understand what was going on there.

PARK: In your life --

THRESSA STADTMAN: So, you'll build on your findings and other people's findings. This is what we all do. We build, build, build and get another little piece of information. That's really what's exciting about it. Because sometimes you go through a period of time when everything seems like it's a black box. What can you do?

And then sometimes—I used to call it my Saturday experiments—when I was younger, I always worked in the lab on Saturday. And on Saturdays I would put a few more samples in. Let's see what happens? Sometimes that was the little accidental discovery—let's look at that?

So that's really the way research goes. I don't think in this field, if you sit down and think you can design an experiment that discovers everything, it's wrong. You're always building and building and building. So, you're adding another bit of information step by step by step.

PARK: Here at NIH, for more than 50 years—

THRESSA STADTMAN: That's right. Recently, they had a little session—unfortunately we weren't there—honoring our 50 years at NIH.

PARK: You have met a number of young fellows. Do you have any words that you want to give to your young fellows?

THRESSA STADTMAN: Of course. What every senior investigator owes a big debt of gratitude to all of the nice young people over the years who have helped to investigate and sometimes brought new problems, new approaches to the laboratory.

It's a pleasure now, when I go to Sweden or to Japan or all these places where in fact you start up where you left off the last time. These are deep friendships. One of these nice Japanese people, one of his children is our godchild. So marvelous and one of these very nice, young guys who was in my lab before he had his Ph.D. and then he came back later from Stockholm and he has developed into—he's a big CEO of one of the companies that supplies lots of pharmaceuticals and laboratory supplies.

So, it's a pleasure to see a lot of these people come and they're important professors at universities. Earl and I think of all of these as our children. It's really very nice. It's very gratifying to feel that maybe you had just a little bit of influence on these people.

PARK: You have many sons and daughters.

THRESSA STADTMAN: Because we remember when we were young and studying and that our professors really taught us a lot about how to do research and the importance of things.

PARK: Thank you very much for your time.

THRESSA STADTMAN: So you heard from me about some of the background of the problem on selenium metabolism and now I would like to introduce Dr. Lacourciere, who's one of the valuable persons in this laboratory who will tell you some of his current research on this problem.

GERARD LACOURCIERE: My research has been focused on the mechanism of the biosynthesis of selenoproteins and bacteria. One of the enzymes that's essential for the synthesis of selenoproteins is selenophosphate synthetase. This enzyme has been characterized in some detail in our laboratory over the last few years. What we have learned is that this enzyme has a very high requirement for selenium as a substrate in order to make selenoproteins. In fact, the concentration of selenium which it needs to perform its reaction is so high that it approaches levels which are toxic to the cell.

So, we have proposed a mechanism which bacteria have evolved to utilize a certain family of enzymes, which can function as selenium delivery proteins to our protein, selenophosphate synthetase. So, we are currently looking at three enzymes which we believe are selenium delivery proteins in *e. coli*.

Much of the work that we've done in the last two years has been focused on these enzymes. We have a collaboration with a group in Japan at Kyoto University. This group has done extensive work on cloning and characterizing these potential selenium delivery proteins.

And we have some *in vivo* evidence which supports their function as selenium delivery proteins. We are currently looking at some *in vivo* which will also support their participation as selenium delivery proteins in *e. coli*.

Most of the work that we do involves biochemical assays, cloning, mutagenesis, purification of proteins and the growth of bacteria. Hopefully, we can have more information available soon about the delivery of selenium in e. coli.

PARK: Thank you.

PARK: This is Room 102 of Building 3 which used to be used by Dr. Arthur Kornberg, a Nobel Laureate in 1959. Everybody in this building seems to notice the historical importance of this place. The people, especially the people in the room, are proud of working there.

I'm here with Dr. Sue Goo Rhee, the Chief of the Laboratory of Cell Signaling. Thank you very much, Dr. Rhee, for having this interview. I'd like to start with your educational background and when you came to NIH and how you came to NIH.

SUE GOO RHEE: I obtained my undergraduate education in Korea and then I came to the U.S. in 1967. Then I got my Ph.D. from Catholic University. This is a local university in Washington, DC. Then I joined the NIH directly from Catholic University in 1973. I came here as a post-doc and then later I started work with Earl Stadtman too. So, I had two bosses in NIH. I joined in '73, the biochemistry laboratory.

PARK: What kind of research are you doing?

SUE GOO RHEE: I was like everybody else, I was working on the glutamine synthetase—*e. coli*—glutamine synthetase to study the mechanism of actions, mainly to understand the nitrogen metabolism in *e. coli*. So that was around 1978, I guess.

PARK: How did you find NIH as a working place back in 1970s? It was an exciting place?

SUE GOO RHEE: It was an exciting place but my background—I didn't have any background in biology at all. My major in undergraduate and graduate school was more physically oriented, chemistry.

But I was interested in going back to Korea after training here and I was, like most Korean scientists at the time, I was interested in the natural product of ginseng. So, we were thinking about synthesizing a biologically active compound from ginseng. I discussed this matter with my graduate school advisor and then since it's so difficult to synthesize a natural product, he actually recommended to me to learn more about enzymology because enzymes can do very complicated synthesis.

At that time most of the chemists could not really introduce a specific group in a specific manner. I took his advice and then he told me that NIH has many famous enzymologists and it's a good place to learn enzymology.

So, I applied for a post-doctoral fellowship. I wrote a grant and then I was accepted to Laboratory of Biochemistry. So that's why I came to NIH. But since I didn't have much biology background and (unint.), he just came from Germany and he had a more physically oriented background. I applied a grant with his name as my sponsor.

That's how I came to this laboratory. I slowly learned biochemistry and enzymology and molecular cloning. So I became very interested in biology so I decided not to go back. That's how I got started at NIH.

PARK: How did you learn the biological sciences at NIH? Just on the bench or did you take any courses?

SUE GOO RHEE: I took several night courses at NIH; just evening courses given here. Then at that time Earl Stadtman was actually teaching intermediate metabolism. So that was a really famous course, so I took that course plus a protein chemistry course and some endocrinology.

Maybe I took about five or six courses here in the evening. But most of them I learned to do through seminars and discussion with a colleague. So, in graduate school I never took any biology course. My biology background was almost zero.

PARK: Could you comment on Dr. Earl Stadtman as a teacher and also as a research advisor?

SUE GOO RHEE: He was excellent. He had a really good amount of patience with me. He knew I didn't have much background, so I was working with him directly. Initially with Boon Chock but Boon also didn't have much background in biology. We tried to do something together and we just had a difficult time with the enzymes and then the *e. coli*. Finally, we asked Earl Stadtman's help. Then I worked in his lab for about a year and a half under his direct supervision.

So, he would normally come in the morning and check my data and then before he left for home, he'd check with my data again. So, I used to see him twice a day every day for a year and a half. So, he was a really excellent mentor. So, I learned biological side from him, chemical side from Boon Chock.

And Boon had a pretty good background in kinetics and more quantitative concepts on biological phenomena. As you know, he was trained with Ike and a Nobel Laureate. So, he had an excellent concept on kinetical phenomena of enzymology.

Then I learned more complicated biology from Earl Stadtman.

PARK: You came as a post-doctoral fellow and then you became a section chief and then finally you became a lab chief. During the course of your professional career, do you feel any difficulties as a foreigner working in the federal lab?

SUE GOO RHEE: Not really. Communication probably was a little bit difficult initially. But since we had so many scientists who had experience with a foreigner, it had become less problematic. But I'm still struggling with writing manuscripts, particularly for good journals. So, this is true. Other than that, I guess most of the scientists are tolerant.

PARK: When did you become a lab chief?

SUE GOO RHEE: '96 or '94. I'm sorry, '94. I became lab chief in '94 and section head in 1988.

PARK: Could you describe your current research projects going on?

SUE GOO RHEE: As I mentioned, I studied with the *e. coli* and nitrogen metabolisms, so I worked on that system many, many years; maybe about 12 or 13 years. Around that time Earl Stadtman already switched to study protein oxidation.

Then I was working on *e. coli* and yeast nitrogen metabolism and then one day Earl Stadtman told me that it may not be a really good idea for me to stay in that area too long because whatever I do independently, he thought outside people would associate my work with him all the time. So, he was afraid that I may not get the full credit. I think that was around '86 he recommended me to move out of this nitrogen metabolism area and then find my own stuff. So, at that time the receptor depended on the signal transcription was evolving rapidly.

So, they knew what kind of compound went into receptors, but they didn't know exactly what was going on inside of the cell so how signaling from outside to inside. But in metabolism was also considered to be important for the signal transcription but exactly what was going on, they didn't know. So, I decided to attack this problem and that was around '87. So, I decided to switch from research in microorganisms.

So that's how I got into current cell signaling research.

PARK: It sounds like you're doing pretty much basic science.

SUE GOO RHEE: Very much basic sciences.

PARK: But at the same time, you see some kind of medical implication or application of your research.

SUE GOO RHEE: This is indirectly. Most of the hormones and the pharmacology (unint.), when they bind to the receptor, they are utilizing this lipidous signaling who we have discovered. This is an enzyme called the phosphatase…when the receptor is occupied by hormones, they activate this phosphatase. And then phosphatase sends a message. Without this signal, you're not going to have any cell to cell interaction. You are not going to have recognitions of a lot of hormone actions. So, this a really fundamental. The importance for the mammalian cell to cell communications. So, it's implicated in cancer. So, it's a very basic block of our life.

PARK: Could you say about the size of your lab? How many post-docs and how many staff members?

SUE GOO RHEE: I have, at this moment, 10 people and 8 post-doc and one technician and one permanent scientist. So we have only 10 people here. My lab is small.

PARK: Finally, could you comment on NIH as a working place these days? How it's evolving.

SUE GOO RHEE: This is a really fantastic place, particularly for people like me without teaching responsibility. Once you go to academia you have to write grants. Not only that, you have to teach. So this is a place we can flourish without writing grants and teaching. You can concentrate on your research. In essence, I think I'm a very lucky person to find NIH.

PARK: A quick question and this follows up on the amount of time you spend doing research. As chief of the laboratory, I was wondering if you spend a significant amount of time on administrative.

SUE GOO RHEE: No, not really.

PARK: Is that because of the size of your laboratory?

SUE GOO RHEE: I think NIH, the climate for administrative jobs—administration is minimal. I don't know … but we had very good scientific directors and normally we could do a lot of business through e-mail or phone calls instead of writing formal memos and so on.

PARK: And there's no need to attend a lot of meetings?

SUE GOO RHEE: Not a lot of meetings. We have just one lab meeting a month but even there, in the summertime we don't have lab meetings. And this month we didn't have it so maybe next month. We'll have seven or eight lab meetings a year.

I spend more time with the fellows. We have four seminars a week. I meet with two different groups twice a week in the mornings. So I spend most of my time with the fellows.

PARK: Do you have close collaboration with the people in the Laboratory of Biochemistry, Dr. Earl Stadtman?

SUE GOO RHEE: Yes. We have a seminar. We meet with them three times a week. Two journal club and one seminar by outside speakers three times a week. And then I publish a lot of papers with people like Boon Chock, Roger Levine, Terry Stadtman and just doing collaboration with them. It's almost like one lab. We have been maintaining this one as just one lab.

PARK: How about collaboration with other scientists in other institutes. The Cancer Institute or NIDDK?

SUE GOO RHEE: I'm very active in those things actually. I have done a lot of collaborations with people in NIH and other institutes too. But I also do a lot of collaboration with the outside, particularly with my former colleague. I had a lot of people who bring Korean scientists over [to work in] my lab. About 50 or 60 of them are professors in Korea at this moment. They are continuously coming here during their sabbatical years and we exchange ideas and we publish together. Recently, their scientific standard has also improved very much and we've published significant papers in journals with good reputations. So I'm very active in that sense.

PARK: Thank you very much. Could you show me your labs?

PARK: Today is March 6, 2001. I'm in B122 of Building 3 with Dr. [Edward] Ed Korn, the Chief of the Laboratory of Cell Biology. Thank you very much for having an interview with me, Dr. Korn.

I'd like to start our talk with your educational background and when you came to NIH and why you decided to come here.

EDWARD KORN: I grew up in Philadelphia, went to the University of Pennsylvania undergraduate school in graduate school and got a Ph.D. in Biochemistry. I actually started in the graduate school as an economics major. I took a lot of chemistry courses because I was interested in that.

Then my brother, who's a few years older than I, had a friend who went to medical school and was doing post-doctoral research in biochemistry at the University of Pennsylvania. It was really talking to him that first got me interested in that as a career.

So I went on and got a Ph.D. in the Department of Biochemistry at the University of Pennsylvania with a man named Jack Buchanan, who subsequently went to MIT to begin a biochemistry group in the Biology Department at MIT.

He retired about 10 years ago now. I had planned to go—after my graduate school work—to go out to the University of California of Berkeley to work in the laboratory of [Horace] H.A. Barker, Professor Barker, who was a very well-known microbial biochemist at the time. He's still alive actually out there. The strange thing is I was most impressed—the reason I wanted to go there was that I was very impressed by the work that someone named Earl Stadtman had done while he was a graduate student of Professor Barker's.

I didn't know Earl at all, and Earl had already gone from there to Boston to work with Fritz Lipmann. But Earl's work on microbial biochemistry handling of oxidation of fatty acids were very impressive. So I made arrangements to go out there. And then about a month or two before I was to go, I got a letter from Dr. Barker saying he was unable to take me because he had a heart attack and his laboratory was not going to function for a year or so. He had contacted Arthur Kornberg, who had just left the NIH and Barker had been on a sabbatical a year with Kornberg here.

Kornberg had gone to Washington University in St. Louis and Kornberg had agreed to take me into the laboratory, all without Barker being aware of this. So Kornberg told me that and I decided not to go to Washington University. First of all, St. Louis in the days without air conditioning didn't seem very attractive, especially compared to Berkeley. But more importantly, I guess, is that Kornberg and Buchanan, the fellow I was working with, were doing very similar things and I wanted to get experience in some different area, in the first place.

And also, they were competing and it just seemed a little bit awkward to go from one competing group to another competing group. My mentor at Penn thought that Buchanan had gone to graduate school with a man named [Christopher] Chris Anfinsen and then they had done a sabbatical together in Sweden; they were very close friends.

And Chris had just come here as one of the first four lab chiefs creating the new institute; the new intramural program. And Chris Anfinsen was one of the people brought down to have a laboratory. So Buchanan and Chris talked and Chris came down here to visit and move to the area and so I decided to come here and that was around May or something and I came in September of 1953.

It would be better if I could say I was surprised to find that Earl Stadtman was here but actually I knew by that time that Earl had come here from Boston and was here. So it wasn't a complete surprise. I was working with Chris and Earl was an independent investigator in the same department. So it was a strange coincidence that that should have happened. So that's why I came and that's how I came in 1953.

Anfinsen had—his primary interest at that time was in protein synthesis and mechanisms of protein biosynthesis, which were totally unknown. He and everyone else in the field were off on directions which turned out to be incorrect. But he was asked at that time, a year or two before, a man named Hahn in Canada had made a serendipitous observation. He was doing some work with rats, I guess, they had just eaten a fatty meal and he gave them some Heparin, which you would do as an anti-coagulant so you could collect the blood.

He noticed that the lipemic animals, who's plasma looked like cream, after the Heparin injection it cleared. So it was something he referred to as a clearing factor which was released or incurred by Heparin.

That was one thing that happened. Then at the same time, Professor John Goffman, out at the University of California at Livermore, had started to redefine plasma lipoproteins, which had always been categorized prior to that by electrofluidic properties due to how fast they move and alpha lipoproteins and beta lipoproteins.

He began to use the ultracentrifuge to separate them based on density, which would be the content of fat that they had, and defined, for the first time, what we all know as LDL and HDL: low density lipoproteins and high-density lipoproteins.

(unint.) showing a better correlation to atherosclerosis associated with the LDL as opposed to just doing total cholesterols, which was the standard at that time. This is a long introduction to saying that Chris, when he came here, apparently agreed to organize a research program looking into this general area. And he recruited a number of people like Bob Gordon and Don Fredericksen. Don Fredericksen became Director of NIH. Bob Gordon was director of the Clinical Center. A number of other people, four or five people. to work in that area. All of who were just out of medical school or just out of an internship or a residency; had no research experience at all. But I agreed to work in that area for about two years and then no commitment. It was a post-doctoral fellowship.

I actually had a Damon Runyon Society fellowship. I had a pen and I brought that down with me here for six months that I was here. So that's what I decided to do.

Of course, being biochemically trained and trained in enzymology, what was not obvious to clinically trained people, it was obvious to any enzymologist that if you have lipids in the blood are clearing, there must be an enzyme being released that's hydrolyzing the lipids. So within a few months we shared that there was a lipase being released which specifically hydrolyzed triglycerides associated with lipoproteins as opposed to just triglycerides like olive oil.

We showed that this enzyme occurred in adipose tissue in the heart and probably other places but was released upon injection of Heparin into the blood stream and had that effect of clearing the triglycerides in the blood stream. So I worked in that area with that enzyme, which we named lipoprotein lipase

because it specifically hydrolyzed triglycerides attached to proteins. We're working now for a number of years—

PARK: And you became principal investigator around that time?

EDWARD KORN: Yes. I came for two years, stayed another two years, another two years. It's 48 years later or something. I guess I never found a better place. So what happened, although I came nominally to work as a post-doctoral fellow with Chris, about six or seven months after I came here, he went away on sabbatical to Copenhagen. So I really worked independently. He wasn't interested in protein synthesis in this area particularly. He just agreed to organize the group. So in fact, I never published a paper with him. I published as an independent investigator from the very first days.

I never really did a post-doctoral fellowship in the conventional sense. Chris went away for a year after I was here about eight or nine months and then came back and I made the transition into an employee as opposed to a post-doctoral fellow.

I was really independent from the day I came. In fact, about six months after I came, this was during the Korean War, and I had a deferment initially because I was married and then when that was no longer grounds for deferment, I was a graduate student. That was a grounds for deferment. I had forgotten all about the draft, in fact, I didn't know whatever happened to it. After I was here, all of a sudden, I got a letter in the mail and they had traced me back from Philadelphia down to here, reclassifying me as 1A.

But I was able to join U.S. Public Health Service Commission of Corps and so I, in that sense, became an employee about six months after I arrived here, or three or four months after I arrived here, and spent two years in the Commission of Corps in the Public Health Service during the Korean War. And then I resigned from that over to regular employment. That all worked out well.

PARK: Already you mentioned something about the atmosphere of NIH at that time; post-doctoral fellows and there were a lot of M.D.s at the time. Could you comment on the atmosphere of NIH as a research institution as compared to at the universities? Was NIH getting a lot of attention from the scientists outside? And is it really similar to an academic environment in terms of freedom of research or doing whatever you want to do or things like that?

EDWARD KORN: At the time when I came here, which was not just a long time ago looking backwards but was really very early in the intramural program as we know it today. Of course, as you know, there's a lot of history of NIH. But as we know it today, it really has just been organized. I think it was not well-known throughout this country or anywhere else and people thought it was a government agency. Why would anyone come to work for a government agency like the Department of Agriculture or whatever? It certainly was not an academic environment.

You must realize that Biochemistry Departments in those days, at least the University of Pennsylvania were really only interested in training Ph.D.'s to go into academia when the faculty was expanding or

replacing themselves. They weren't interested in training people to go into industry at all and government positions. So I think it seemed a strange thing to many people to want to come here. The place was not well-known.

There are many similarities to universities and there are obviously quite a few differences. When we came and in fact, still today, in terms of academic freedom, I think there's as much academic freedom at least in the Heart Institute as it was then and as it is today.

Institutes varied in their approach to controlling their programs. But we were free to do what we wanted to do. What we did was reviewed, not as formally as it is now where it's really very intensively and extensively reviewed by external boards assigned to the counselors. We reviewed but it was a retrospective review. So you really were, in a sense, more free. I could change my research—and I did this three times—totally without asking anyone's approval to change my area of research knowing that I would be judged a year or two later on how well that went.

But I didn't have to write a grant application and get that approved and wait nine months to a year to start something new. To do something, I could just go right ahead and do it. I think to a great extent that's still the case throughout certain of the Heart, Lung, and Blood Institute.

So, in that sense, just as much academic freedom to do what you wanted to do and certainly in terms of daily sorts of things. Come to work you're much more free. You don't have classes to meet. Except for the Scientific Director and a few other people, no one's on a committee, no one's doing anything except the research.

They work long hours, but they come and go when they want to go. The difference, of course, is there's no students. There are post-doctoral fellows and a few graduate students who are getting their degrees from schools in the area and do a little research here. But basically you'll have an undergraduate campus and a graduate campus so you don't have a basketball team or a football team. So the important things of academia we don't have here.

When I came here it was very much smaller. The Clinical Center, Building 10, was still under construction. It was completed but not inside; it hadn't yet been occupied. I came in September '53 to this building up in the attic and we moved into the Clinical Center in April of '54, about six or seven months later.

And the building was slowly occupied. So it was a very much smaller place. The tradition then was, and for several years thereafter, that once a week all the biochemists at the NIH, through all the institutes, met once a week. So individuals took turns discussing their research.

PARK: In this building?

EDWARD KORN: No. It was Top Cottage. I'll get back to Top Cottage in a minute. And then once a month the Johns Hopkins biochemists and other biochemists would alternate in Baltimore or near here. So I probably knew and interacted with more biochemists/scientists then than I do now because soon thereafter, four or five or six years, there were so many groups and too many people to get

together all this way. You couldn't have invitations and include and exclude various people. So that sort of fell apart.

Those meetings were held in a little structure that doesn't exist anymore called Top Cottage. There was a caretaker's cottage or a guest cottage on a hill where the Clinical Center now is. Apparently, the Clinical Center, there was a hill that went up, I was told, where the fourth of fifth floor of the Clinical Center is. And that hill was knocked back behind the Clinical Center now. It had been a high hill and a valley that sort of flattened out. The Clinical Center, the ground is still the highest point at the NIH. But there was a cottage there. So when the Clinical Center was built, they picked the cottage up and they took it over to where Building 31 now is and it sat there. That was huge for just this kind of meeting or for parties. It was allowed to serve alcohol there; the only place on campus.

PARK: Do you remember how many people were coming?

EDWARD KORN: I really don't know. I would say it was 25, 30 people would certainly be there and they were from all the institutes. What is now NIDDK was quite a large group. And then the National Chemistry Society has a biochemist who was there.

That Top Cottage, they could serve alcohol at Top Cottage. Obviously, they couldn't do it anywhere else on campus. When Anfinsen went on a sabbatical, which was sometime a year after I came, they threw a farewell party for him there.

And Jim Shannon was invited. He was by then the Director of NIH, but he had been the first Scientific Director of the Heart Institute and he had been the one who had recruited Chris. I was in the kitchen with another young scientist helping make the martinis that we were serving. The entrance to the Top Cottage came into the kitchen. Jim Shannon, who I didn't know at the time at all, came into the kitchen about a half hour after the party had started. He said, how many have I had. I said about two or three.

So he quickly poured himself in succession three martinis and threw them one down in a single gulp, then poured himself a fourth one and said, now I'm even and he walked out to join the party. That was my first introduction to Jim Shannon, who obviously had more impact and influence on what extramural and intramural NIH has become than any other director.

He really set the whole tone for this place for quite a few years.

PARK: When did you become the chief of the laboratory? And what does it mean by having your own lab rather than just principal investigator? Do you have any extra burden of administration or do you have more manpower to expand your research? Could you say a little bit about that?

EDWARD KORN: When I became Chief of Laboratory of Cell Biology, I'm not sure exactly when it was.

PARK: First, when did you become that?

EDWARD KORN: It's been about a year and a half since I stepped down. I was there about 10 years, 12 years. Jack Orloff was Scientific Director for about 15. So probably about 20 years or so years ago.

About two or three years after Jack Orloff became Scientific Director then he asked me, because of some administrative problems, he asked me would I agree to become chief of a laboratory. At that time, I should say that Chris Anfinsen had come and gone from the institute and Earl Stadtman had become the lab chief.

And over Earl I was a section chief and Wayne Kielly was a section chief and Earl had his own section. But Wayne and I really operated independently, basically as if we were lab chiefs. We didn't report to Earl in any way whatsoever.

But then some administrative problems arose and Jack Orloff asked me would I agree to become a lab chief, which I did… about 20 years ago or something. Then I continued to serve in that capacity.

I would say generally, the position of lab chief, it's dealt with differently by different people and varies. There are situations where a lab chief really dominates the laboratory. It's sort of as if the Laboratory becomes his laboratory. There are others, which ours is an example, when that's not the case. I didn't assume, acquire—I guess I could have, I suppose—but I didn't.

I wasn't interested in acquiring any more space or any more people to work with me and get my group to be larger. So it was nothing gained in that sense by me at all by becoming a lab chief. On the other hand, there was not that much work involved in it either because there were other senior people who were independent investigators who did their research and took care of the research.

There were some formal things I had to sign: annual review, personnel performance appraisals or such and I signed all the requisitions that went out and that sort of thing. But really, being a lab chief takes very little time at this institute, in my experience.

PARK: So there's not much difference from the section chief responsibilities?

EDWARD KORN: The section chief here in this institute without exception, certainly in this laboratory and I guess it's true throughout the institute, a section chief is really just the PI over his or her research group. All the people under a section chief, with a few exceptions, are his or her post-doctoral fellows and technicians and no other independent investigators. So a section chief is a very important title to have but it has no meaning beyond that.

I felt strongly about this but it became an issue at several times as to whether there were too many section chiefs and too many titles.

You asked the difference earlier between academia and here. Someone at a university can sign a letter—associate professor, a full professor, and so on. Someone that's equivalent here could sign a letter, GS-15 or something, which is hardly what you want to do.

So the title of section chief has just that. Allows his name to be posted on a board which says they're section head but also allows them correspondence and other sorts of things to have a title which has some implications other than just to sign themselves as either a commissioned officer or a civil servant.

So Section Chiefs I think are very important but it gives no benefits other than you have as being a PI. So a tenured track investigator has exactly the same degree of independence and freedom for the period that they're in a tenured track.

If they're unsuccessful during their tenure, that's it. But during that period that they're in a tenured track, they have complete independence, have their own research group and they function like the independent investigator functions.

There will be some sections in NIH which are much bigger; some other institutes especially. Where they're much bigger and the section head will have almost the size of a laboratory here and then there will be some administrative….

The other thing is we've also adopted, it's now been 15 or more years, in a budget process each individual PI has her or his own budget and own account number.

PARK: So budget was decided by Congress or scientific directors?

EDWARD KORN: The budget is decided to begin with by Congress. The appropriation—there is a line item in the appropriation which Congress—the intramural research and—I stepped down for two years as Scientific Director and I forgot the terminology.

The cost of the staff in the extramural program, the directors of the institute cost, is obviously the personnel office and all the extramural divisions who run the grant program, the cost of them, not the grants. But the administrative costs of that are in a combined budget. So that comes from Congress. Basically, that then becomes the portion of that is the intramural budget and that's a line item and may need to be adjusted to some small extent after that but not much. So that becomes the intramural budget.

The Scientific Director, working with the Institute Director, will then apportion that budget out to the laboratories and branches. I can't speak for the current situation, but as a general rule for a significant portion of that budget, you're to carry over the previous year. So if someone had x amount of dollars in their budget the previous year, they're doing good research, I'm going to support them at the same level which you were supporting them, then that defines their budget for the next fiscal year maybe with an adjustment for inflation. If the budget went up a little bit you can give revenue to his budget. Aside from that, if you want to take the new initiatives, to build a new program in some way or another, small or big, you want to put aside some money for that.

Each individual PI—when I was Scientific Director, there were about 65 or so and probably not very different now—have to have non-recurring expenses or equipment. Let's say one year you go and buy a new electron microscope and it's several hundred thousand dollars. You're not going to do that every year so the Scientific Director would then decide a certain amount of money for these non-recurring, large expenses. But the heart of the budget is carrying it over from year to year because your research staff carries over from year to year. And you may be increasing someone's group a little bit and reducing someone else's group a little bit and those adjustments come into play. So that's basically what it is.

PARK: You have already talked about your experience as Scientific Director. But I'm curious whether you wanted to be a Scientific Director, or you were just invited and you took it a bit reluctantly? I was told that some people at NIH do not want to go high on the administrative ladder. I'm curious what's your case and how do you think that the role of Scientific Director is in shaping the intramural program in general and in particular at NHLBI?

EDWARD KORN: I would say that—I could talk about my experience. I think that it probably varies from institute to institute and from individual Scientific Director to Scientific Director and the relationship between the Scientific Director and the Institute Director would also vary or may have changed.

The first question I think you asked was why did I become Scientific Director? It's easy now 12 or 13 years later I can put a nice gloss on it. I mentioned before, the Scientific Director just before me, Jack Orloff, as it happens, this Thursday and Friday, there's a symposium to honor his wife, his widow, Martha Vaughan, who also came just about six months before I came to NIH. I knew Martha quite well from the time I came here but didn't know Jack really at all. As I said before, after he became Scientific Director, he asked me would I become a lab chief to help resolve some administrative difficulties so I agreed to do that.

Then I got to be closer and closer to Jack within NIH but also as a personal friend. Somewhere the last several years of his tenure as Scientific Director, he asked me would I become Deputy Scientific Director. He had been Deputy Scientific Director. I think he really wanted a deputy not to do anything really—I didn't do anything really as deputy—but someone he could talk to and bounce ideas off of. That it might be confidential, but it relaxed him to have someone to talk these things out.

So I met with him for lunch almost every day and that was it. Then sort of the last year or two he was Scientific Director, it became obvious that we should have individual budgets, which we hadn't had before. The laboratories had budgets but not individual PIs.

So I agreed and in fact, to look historically in the previous year, four or five years what people have spent, we had those records. Then base the first budget they were individualizing to the laboratories for the next year based on historical budgets. So that was really the first thing I did as Deputy Scientific Director.

Then in the last year of his life, he became ill and died of prostate cancer and metastatic prostate cancer. Then the job was advertised. Why did I apply for it? In part because by that time I was far enough along in my career that I felt somewhat of an obligation to NIH and the Heart Institute for supporting me at NIH.

As I said, I had been totally free of any administrative responsibilities for this whole period of time. Then I wasn't quite 60 years old. It seemed to me it was not a sacrifice. It was going to take time away from my research but that was a stage in my career and that wasn't important. I had some concerns as to who might be the Scientific Director if I were not. There was just a little bit of a protective sort of feeling there. I did apply with other applicants from internally and outside the NIH. Why I was selected, you'll have to ask other people.

But I did not gain anything from this in terms of the laboratory. I think there were one or two Scientific Directors at the NIH in past years who did use that position to expand their own resources but neither the Laboratory of Cell Biology or my research or old research group got an extra penny or extra person during the time that I was Scientific Director. And that was not an easy comment to make as Scientific Director. So I didn't anticipate nor receive any benefit. In fact, there was obviously much more administrative work. The Scientific Director has a lot of administrative work. And that grew over the 10, 11 years that I was Scientific Director.

By the end, I was, possibly because I didn't delegate it as much as I probably ought to have done…. But I would spend essentially an 8-hour day there in that office and spending another 20 hours a week back here in the laboratory on weekends. At the end of doing this for 10 years or so, I thought it was now going to be, for a number of reasons, to continue the research and as Scientific Director and one or the other had to go and I decided to resign as Scientific Director.

I had been talking about that possibility for probably a couple of years before that off and on saying that sooner or later I want to step down at some point. There was never an obvious time to do that so at some point I just decided.

PARK: Are there many Scientific Directors having their own labs going on while doing administrative things or just abandon the laboratory work and focus on—

EDWARD KORN: I think today most of them probably do. I think probably all of them do today. Jack Orloff did not. He had been an investigator but decided that he would discontinue research. There's another Scientific Director in the past who didn't have a laboratory and today they all have laboratories. I think that's very useful. It certainly continues to keep you a scientist not so much in terms of understanding science but just day to day needs of the laboratory investigator. If they're complaining, as it used to be, things are much better now, but complaining about the requisition process. It's hard to get an order replaced, it's hard to do this or hard to do that. If you're sitting in the office, it's very easy to tend to take the side of the administrator. If you're in the laboratory, experience the same problems yourself, then you understand where they're coming from.

I think that's very, very useful to maintain that perspective. I think if you can keep your scientific base it doesn't really affect much because it's what you do. In the laboratory your work is more narrow than the scope of the institute's program, the Heart and Blood and Lungs area where from biophysics to clinical cardiology.

But that spectrum of science is so great that your own particular scientific efforts are not much help in that. But I think in just knowing what the place is like on a day to day basis. The Scientific Directors meet on a monthly basis and try to coordinate their institute policies as much as they can. But also to address the specific issues. Salary issues and more often the general climate of facilities. Having that perspective helps. Which also brings me to something else which is why I became a Scientific Director.

A Scientific Director was in a position to have more of a voice in establishing trans-NIH policy. I would say I was interested in the job of Scientific Director as much as for its potential in terms of being able to have some voice in trans-NIH affairs. You know things like the Foundation for the Advanced Education in the Sciences, which was begun by Chris Anfinsen and a half dozen other people, there always were a core of 15, 20 people who kept that going. And various personnel policies, had I soured on those policies and this sort of thing. It's really much easier to be heard if you're a Scientific Director than if you're not. Not that anyone can't, and people do, speak up and are heard on all levels.

PARK: Some people compare the Scientific Directors of NIH with Deans in the universities. Do you think that that comparison is fair? Or do Scientific Directors have more power or are more prestigious?

EDWARD KORN: No. It's hard for me to make the comparisons in a meaningful way since I've spent my whole adult professional career here. So I think there's probably not a good way to compare them. The institutes vary in size. The intramural programs vary in size, of course.

So that a program in the Deafness Institute or the Musculoskeletal Institute, these are very small intramural programs. The Cancer Institute is enormous. At one time, I don't know what it is today. but it was like 40 percent of the total intramural program was NCI.

The Heart Institute had about 65 PIs with a total of 700 people, if you include everybody, doctors, fellows, guest workers, and laboratory aides and that sort of thing. Very much smaller than a medical school, larger than any department in a medical school.

Scientific directors have the responsibility of somewhere between a department chair and the dean of medicine just in terms of the size of the job and the scope of the work. Perhaps I could have more influence on the research that goes on since at a university scientists individually apply for grants to NIH and get their grant monies to support their research. And they bring money into the school, the overhead is bringing money into the school. Whereas here, the budget comes from the top down. One could exert more influence on directions of research. Again, this varies with the institute to the extent to which the Scientific Director might try to encourage his or her own policies.

And the Institute Director. The Institute Director have appropriately become much more involved than they were when I came here. When I came here, in the Heart Institute and in many other institutes, if not all, the intramural program operated almost independently of the Institute Director. …I always have

close interactions with the Institute Director when I was Scientific Director, I not only kept him informed of everything I thought he'd be interested in hearing, but also in many areas seeking his advice.

In the budget areas, the big expenditures or change of program areas, he was very much involved, not necessarily at first agreeing and supporting. He was the key person to get the extra appropriations.

So we worked closely together and I'm sure that continues. But initially there was really—it sort of ran as an independent sort of operation.

PARK: I have a lot to talk with you about but before closing our interview, I'd like to ask you to briefly describe your current research activities and current projects and goals.

EDWARD KORN: As I mentioned in the very beginning, when I came here, I agreed to work in the field of lipid transport. I did that for a number of years and then it looked as if a process of endocytosis would be important in the uptake of the products of lipid hydrolysis, uptake from the blood stream into adipose tissue or other tissues. So I thought I would shift over and look at that process and how to do that as a biochemist and train them to look for the possible organism or assess the study with the confidence assumption and confidence that would be found in one system and applied to another.

I thought that the organisms that are most active in endocytosis, amoeba, which essentially depends entirely on endocytosis for its nutrition. …. which at the time was the only amoeba that could be grown in a defined culture medium. We were trying to look at changes in the plasma membrane of the cell during the fission and fusion processes involved in endocytosis.

We didn't make a lot of progress on that. But we were struck very early on that underneath ….there was an accumulation of what looked like actin filaments.

Actin and myosin had been strongest to muscle proteins and really essentially—this is an overstatement—but essentially not been looked at in non-muscle cells, either in … or vertebrae or certainly amoeba although there were a few experiments in that area. So we went ahead and started to characterize the actin and show that the actin was in fact, by sequence, 96% identical to your actin and my actin, yet its properties were very different in the cell. We worked on that awhile. Then said, there's actin, there must be myosin and we looked for myosin. We found the … who was a post-doc who ran the lab in 1970 or thereabouts, a myosin from the …. but it was not the typical myosin like the only one that had been known to exist. It was a lot smaller myosin, a singular polypeptide heavy chain to a single, much smaller … were different, which everyone else thought was a degradation product of the true myosin. But we had evidence to suggest that it was a real myosin.

So this turned out to be the first, so-called, unconventional myosin. Over the last 25 years, there now have been described by sequence about 150 myosins, at least, which fall into 18 different classes based on where their sequence is.

One of these classes, the largest class, is a conventional myosin that had been known to myosin 2. The second biggest class is myosin 1, which is the one which we had discovered. So our work since then has been now exclusively with the myosins.

We're really interested in two things: the mechanism with regulation of the ATP activity of the myosin and particularly myosin 1 …. But the myosin 2 is regulated differently than most myosins.

So we were interested in the mechanism regulation by phosphorylation of these myosins and … intimate structural function of relationships…. And a given cell can have 11 or 12 different myosins in five or six different classes.

So why are there myosins in a cell? What are they all doing? How are they regulated independently, one from the other, to do what they have to do? One thing we know for sure is that one of the functions of myosin 2 is muscle contraction, for example, the heart muscle. And also myosin 2 and that's involved in the dividing cells. When a cell divides it pinches off in the middle and ultimately there's nothing to separate that rip but that closure is by active myosin and it's class 2 myosin that's involved there. Most of the other myosin, the 70 other classes, we're just beginning to get a feel on what they're doing in the cell or how they differentiate and regulate. So we're doing this.

It goes through a lifecycle of development and differentiation, not just amoebal stage but a more complicated, multi-sited stage. And we've done some collaborative work recently, which is very interesting, with Greg May at the University of Texas in Houston. And Dean Anderson, who was working with… a fungus which is used very actively in the pharmaceutical industry to produce drugs. We've done some interesting work with him on the role of myosin 1. So basically, that's it.

PARK: Thank you very much.

PARK: This is Room 312. I'm here with Dr. Julie Donaldson. Thank you for having an interview with us. I'd like to ask you first about your educational background and when and why you came to NIH.

JULIE DONALDSON: I got my Ph.D. at the University of Maryland in 1988. I came to the NIH as a post-doctoral fellow then, working in [Richard] Rick Klausner's lab in the Child Health and Human Development Institute. I came over to NHLBI as an independent investigator in 1995, which is my current position.

PARK: How did you find NIH as a scientific institution at the time and now?

JULIE DONALDSON: I found it then a very exciting and rewarding experience, both my post-doctoral experience as well as coming here. NIH provides a special environment for scientists to work together and to work in creative and innovative ways; expanding their research in ways that it's more difficult to do at other institutions.

PARK: In the course of your research, did you have a lot of collaboration across the sections or across the labs or across the institutions?

JULIE DONALDSON: Indeed, both as a post-doctoral fellow, I interacted with other labs on campus and other institutes, the National Cancer Institute, and since coming over here and setting up my own group in the NHLBI, I continue to have interactions with people in the Child Health and Human Development. Scientific collaborations directly and also just intellectual interactions as well.

PARK: In terms of choosing the research topics, is it always up to you or your own choice or is there any directions going from some areas?

JULIE DONALDSON: The project that I've been focusing on in my own group is a bit of an off shoot of the research that I was engaged in as a post-doctoral fellow. I've continued to focus on this one particular area, although you get feedback from Board of Scientific Counselors, from my boss, Dr. Korn, in terms of the direction of research.

One of the advantages of NIH is the freedom to actually develop these areas. Of course, you have to publish things and your research has to be competitive such that you are successful, the fellows that work in your lab importantly are trained and become successful and publish. So I think it selects itself and that NIH ends up supporting good research.

PARK: One tricky question. How much is it difficult to be a principal investigator at NIH? Is it a lot of competition? Could you comment on that?

JULIE DONALDSON: I think when you first become an independent investigator wherever you are it can be difficult as you're finding your niche scientifically, you're setting up systems to be able to study your subject area. At NIH and particular in my situation, I felt like I was very well supported both in terms of funding support, intellectual support. Such that I've been able to bring in post-doctoral fellows to do the work. I feel overall it's quite a good environment.

PARK: Do you miss any teaching?

JULIE DONALDSON: I miss the academic environment in that I think although it's great having all of these post-doctoral fellows from all over the world and there's a lot of interaction intellectually in the lab, that we miss the energy that students bring that you see in an academic environment.

However, I do actually give a number of lectures at George Washington University that I do in part just to keep in touch with students. I think that's a good thing.

PARK: Could you describe your current research activities?

JULIE DONALDSON: My lab has been -- over the past five years, has been studying a low molecular weight GTP binding protein called ARTH. The ARTH proteins are regulatory proteins. They function at two states: kind of an on state and an off state.

By switching between on and off, they actually regulate movement of membranes within a cell that have an impact on cell shape and cell motility. We've been studying this protein both at a molecular and biochemical level; understanding what are the regulators that regulate this regulator.

What are the things that turn it on? What are the things that turn it off? What are some of the molecules that are affected when this ARTH protein is turned on? In addition, we've made extensive use of cell imaging to do these studies.

I'm a cell biologist so a major aspect of my work and what we use to characterize what are these proteins doing in cells has actually been at the cellular level. Imaging the cells using immunofluorescence, fixed preparations, to understand how this ARTH protein alters cell shape, the structure of the cell in terms of the actin, cytoskeleton, the behavior of the cell.

And how it regulates this movement of membranes. This activity of this ARTH protein is critical and has been shown to be involved in important cellular activities that occur during development, that occur during cell migration. They're also involved in wound healing and very likely involved in events that trigger cancer cell metastasis; when the cell gets up and leaves the solid tumor and invades the rest of the body. This ARTH protein and other regulatory proteins like that are involved in the regulation of how a cell behaves.

PARK: How do you actually take the image? Do you take the image from the microscope first and reconstruct it on the computer? Is that the correct process?

JULIE DONALDSON: Yes. Actually, in the old days—just a couple of years ago—you would typically have a fixed cell preparation that you would view under the microscope and you'd take photographs with film, go back to the lab, develop the film and print the pictures.

But today, with the new instrumentation with the really nice state-of-the-art microscope that we have upstairs on the fourth floor, you can now, also with new molecular techniques, actually watch living cells in action with ridges of the cells labeled with this interesting molecule that you can append to your protein of interest, called the green fluorescent protein.

So this little protein tag that you put on the end of your protein that you want to look at, allows you to actually watch that protein in a live cell on this microscope and you can capture images, typically every six seconds or so, and make a little movie and then actually see in real-time what's going on with the cell.

PARK: I'm just curious how this kind of visualization of the movement in the cell helps you to further research. Did you get some insight from those kinds of movies to set up on other kinds of topics?

JULIE DONALDSON: Definitely and I think scientists are always aware, when you are studying your subject, that you're only seeing what you're measuring. Typically, in any kind of an assay, be it biochemical or cellular, you might make measurements at certain time points where you have snapshots of what's going on. Obviously, the more time points, the more variables that you can look at, you'll have a better understanding of your system. That's especially true in cell biology where this new technology has allowed us to—when you see things in real-time, you actually see aspects of the membranes.

I can show you some of them right here that are not so apparent. Some of these membranes that you will see in a live cell actually aren't preserved when you fix them, for example.

PARK: Before showing this movie, could you comment on the technology, when it was available and how fast it is growing that this moment?

JULIE DONALDSON: Yes. I'd say this green fluorescent protein, which really revolutionized the field was first discovered maybe about four or five years ago. So it's fairly recent but cell biologists quickly have taken advantage of it and put it on their protein of interest. Additionally, people are working now on making variance of it so they actually have not only green fluorescent protein but yellow and red so that you can actually now make movies of one cell looking at simultaneously three different molecules in the same cell. You can make a movie with these three images and essentially have an understanding of the interactions between those three molecules. Having said that, we're seeing so much looking at one molecule, looking at our membranes that are affected by ARTH-6.

There's so much to look at from what we've seen in these movies, I'm almost afraid to look at more markers because the story becomes very complex.

PARK: That's great. Could you show us the movie?

JULIE DONALDSON: This first movie is of a … cell, again live, and it's expressing one of these GFP-tagged proteins. In this case, a pH domain of a protein that specifically recognizes a particular polyphosphoinositide pep-2 in the cells.

The important thing for what I'm talking about is that this protein marks, in particular, the membranes that are being regulated; their movements by ARTH-6, which is the ARTH that I've been studying. And if you watch this, this is a cell that's not stimulated so you're just looking at these membranes when ARTH is just kind of turned on but not particularly.

What you see in these cells is that they're roughly now along the edges. Then when you look down here at the bottom of the cell, these are actually internal membrane compartments that label with this marker that are extending out membranes out to the periphery. And you also see a fair amount of ruffling occurring in these cells.

PARK: Explain that?

JULIE DONALDSON: This was just a resting cell expressing this construct. Now if we look at a cell that's expressing a protein that activates ARTH, that turns it on all the time, we'll see something different.

These are the same kind of cells. You're looking at the same membranes, but you'll see that these cells have altered shape. They have a lot of protrusions. These are areas where the cell puts out membrane and there's a lot of acting associated with them.

You also see that the cell is taking up membrane. There are these large, round vacuole-type structures that you'll see coming in from these protrusions as the cell—you'll see it's quite active. So watch the protrusions around the edge and then all of these membranes that are coming into the cell and then disappear at the bottom.

We'll put this guy in motion. Very different looking cell; really active, ruffling at the edge. And look at all these membranes that come into the cell and then kind of disappear down at the bottom.

PARK: Thank you very much. I hope your research is going very well. Thank you.

PARK: This is Room B-103. I'm here with Dr. John Hammer. Thank you very much for having an interview with me. Could you tell us about your educational background and when and how you came to NIH?

JOHN HAMMER: I got my undergraduate degree from the University of Delaware. There I was in the pre-veterinary program and I wanted to be a veterinarian. It's better now but at that time in 1980, if you were from a state that didn't have a veterinary school of its own or a contract with another state that had a vet school, it was almost impossible to get into veterinary school.

So what I decided to do was enter graduate school in Pennsylvania, establish Pennsylvania residency and then apply to the University of Pennsylvania for their veterinary school. Basically, I went to graduate school at Penn State and to medical school in Hershey. And I decided actually then I liked doing science instead of veterinary medicine. So I got my Ph.D. degree in the Department of Physiology at Penn State. When I was looking for post-doctoral positions, I really wanted to do a post-doctoral position in neural biology. So I applied to a lot of neural biology labs and I was accepted at some and I was trying to decide which one to go to. About that time, we had a lecture by Solomon Snyder, who is a very famous neural biologist at Johns Hopkins.

I went up to him after his lecture and introduced myself and asked him if he could give me some advice on where to go. He said, why don't you call me? Right at the same time, I received, or actually my department chairman received, a letter from Dr. Edward Korn, who was looking for post-doctoral fellows to work on acanthamoeba, which I knew nothing about and really wasn't that interested in.

Although a post-doc in the lab said, that's a very good place, you should go there. But anyway, I called Solomon Snyder and I told him my situation and that I also had this offer from Ed Korn. He said, to get post-docs who can do neural biology research like receptor binding acids is very easy; they're a dime a dozen. But what I can't get is post-doctoral fellows who really know how to do protein biochemistry and Ed Korn is a terrific protein biochemist. So why don't you go to Ed Korn's lab and learn protein biochemistry, then you can come to our lab and do neural biology.

So that's how I ended up coming to Ed's lab. I had an interview and he accepted me, so I came to NIH in October of 1980. So I defended my thesis, got married and came here all in that month in 1980.

PARK: At that time, how did you find NIH as a research institution? Is it comparable to an academic atmosphere in the universities or is it just one of the federal agencies?

JOHN HAMMER: NIH has its mixture of oddities that are unique to NIH. But in terms of a place to do basic research, I'm really lucky to be here and I'm really happy to be here. As a post-doc, it's a time when you really learn a tremendous amount. You think you know a lot when you get your Ph.D. but actually you know very little. One of the nice things about being a post-doc here under Ed is he really gave you freedom to show what you can do. You work your problem on your own and basically show what you can do.

The first several years I was here I learned protein biochemistry primarily by working with another post-doctoral fellow who was from a very good lab at Duke and he taught me a tremendous amount. Then what really—one important event in my career here was after I'd been here about four years.

Ed asked me to visit with him and come to his office and talk. He said, tell me what you think you would like to do next? That's a little unusual for Ed because he usually has some idea what he wants you to do next. It just popped into my head at that moment, I said, we're studying all these proteins. Why don't you send me to another lab at NIH where I can learn molecular biology and I will clone the genes for all of these myosins we're studying and then we can express them in *e. coli* and make milligrams of protein in two days instead of in the cauldron for weeks doing our protein purifications from acanthamoeba.

He actually—he sort of stared at me and didn't really answer me. He changed the subject. So, the next day I went into his office and said, I was really serious. Why don't you let me get this training? He then immediately bought into it.

And I ended up for two years in Bruce Patterson's lab in the Cancer Institute just doing very nice work on the regulation of muscle protein gene expression. So I went up there and was able through those two years to clone the genes for a number of the myosins that we were studying in this laboratory.

And then I came back and at that time, shortly after that.

PARK: That was during your post-doctoral years?

JOHN HAMMER: That was the last two years of my post-doctoral fellowship. So in '86, then I got a tenured position here.

PARK: Did you learn your molecular biologist technique primarily on the bench or from the classes or lab chairs?

JOHN HAMMER: The bench. My opinion is most things like this go much better if someone tells you how it works and shows you and you basically go in there and do it. I also like to read method books and integrate what people tell me versus what the books says. But if someone walks up to me and says, this protocol works and here's how you do it, I always go with that rather than tinker with it or change it. Hopkins has some graduate students here and there's a very good Hopkins graduate student named Colin Schmidt, who was actually the bench next to me. And he really taught me about 80% of what I learned up there based on that: giving me protocols and saying, do this, this and this, and then I did it and it worked.

PARK: Up there, did you do your own experiments while learning?

JOHN HAMMER: Oh, yes. That's the beauty of this place, at least as far as I'm concerned. Most people on the outside say, it must be nice not to write grants. And of course, it is but that's—I don't sit around everyday saying, gee, isn't it nice I don't have to write a grant. I don't write them, so I have time to do other things. I don't teach. So what it allows you to do, if you so wish, you don't have to, is work at the bench. I work at the bench 50 hours a week still. It's really what motivates me to work.

I like doing my own experiments but also to create reagents for post-doctoral fellows who come into the labs so they can get a quicker start and get going.

PARK: Do you do a lot of collaborations with other sections in this lab or other laboratories or other people in other institutes?

JOHN HAMMER: Yes. We collaborate a lot with [James] Jim Sellers, who's in the Heart Institute. Then we have a lot of the not formal collaborations but a lot of very good interactions with several other labs who know a lot more about certain things than we do. For example, we have interacted quite a bit with Child Health because they're really one of the best labs in the world in doing TFP imaging, TFP fusion producing living cells so I've learned a lot from her.

That's one of the really nice things about this place is if you want to know something, if you ask around a few people, this place is big enough that there's usually a person in most things you're interested in. Then you just call that person up. It never matters what institute you're in. They don't say, you're in the Heart Institute, I can't talk to you. They just say, come over at 3 o'clock tomorrow, we'll talk. So, I just called a fellow, Paul Randazzo, who's in NCI because he's a very good with working with RAD. And he can help us do a small experiment which is an important control. He just said, all you need is such and such. Come up Thursday afternoon, give me the protein. I'll have the answer on Friday.

PARK: How do you think that that kind of openness throughout the people is possible at NIH? Somebody may say, it's interesting but I don't have time, or I'm too tied up.

JOHN HAMMER: I think that's not the common experience. There have been a few people I've tried to collaborate with who for whatever reason are not interested. They don't find my problem that interesting or don't have the time but by and large that's not the case. People have been eager to interact.

PARK: How about the interactions of the sections within the Laboratory of Cell Biology? Do they interact a lot through Journal Club or any formal or informal discussion?

JOHN HAMMER: Yes. As in everything, there could be more of it but I think there's a fair amount. And certainly, everybody's always—the other sections are always open to talk with you. So in this laboratory, we get a lot of benefit.

Their interests are getting closer and closer to our interests, the interests in my lab. There's a lot more shared technology and they're very insightful. And Julie's been a terrific addition to the lab and she has a lot of experience in things we're getting into which she always shares her information and knowledge. We give her reagents and vice versa.

PARK: Could you describe your current research projects and what's going on in your lab?

JOHN HAMMER: To just give you a small history and fill you in on what we're doing, bringing you to what we're doing now and how we ended up there. When I had gone to the NCI and come back with these genes, the next several years we basically sequenced those genes.

That was back in the day when there weren't companies and sophisticated machines to sequence; we did it all by hand. So we obtained the sequences for these genes. One of the sequences was I think pretty important and that was the sequence of myosin 1. So this was the founding member of these so-called unconventional myosin's. So people had been studying myosin in muscle for 30 years. The organization of muscle and the sarcomere, which is the basic unit of muscle, is pretty well understood. People were just starting to venture into studying myosins in non-muscle cells like in macrophages or neurons. So Ed Korn and Tom Pollard discovered myosin 1, this small, oddball myosin.

Quite frankly, although they had been studying it for almost 10 years, many people didn't believe it was a real gene product. So when we actually cloned the gene for myosin and sequenced it, we really were able to resolve some of the issues about this. First of all, we proved it really was a real gene product. And secondly, that part of it looked like a myosin and part of it was totally different from conventional myosin. And that was consistent with the biochemistry because it had some properties that were myosin-like and other properties that were really unique to it.

That was the first unconventional myosin sequence. The next big change in the lab happened around 1989. We were working on these myosins and acanthamoeba and then [James] Jim Spudich, who was in Stanford, was working on another organism. In that paper, which made the cover of *Science*, in which they showed that you could make gene knockouts. In other words, if you're interested in gene x, you could create a cell line that doesn't make protein x that because gene x is inactivated so it doesn't make protein x.

Of course, this is a powerful molecular genetic tool. One that's been used in yeast along with…of yeast genetics to make that such a great system. So a lot of this interest in proteins involved in cell movement.

I decided to switch,,, because if you wanted to know the function of your protein—of your particular myosin—one of the things you could do using that system is create a modified cell line that doesn't make that myosin and ask what's wrong with the cell. Whether it be behavior or defects. You take that information and other information, such as where does that myosin localize in the cell? What are the biochemical properties of that myosin? What other proteins does that myosin contact?

Then you can build a picture of what this particular myosin does in the cell. That really, in a nutshell, is our main interest in this lab over the last 20 years. We've created lots of different reagents. We analyzed the phenotypes using a variety of cell biological methods and microscopic-based methods. We localized these myosins. We purified some… in biochemistry. We were able to build a relatively nice story about what some of these myosin 1 types, what the function is in this particular cell.

That sort of brings us up to about 1994, '95 and since that time we've basically pursued two questions. One is really a direct outgrowth of the studies I just told you about and that is that we went looking for other proteins which contact myosin 1.

So inside the cell, myosin 1 interacts with actin, its main player, but it also touches other proteins. And we asked, what other proteins does it touch? It turns out to touch another protein nicknamed CARMIL for reasons I won't go into. The CARMIL protein is a scaffold.

And two other things stick to the CARMIL protein besides myosin 1. One is capping protein and the other is yet another complex of protein called the ARTH 2, 3 compounds. To try to simplify this, capping protein is the major terminator of actin assembly.

So inside cells, actin assembles into filaments. The capping protein stops that assembly. ARTH 2,3 complex works at the other end. It's an initiator of actin assembly. ARTH 2, 3 creates new actin fillings. What we have then is a complex we've identified in which myosin 1, our substance we've been studying for 20 years, is attached to a scaffold protein and then attached to the scaffold is a terminator of actin assembly and a nucleator of actin assembly. So this is a pretty interesting complex of proteins.

So right now we're looking at mutants of this CARMIL protein. We're localizing the protein. We've biochemically purified the CARMIL and have been looking at the function of this complex.

The other major effort in the lab involves analysis of the movement of a particular type of organelle within a particular type of vertebrate cell type. The organelle is the melanosome.

This is an organelle which creates pigment and it gives your skin color and your hair color and your eyes color. And the cell type is the melanocyte. The melanocyte is a cell which creates these pigment granules, fills them with pigment and then gives them over to the keratinocyte, which is the major cell type on your skin and hair. It allows you to get a tan. It gives you color. It gives you hair color. We decided to work on melanocytes and melanosome movement because there was a very nice paper published in *Nature* in the early '90s.

These are mouse mutants in which the pigmentation of the hair is abnormal. One of these mutants, called Duluth, was shown to encode a novel type of myosin; another unconventional myosin. A so-called class 5 myosin. This myosin is ubiquitously expressed. There are people studying myosin 5 in all of the major model systems including worms and mice. So we imagined that this myosin played a role in the movement of this pigment granule because mice in which this myosin is missing have defecting pigmentation.

So what we've been doing is basically isolating melanocytes from all of these mutants and asking what's wrong with them. Second, where do the various proteins encoded by these genes localize? Third, how do they interact with each other? Fourth, eventually reconstruct *in vitro* experiments which prove our models about how the movement and position of this organelle is controlled by these genes. So about half the lab is studying melanocytes from these mouse mutants and the other half is studying mutants' melanosomes.

PARK: Could you describe the basic procedures of your experiment just from the start to the end and just before writing the paper?

JOHN HAMMER: Most of our papers we try to combine a number of different disciplines. So it would take quite a long time to explain so just give you sort of an overview. We just recently published a paper in which we showed that the product of the …, which I told you is a novel …, that this RAD actually is in the membrane of the melanosome. And it actually recruits the myosin 5 onto the melanosome. To show that we had to do a number of things. First, we had to isolate the mutant melanocytes from the skin of newborn mice, culture them and characterize them.

Second, we wanted to show that we could rescue the mutant phenotype by reintroducing the missing proteins back into the melanocytes. So we had to clone the genes for the players and then we have to introduce those genes back into the melanocytes by intranuclear microinjection. And then watch what happens to the melanocytes as the phenotype is rescued.

PARK: Could you say a little bit about video microscopy? It's kind of a new term to me.

JOHN HAMMER: Basically, it's using a video camera to watch a particular process in the microscope in time labs. So we use this, for example, to watch the movements of these melanosomes inside the melanocyte under various experimental conditions. And we can also use it to watch the movement of fluorescent molecules inside the melanocyte. So you'll see, if you go upstairs, some of the microscopes we use for this. When we originally set up to do the video microscopy of living melanocytes, we wanted to establish an environment where the melanocytes would be very happy.

So to keep them happy, you've got to keep them at 37 degrees and you've got to keep them in their culture media, where it's possibly being profused with fresh culture media. To keep the sample at 37, the entire microscope is enclosed in a box and the entire microscope is maintained at 37 degrees. To keep the melanocytes in the right buffer, we place them inside very specialized profusion chambers which fit into the microscope so you can watch the cells. And in which we can profuse the media, with CO2 and warm to 37 degrees, through the chamber. That allows us to keep the cells happy and also allows you to, for example, change the conditions.

If you want to introduce an inhibitor, for example, into the media, you can add that to the profusate and the cells would be in the presence of the inhibitor. Then you could wash it out and things like that.

So you'll see that microscope in which it's completely enclosed in 37 degrees and is hooked up to specialized cameras and equipment to record images, either digitally or in an analog fashion. Then for imaging of fluorescents, we use that same microscope but with a different type of camera. And it is a very sensitive camera, which can pick up extremely low light. And we also use the other microscope I'll show you, which is a laser scanning confocal microscope, which is a microscope we purchased for half a million dollars.

And this is a very sophisticated microscope for looking at cells and fluorescents, which has the advantage that the quality of the image is extremely clear because it's a confocal microscope, meaning it only captures the light in a very thin optical section and it removes all of the out of focus fluorescents. So you can create, by optical sectioning, three-dimensional images. You could reconstruct digitally

three-dimensional images of the movement of fluorescent molecules inside the cell using this microscope.

PARK: Before closing out our interview I'd like to ask you about kind of trends in science, particular at NIH in the 1980s and 1990s and the new century. Is there any particular changes in terms of atmosphere in the scientific community in general?

JOHN HAMMER: I think a lot would depend on each individual scientist. That's the overriding thing that determines peoples' happiness in this business and things now are going extremely well. I really see—I really feel like with the tools we've created and the techniques we've mastered, we really can resolve a lot of basic questions about how melanosomes are transported and distributed inside pigment cells.

Although we are a basic science lab, that has important medical indications. As the ozone layer disappears and more and more people get skin cancer, if we can understand the molecular basis of the movement of these pigments, we may be able to make a lotion which gives you an instant tan and reduces your re-incidence of skin cancer by tenfold or something.

So things are going really well in our science. I guess I would say, in terms of trends, I could say a couple of things. One is that at least so far, the ability to do basic research that has no obvious medical application has been protected, at least in this institute. I don't think that's the case in some other institutes. I think there's been a lot more pressure to do things that have medical relevance. And in other institutions also there is more pressure to do projects that are more closely aligned with the mission of the institute. Some of my friends in the Hearing and Deafness Institute, they really have to work on something related to hearing and deafness. I'm working on melanocytes. What does that have to do with heart, lungs, and blood?

I've been allowed the freedom to pursue my interests and I think as far as I'm concerned, that's a really great freedom and it's really been fun. The second thing is the bureaucracy here is much worse than it was when I first came. Every year it's more and more complicated, it's more and more difficult to deal with. I guess this is the way the government works. But a typical example is travel. We're not supposed to collect honorarium because—although I'm not probably correct on all my facts. Because Congress is not allowed to collect a $25,000 honorarium, we can't collect a $150 honorarium. But because someone in the government was worried that a few scientists might grab $150 under the table, they then removed from the scientist the ability to arrange his travel directly. Cornell wants me to come and give a talk. I cannot work with Cornell. What the government did was institute what must be a really big bureaucracy to control my travel. So in other words, I cannot receive any money directly from Cornell, even for reimbursement of my travel expense. It first must go to NIH then NIH gives it to me. As far as I'm concerned, this was totally dumb because a few people were getting a few $150 honoraria. To me it's just a huge waste of time and money but this is the way it works.

So there's that. But overall, the atmosphere here has improved tremendously with his [unclear who he is referring to] just being who he was and with his institution of interest groups. I think there was an enormous improvement in this place over his tenure here versus what was going on before.

And I think most people who are in science right now can't be anything but happy. There's so many great tools now that didn't exist. When I started cloning, you can't send your DNA to get sequenced. There was no PCR machine to generate your DNA in three hours where it used to take weeks of complicated work. There was no GFP to image your proteins in the living cell. There was no genome sequence. There was no mass spec sequencing and now you can identify protein players very easily. So it seems to me if people are griping about science right now I couldn't understand it because right now it's a great time.

The competition's bad. Everything we do we're worried about getting screwed but that's business.

PARK: Do you expect that the technology and the knowledge from the human genome project may or may not affect your research?

JOHN HAMMER: Absolutely. It's going to permeate all aspects of clinical and basic biology. We're maybe slightly more interested in getting the mouse sequence done because we've worked with mice in our own system. But I think you can't estimate how important it's going to be. It's going to affect people's work at various levels. Not only things that are directly obvious like mapping disease genes and things like that but even if, for example, we identified this CARMIL protein.

But in order to make it more generally interesting, we'd like to show that it exists in a higher organism. So we find it in the EST database for mouse and human and that's simply—15 years ago we'd have to go searching for it. We'd have to do probes and screen libraries and spend months doing that. Now you just type it in the EST database, plug your sequence in and two seconds later you get matches. You call up research genetics and for $35 you get the EST and you're in business.

And of course, sometimes EST is a partial clone but when the genomes are fully sequenced, you'll have the whole thing in five minutes on the computer. So it'll benefit this lab a lot.

PARK: That's great. Thank you very much for your interview.

PARK: This is Room 413. I'm here with Dr. James Ferretti, the Section Chief of Structure Biophysics of the Laboratory of Biophysical Chemistry. Thank you for having an interview with me. I'd like to start our talk with your educational background and when and how you came to NIH and a little bit of a description of NIH at that time.

JAMES FERRETTI: I got my Ph.D. from the Chemistry Department at the University of California at Berkeley in August of 1965. I then did a post-doctoral fellowship in Europe for a little bit over one year. Then I came to the National Institutes of Health starting about October of 1966. I was originally in what was then known as the Division of Computer Research and Technology. It's now known as CIT. I don't know what the initials stand for. I moved to the National Heart, Lung, and Blood Institute around the

period 1981-1982. It was around the end of the year and I don't remember actually when all of the paperwork was formalized. But since that particular time, I've been in this particular institute. Not originally in Building 3 but originally in Building 10.

I'm actually one of the senior people here. I'm the newcomer in Building 3. I've been here since approximately the end of 1989, the middle of 1990. It's not that I don't know, it's just that the move occurred over a period of months when we moved in our equipment and then we moved our whole lab over here, then the lab moved to its new spot and grew to its current size.

PARK: What kind of research did you do at DCRT?

JAMES FERRETTI: I did many of the same things that I'm doing now. The only difference is that we never really had formally our own laboratory. I did work in collaboration with people in other institutes. I did NMR [nuclear magnetic resonance] spectroscopy, trying to understand the stability of peptide structures initially, long peptide structures, order/disorder transitions in peptides.

Then we switched to proteins when I moved over to the Heart Institute and became really significantly interested in the three-dimensional structures of moderate to large-sized proteins starting in about 1989-1990.

PARK: At DCRT you did a lot of a collaboration with scientists in other --

JAMES FERRETTI: That's correct. Because as I said, we didn't have our own individual laboratories so it was a question of finding a home where we could do some experimental work. Later I established a strong collaboration with the people in what was then called the Laboratory of Chemistry in the Heart, Lung, and Blood Institute. They ultimately invited me to move over and physically work in that laboratory. It didn't change anything that I was doing but I formally became attached to that laboratory for administrative purposes. It was nothing profound about that move.

PARK: What do you think of the characteristics of NIH as a research institution as compared with other places like universities or industrial labs or other federal labs?

JAMES FERRETTI: I'm probably the worst person in the world to ask that since I've spent essentially my entire career here at the National Institutes of Health. I remember what life was like when I was a graduate student back at Berkeley and when I was a post-doctoral fellow. But I really have no basis for comparison of a real professional life since I spent it here. I have traveled extensively and visited universities in many countries, including Korea. I would say that the intellectual atmosphere around here is fairly stimulating.

The environment, in terms of work atmosphere, is collegial and pleasant. I can't really make any comparison to other places; certainly not to industrial positions because I have no experience. I know what some of my former post-doctoral fellows have told me about their lives in other the government labs and industry. I would say that NIH compares quite favorably. There are a lot of very, very smart people around this campus and it's a very stimulating intellectual environment. Perhaps one that is unique in many respects. So I, in many ways, feel very, very privileged to have the chance to spend so many years here.

PARK: As a section chief, are you involved in many administrative works?

JAMES FERRETTI: No, I would say that my total administrative responsibilities might take me 15 minutes a week, 20 minutes a week. That doesn't include discussing science with the individual investigators. I'm in the lab myself but I spend a lot of time talking over their research projects with them. And trying to give them, as best I can, some advice. But I don't consider that an administrative responsibility. I consider that a training responsibility that's part of my scientific research.

PARK: Could you comment on the size of your lab or your section? How many post-docs?

JAMES FERRETTI: The number varies but the last time I counted I think the total number of people that we formally had attached to the section was of the order of 13 and continuing to grow. I have a tenured track fellow who is actually going in front of the tenure committee this afternoon in about 20 minutes. He has his own separate research group which is part of my section. That number that I quoted, 13, includes five people, including himself, from his research group and my research group, including my secretary, might consist of roughly seven or eight people. It's likely to grow a little bit in six months or a year.

PARK: Do you have any group meetings or weekly meetings?

JAMES FERRETTI: We have typically seminars once a week. I must admit we're not formally religious about having them every week, but we have them on a fairly regular basis. I would say two to three out of every four weeks we have a meeting. When there's an invited speaker and only on the occasions when I have something specific to tell people and I want everybody together do I call a formal meeting. That doesn't happen all that often. It's mostly for seminars and other sorts of research opportunities that we get together.

PARK: Could you describe your current research projects in terms of research procedures and the instruments you are using and the goals?

JAMES FERRETTI: My current research is in the area of the three-dimensional structures of proteins, both in their free and in their DNA-bound states. More specifically, the research that I am really interested in has to do with single amino acid residue replacements that occur in these proteins.

And to be again more specific, ones that are related to congenital heart disease. It involves a specific protein where these single amino acid residue replacements do result in congenital heart deformations. What we are trying to do, in detail, is to understand the molecular basis of the disease by understanding how the three-dimensional structure of the protein is modified. Or how the ability of the protein to re-target its receptor, it happens to be a DNA molecule, is modified by those changes on those individual amino acid residues. What is involved is that we must make the proteins express, synthesize the proteins, and make the modifications of the relevant DNA to make the modified proteins.

This is all done in the laboratory that you see right around here or in another laboratory across the hall. Then we go downstairs to our nuclear magnetic resonance spectrometers where we acquire all of the data that is necessary to provide us the information to determine the three-dimensional structure.

Once we have that data, which takes two or three months to acquire, we sit at our workstations for the next six months to a year translating all of that data into the real three-dimensional structure of the molecule. Or more appropriately, the three-dimensional structure of the molecule and the modifications to the three-dimensional structure of the molecule that occur when those individual amino acid residues have been modified. We're also in collaboration with Marshall Nirenberg up in Building 36 doing some transgenic experiments.

We tried to see what happens if we introduce very specific mutations in very specific positions of a given gene and see whether it is viable for life. But the similarities in terms of these particular proteins is really rather shocking. They're families of proteins that are preserved across all species throughout evolution. So it's a very, very interesting class of proteins.

PARK: What kind of NMR do you use? The maker and the power and things like that?

JAMES FERRETTI: We have a total of four spectrometers in our laboratory. They range from 800 MHz down to 360 MHz. They're all manufactured by the Bruker Instruments Corporation of Billerica, Massachusetts.

We intend, probably in the next two or three years when it's really commercially available, to buy a 900 MHz spectrometer; 800 being the highest frequency which is currently available commercially and we have one of those. And we are in fact going to take delivery of a second one probably before the end of this current calendar year.

PARK: That's quite impressive. How do you select your post-doctoral fellows? Do you have many applications around the world?

JAMES FERRETTI: That's always a very hard question to answer. Information about them comes by word of mouth. I receive letters and then I make inquiries. Or in some cases I've gone out and solicited applications from individual scientists with whom I am acquainted. So it varies. The last two post-doctoral fellows that I have acquired actually came from Korea and were recommended to me by people that I know there.

PARK: So kind of informal and formal channels.

JAMES FERRETTI: That's right. The important feature is to get the most qualified ones possible and that takes some effort sometimes.

PARK: Final question, once you move to Building 50, how long does it take to get started over again?

JAMES FERRETTI: Probably much longer than I would hope it would take. The laboratory I'm anticipating will be up and running—the upstairs part, the Molecular Biology Laboratory—I'm anticipating will be up and running almost immediately.

The spectrometers, of which we will have four down in the sub-basement—there will be a total of eight—I don't know. Just the logistics of moving them from this building and the other buildings, in the case of the other scientists, is a real logistic nightmare.

I'm hoping that the physical moves will be completed by the end of April and that sometime in the middle of May the spectrometers will be up. Will they be running? Will they be functional? That's a totally separate question. I would like to believe that sometime around the first of June we will be acquiring data again but that may be somewhat optimistic.

PARK: Thank you very much.

PARK: This is the fourth floor of Building 3. It is really a pleasure for me to talk with Dr. Robert Berger who used to be the chief of the section on biophysical instrumentation of the Laboratory of Biophysical Chemistry. It's really a pleasure to see you. Could you talk about when you came to NIH and when you joined the group in Building 3?

ROBERT BERGER: Yes. I came first in 1962. At that time, it was the Laboratory of Technical Development. We were over on the fifth floor of Building 10. In 1989, when the laboratory was closed, Dr. Ferretti and I were moved over here to Building 3 and we were a part of Dr. [Henry] Fales laboratory.

Originally the Laboratory of Chemistry and renamed the Laboratory of Biophysical Chemistry. As the Technology Development Officer in the Heart Institute, I managed to get them to give me an office up here where Dr. Ferretti is now.

When we first came up here this was pretty much a storage area. There had been animal surgery here and that was all moved to Building 14. So, this was a nearly empty hallway. Dr. Ferretti occupied most of it; I just had my office up here. He made this his computer room, in which all of the structural work on the computer is done. These were offices along here for his post-doctoral people. This laboratory across the hall became the protein physicist group because the start of all of this was the idea to be able to do protein structure by NMR.

The first protein they were looking at had to do with HIV. Along in there Dr. Marshall Nirenberg started getting interested in using NMR to follow some of the reactions that he was interested in.

The poster down there on the wall explains one of the very interesting uses of work that Dr. Ferretti and Dr. Nirenberg did together. I used to enjoy walking out of my office and seeing this Nobel Prize winner and Dr. Ferretti bending over the table plotting where all of the molecules went.

PARK: When was that time?

ROBERT BERGER: This was about 1990-1991. I was here until 1994 and then I went on a special detail work at Walter Reed. So, there isn't much more to say about this lab. It's still being used for a variety of people. Dr. Ferretti has some preparations laboratories. His machines are all down in the B2 level, but he has to do the chemical preparations for the high-resolution NMR up here. Then the rest of the area is mainly storage.

PARK: Thank you.

UNKNOWN SPEAKER: This is a good example of the work that Dr. Nirenberg and Dr. Ferretti have done. These various structures that you see here are the things that mathematicians have to do to build up … as they want to express after they have done the NMR to determine the positions for these various mutants.

On this floor the laboratories are divided up between various of the laboratories in the building. These labs along here are a part of Boon Chock's Laboratory of Biochemistry. This is a tissue fermentation unit; those techniques have become extremely important in the advanced record of biology.

These are facilities that are used by anyone who needs to sterilize their materials, sterilize their equipment. As you can see, the instrument is used by anyone who needs one. They have to sign up to use it. We try to have as many shared facilities as possible.

As you go down, you'll see other laboratories and a large part of the rest of this floor is that of the Laboratory of Cell Biology. One of the important features of cell biology today is what's called ultra-structure. That is the detailed structural biology of the cell membrane and the cell structure itself.

These laboratories along here deal with the preparation of the samples which will then go to either the confocal microscopes or the electron microscopes. We can walk on down now and while we're touring we'll see mainly laboratories in which the various preparations, clinical identification and so forth is carried out. This is mainly done by post-doctoral students with a few tenured employees who are the senior investigators. I think the sign over here makes it very clear, although this is supposed to be the biochemistry laboratory. All of this is part of that.

On the end down here in the last laboratory is Dr. Korn's electron microscopy room. That has been one of the mainstays of Dr. Korn's ultra-structure program for the last 30 or 35 years.

This is all about the third floor of Building 3, which was shared by all the laboratories in the building.

ANNE GINSBERG: My name is Anne Ginsberg . I came to this laboratory about 1968. I'm head of the section on protein chemistry and I presently have three post-doctorates, whom you'll meet, Drs. Gregory Piszczek, Martin Gonzalez, and Maria Dimitrova.

The office you're standing in has been remodeled about five years ago, but it originally was the area that Roy Vagelos was in because I came to this laboratory when Roy left. Roy later became president of Merck so most people know him.

These are some laboratory photographs. Also, some family mixed in there. This is the president of Israel, Ephraim Katzir, when we went to visit Israel in the '70s, I believe. This is some electron micrographs of a large enzyme we worked on for many years, glutamine synthetase. This shows time shots of the stacking reaction. You see some more electron micrographs there. Presently we're working on different problems in protein folding and refolding and homeodomain protein binding to DNA.

This is a Jasco CD we're measuring for UV CD measurements to monitor changes in secondary structure that we induce with heat. You can also monitor tertiary structure with that instrument.

All of the instruments are connected to computers. This is a photometer we use for fluorescence measurements and we can also follow intrinsic … residue exposure during unfolding reactions.

If we move here, this is our original differential scanning calorimeter and you can see the size of this compared to the one you just saw. Advances in technology. This is also a sensitive differential scanning calorimeter called the nano-DOC, which has a different cell design and is useful for certain purposes.

Let me introduce Martin Gonzalez of Argentina. He's been here for two, almost three years.

He is actually working on protein DNA interactions and he's getting help with his computer. That's our help desk for the computer malfunction. So now we're coming out of that room. This is our lab bench working area and this is Dr. Gregory Piszczek. He's from Poland and he's been with us about six months or so. Four months. Now we'll move out to the hall, I guess, coming out of Room 212. My office was in 208. Now we're moving to 206. To the right is our room for preparations. That's our preparative centrifuge there.

This is Dr. Marianna Dimitrova, who's from Bulgaria and studied in Japan and then came to this laboratory about a year ago. She's been working on several different proteins and enzyme 1 and the sugar transferring system.

And we're looking at protein folding and long-range reactions in that molecule and stability. We have an HPLC unit here as do a number of laboratories here. It's for separation of molecules. We have an older ITC unit, isothermal titration unit.

And you saw the newest one next door in 212 and you can also see the reduction in size due to the technology of the chips.

PARK: Today is March 7, 2001. Here is Room B-208. I'm here with Ms. Mary C. Richardson. Good morning. Thanks for having an interview with me. Could you tell me about your educational background and when you came to NIH and how you came to NIH?

MARY RICHARDSON: I was working at the House Office Building; I started there in 1966. I transferred in 1969 to NIH. I came under the interview of Dr. Earl Stadtman and Terry Stadtman. When I came here, I had a high school education.

In '79, I lost my mother and I went home, and Dr. Poston put my name in a lottery. At that time, it was giving minorities a chance for education. When I came back, I was selected to be in the school. I received a B.S. degree in Science.

PARK: In what school?

MARY RICHARDSON: It was Federal City College but then it became University of DC. That's what it is now.

PARK: Could you describe your job and the job title?

MARY RICHARDSON: The job title is Laboratory Technician. I select the glassware. I bring the glassware back down here for sterilization and washing.

PARK: At what time during the day?

MARY RICHARDSON: I get here very early in the morning. I get here around 6 o'clock and that way I'm out of everybody's way. So, I make sure when they come in their glassware and laboratories are clean and this is where I start. At first, I had a room upstairs but then I was moved down here.

First of all, getting back to that, before I started bringing the glassware into the room, when I came here, I was doing the glassware in each and everybody's room and I would get here early also and try to get out of everybody's way. But that was kind of difficult. Then Dr. Stadtman [set aside a washing room] and then that way I went to everybody's room and selected all the glassware and brought the glassware back into the room and washed the glassware.

PARK: When was it that time you were having your own lab?

MARY RICHARDSON: I guess about 20 years ago, at least 25. It wasn't too long after I came here so I've been here about 30. So, it wasn't too long after that. We had two people working at that time.

PARK: These days there are many disposable things and how does the use of disposable apparatuses affect your job? Does the workload diminish?

MARY RICHARDSON: When the disposable—a lot of disposable came in that's when one person went to another place to work and they kept me. But anyway, I was kept. We used to have a lot of tubes to wash and now we don't have a lot of tubes. Sometimes we have a lot of glassware, sometimes we don't. But we have a heavy load most of the time. But by getting here early and getting out of the way, I have time to set it up to know exactly what I'm going to do in that room.

PARK: How was your relationship with scientists? Is it a very close relationship? Being invited to the parties and other places in the building?

MARY RICHARDSON: The relationships with the scientists are great. Dr. Stadtman and them never refused you from going anywhere. I always was included even if I didn't go. They always have asked me to go places and to do things. We have picnics together even now and parties and so forth.

It's like a family. And I know when I came here my name was Mary Lou Corby. During that time, I got married in '79 and to tell you how close it was, the majority of them came to my wedding. The ones that didn't come, they also brought me a lovely gift. So, we are very, very close. You couldn't be any closer than them. They always talk to you. They're always doing things. So, it's very, very close. They have birthdays upstairs and they always tell you to come upstairs to join in. So everybody's very, very close.

PARK: When you came to Building 3 in 1969, were there many African-Americans working here?

MARY RICHARDSON: Yes, there was quite a few working here. I can't remember all of the names, but I know there was Joe Davis. There was Clarence Slaughter. There was Henry, Maurice Miles. There was another one that's in Baltimore right now; I talked to him not too long ago. But I can't think of his name. There was quite a few who was here who came in.

PARK: These days I could see many Asian scientists working in various labs. When did that happen—many, many Asians coming into the laboratories of this building?

MARY RICHARDSON: I think they've been coming all the time but in the last five or six years you probably have more now than you had before. They've been coming in quite often because ever since I have been here, I have had all types of people that I have worked with.

PARK: Do you have any memories or anecdotes to share with me; interesting memories that show the atmosphere of this building and the relationship of its scientists and the people?

MARY RICHARDSON: I'm going to miss this building for one thing because I really have enjoyed working here. Memories, there were so many people that came in here. I often—there was one doctor here, Dr. [Stanley] Prusiner, he's a Nobel Prize winner. I used to enjoy coming in and talking to him in the morning. We used to get a kick out of talking but I think he may probably have forgotten those days now. I used to really come here and we used to have a good time early in the morning. He was one of those early people that came.

PARK: So you must be very excited about the news that he got a Nobel Prize.

MARY RICHARDSON: Yes, it was him and also there was another one that I was excited about. I don't know whether he remembers me now but Dr. Mike Brown. Those two I remember very much when they both were working here.

PARK: Thank you very much. Could you show us how you do your daily job and how you are paying particular attention to something toxic or acidic?

MARY RICHARDSON: Yes. This is the machine that I'm working with. This is an old, old machine but it's very reliable and I love it very much. The reason it's making this noise now, it needs some repair on it. But we're moving to another building, so I thought it wasn't ready to have the repair did because we're not taking it over there.

When I go up in the morning and pick up the glassware—these are dirty glassware over here. I take the dirty glassware and I put it on the machine. The ones that are cleanable, I put it in. Some of them have something in it so therefore I have to wash it in the pan and then put it on the machine.

After the glassware is washed, I put it in pans like this with towels in it and then I take it upstairs; they are dried. I used to put them in the oven, but our oven broke down as well so now they're hand dried. Some glassware, if that can't be cleaned after they come out of the machine and so forth, there's an acid. We have some acid here. I use this acid to clean the glassware with. Once I take these out of the acid, I rinse it with water.

After I rinse it with water, I put it in this rinse right here and therefore I let it stay in here for about five or six hours. After I take it out of this rinse here, I use this distilled water with this container. I go over here and I put it with this distilled water and this is the final rinse for the glassware.

PARK: This is Room 106. I'm here with Dr. Rodney Levine and I thank you very much for having an interview with me. I would like to ask you first about your educational background and when and how you came to NIH.

RODNEY LEVINE: I think I would start by mentioning that I went to public schools in Denver, Colorado. That is important because that's clear in my mind that it's where my interest in science was being stimulated. I had superb teachers in a variety of subjects but certainly I remember in particular many of them were in science.

That led me to head a little further west from Denver going to undergraduate at Stanford University where I got my bachelor's degree in Biology and also a bachelor's in Chemistry. At that point I had to decide whether I wanted to pursue this interest in science by going into a Ph.D. program or going to medical school.

But at that time Stanford was quite unusual which made my decision rather easy because the medical school itself had a great emphasis on research. In fact, the program was not the traditional four years, but five years and one was expected to spend at least that long in something other than medicine, such as research.

So, I did enter Stanford Medical School. I ended up never having to make the decision because I obtained both M.D. and Ph.D. there. I went on to the University of Colorado Medical Center and took residency training in Pediatrics and then subsequently a sub-specialty.

I'm still on the Board of Pediatricians. I began in the Department of Pediatrics doing independent research at that time and was quite hooked on it. But I recognized that I needed to experience additional training and I wanted it to be as rigorous as it was possible.

And that's something that I've known even while I was at Stanford. So, both at Stanford and at Colorado it was clear that the place to come for that sort of rigorous training was NIH. When I discussed with my mentors where at NIH, one name kept coming up again and again and that was Earl Stadtman. If you want to learn biochemistry that's where you go and that's what brought me here in 1977.

PARK: 1977. So you came to Dr. Earl Stadtman's lab as a post-doctoral fellow?

RODNEY LEVINE: Yes.

PARK: In what subject did you work?

RODNEY LEVINE: At that time, he was heavily focused on studies of the mechanism by which cells regulate their cellular metabolism and the model system which he studied was glutamine synthetase. However, his interests were broadening and one that he was becoming interested in was: How do cells regulate the level of protein, not simply by how quickly they make it, but how quickly they dispose of it—protein turnover, protein regulation? I had become interested in that as well from my focuses in pediatrics and developmental biology. So, the initial project was to try to look at the simple system which might be able to dissect out the mechanisms by which cells degrade specific proteins.

PARK: You continue on that?

RODNEY LEVINE: That actually, as often happens, led down an unexpected pathway. As we began to look at this mechanism for *e. coli* bacteria, we found that there appeared to be two steps. The first step seemed to mark the protein for the subsequent degradation.

And the second step was the actual garbage disposal, if you will. That first step required oxygen and after a fair bit of time and effort, we were able to show that this was actually … modification. It was actually a physical and chemical change in the protein that led to its modification.

That in turn has opened up an entire area of study that the Laboratory of Biochemistry is focused on and I remain today very interested in the significance of oxygen modification in proteins.

PARK: Could you comment on Dr. Stadtman's mentoring style or his style of managing his lab or training his post-docs and the relationship within the lab?

RODNEY LEVINE: I can comment on a couple of those. First of all, I suspect—I will say specifically, you will hear from many other people because he's very well-known for the approach he takes to mentoring. Once when he was asked about this, his comment was, I try to get good people and then I leave them alone. It wasn't quite that simple, but I think you understand that his point is that if we try to guide bright people too closely then you and an advancement in science are the losers. So, he's always immediately available. One never has had to make an appointment to see Earl Stadtman. You simply walk in when you have something to discuss and talk about it or you talk about it when you meet in the hall or over lunch. The second thing I would say in response to your question on his mentoring is that it was clear in my mind that I was coming to NIH for two years, a maximum of three. After which I was returning to a position that was very attractive to me at Stanford. But that was 24 years ago.

PARK: So you stayed here primarily because of Dr. Stadtman's influence.

RODNEY LEVINE: And the environment he created, absolutely.

PARK: Since you came to NIH in 1977, NIH grew a lot and there are many other labs established on this campus and the institute has grown and the number of people has grown a lot. Could you comment on the changes, especially in terms of the atmosphere for research? In the '80s and in the '90s and currently, what's the major changes, if there is any?

RODNEY LEVINE: I can think of several that come to mind without reflecting too much on it. First, one thing that hasn't changed when you look around is the tradition at NIH of utterly cramped quarters. In fact, many people would say that this is fairly roomy by NIH standards.

When people come to visit us from universities in the United States and abroad, if they've never been to NIH, we know that they're going to be shocked when they come in the laboratories because the quality and impact of science from NIH is recognized around the world. So, they're more than surprised to discover that we work in very cramped quarters. I think that perhaps it's considered a badge of honor by some. I don't know about that, but it clearly does work; that hasn't changed. Indeed, the NIH has grown.

One thing that has changed is that the administrative support bureaucracy—not using that in a negative sense—has become less attuned to the purpose of NIH. I think it's quite evident to me that it is much more difficult to accomplish things at NIH now to get our science done. And this is because of the increase in the layers of the administrative burden and the lack of recognition of those people who are important to us for that support; that our purpose is to do biomedical research. So obviously that's a negative that has occurred.

But the positive is that we continue to have, through the support of Congress and senior people at NIH, superb support for cutting-edge biomedical research. Importantly, what has continued is that senior

scientists within NIH continue to support long-term projects that are very difficult to accomplish elsewhere.

PARK: Could you comment on the size of your lab, your section? How many post-docs and how many assistants?

RODNEY LEVINE: I have a relatively small group. I generally have two or three post-doctoral fellows and a fourth one who's visiting, and a person supported outside of NIH, and one technician.

PARK: I could see oftentimes you are working on the bench. Is that common to other section chiefs or is a section chief primarily writing papers and the post-docs are providing data?

RODNEY LEVINE: That varies a lot at NIH. One of the things that I really do enjoy is just what you observed. I continue to work on the bench. If I have been spending a fairly long stretch at my desk writing manuscripts and revising them, doing letters of recommendations, what have you, I find that after a certain period of time—and it's not that many days—I simply have to put down my pen or my keyboard or my mouse and go to the bench so that I can feel happy again about working here.

It's always amusing at meetings to be chatting with graduate students and post-docs who assume that those of us at NIH must be in a similar setting and they find it remarkable that indeed we can discuss the nitty gritty techniques that they're doing just as we are. Many of us who choose that obviously do it because we enjoy it.

PARK: Have you not thought about the possibility of going to the university and having a much bigger lab and expanding your research areas and kind of building your empire?

RODNEY LEVINE: Yes, and I think like most people at NIH who are successful, I have had offers from universities to do just that. A good friend of mine convinced me to come look at a such position a few months ago, even though I wasn't particularly interested in the moving, and it was a wonderful offer. But still, I wasn't thinking that it could change my ability to do science—that, I think, matters—and to enjoy it while I'm here.

PARK: Thank you very much and could you show us kind of a demonstration of a standard procedure of your experiments for say seventh grade students?

RODNEY LEVINE: I can try. I'd probably like to add hopefully there aren't too many standard procedures in our work because one of things I like to stress to the folks who work with me is that in the limited amount of time we have to do research, let's try to do things that other people haven't done rather than simply reproducing it in a slightly different system. If someone has done it on an animal tissue culture but I'd rather start with something different. Overall, I hope that there aren't too many standard things but of course I know what you mean; there's certain standard techniques.

Right in front of us—and this wasn't planned, it's here from an experiment done by my colleague, Yung Su Kim—are a number of tubes which were collected during the course of attempting to separate proteins of different sizes so that we could have a pure protein to study.

In order to find where that protein is, we need to look at its spectrum; really at its snapshot or portrait. If we look at some of these tubes which happen to be sitting right here, you'll notice that they have color. So, you can see one looks pink and then blue and then they become colorless. They're not really colorless in the other tubes but of course our eye can only see in a certain range. So, we can see this color. We can't see down in the ultraviolet. And that's where proteins will show their color, so to speak.

So, we like to take the spectrum of these various fractions and that's what our research is in the process of doing. I don't think you're going to be able to see it given where we're standing but there is an instrument here called a spectrophotometer, which is what we actually use to make this determination. It's effectively a camera like the one that's being used to record this discussion. So, we will go through all of these tubes, fractions we call them, and determine by taking the spectrum or the portrait of the contents where the proteins of interest have come off so you can study them.

It's easier to show you if I take this first color tube and we need to transfer it to a special cell called a cuvette. That's then placed in this instrument.

One wonderful thing about NIH is that we have, in general, excellent support for buying instrumentation. It really extends our ability to do studies with fewer people. We have a lot of new, modern instrumentation. I have lots of salespeople come through trying to sell me a new, modern instrument to replace this one because this was actually purchased in 1980.

But it's still, in my mind, the best instrument available for the purpose and that's why we do everything we can to nurse this along. It works beautifully and we're hoping we get another 20 years out of it. So, it has an ancient, primitive computer built into it that works beautifully.

And I simply press the button that says measure and for how long and execute and it's going to be difficult for you to see but I can see on the screen that I have a picture of a pink compound. I would then go through each one of these fractions and record it and save it on old floppy [computer] disks.

But actually, this was a new innovation. We used to use string and tape…. Then having done that, we can print it out to study it again on what, at the time, was a pretty impressive instrument. It actually was a color plotter. And color's important so we can distinguish the differences that exist. So, the computer that's controlling this would plot out the spectrum or the portrait, which I can then examine and study and that's precisely how we would find the fractions which contain the protein of interest.

PARK: That's great. And could you say a little bit about your very current project and its importance?

RODNEY LEVINE: It actually comes back to what I started to mention to you and in the interest of focus in how cells regulate the disposal of proteins which they no longer need or must rid themselves of because their metabolic needs have changed.

In collaboration with people here at NIH, particularly Tracey Roualt in the Child Health Institute, we're focusing on the mechanism by which cells regulate their iron metabolism. There's a key protein which coordinates this regulation called iron regulatory protein 2.

What we've been able to show is that it is indeed an oxidation of that protein which allows the cell to recognize that it needs to be removed. So, under conditions of sufficient iron, the protein is susceptible to oxidation. As soon as it's oxidized, the machinery recognizes that it has changed shape and sends it to the garbage disposal system. And that's one area that we're focusing on. In addition, we're looking at other types of oxidation of proteins to try to determine their significance in cellular metabolism.

PARK: That's great. Thank you very much.

PARK: This is Room 311. This room used to be used as an animal surgery room. The first pacemaker was implanted for animals in this room. But it was renovated for the laboratory of Dr. Boon Chock who is currently the Chief of the Laboratory of Biochemistry.

Thank you very much, Dr. Chock, for having an interview with me. I'd like to start with asking you about your educational background and when and how you came to NIH.

BOON CHOCK: I'm a chemist by training. I received by Ph.D. in Chemistry from the University of Chicago. Afterwards I went to Germany to do my post-doctoral work in biophysical chemistry. I worked with Dr. Manfred Eigen. He was a 1967 Nobel Laureate.

PARK: And when you came to NIH?

BOON CHOCK: I came to NIH—before that I heard something about NIH as a graduate student, particularly the work of Marshall Nirenberg on solving the genetic code. When I was in Germany, I was not thinking about coming to NIH at the time because I had a job interview at Argonne National Labs at the University of Pennsylvania.

However, in the summer of 1970, I was going to England with Eigen for a meeting. So, I had told him that I would be going to the states for a job interview and Eigen told me, there's the guy by the name of Earl Stadtman at NIH who wants to interview you for a job in his lab. Being a chemist, not knowing much about biochemistry, I said, who? He assured me that Earl Stadtman is an excellent biochemist and also the biochemists in the laboratory also told me about Earl's work. So, I applied for the job.

At the time, I think Earl was interviewing for somebody to take the place of Bennett Shapiro, who left his lab to go be a professor at the Biochemistry Department at Washington University in Seattle.

I came to the interview that summer and I remember after my talk with him, I told Earl that I'm going to Chicago for an interview with Argonne National Lab. They tried to offer me a position. Earl had told me, he had said, don't accept the job until I talk with you. So, he asked me to call him before leaving Chicago. After the interview I called Earl and Earl told me that the position is mine so if I'm ready to—he hoped that I would take it. So, I thought everything was settled. I went back to Germany to wait for months and never heard a single word from NIH.

So, by about November, I thought, I'm giving up with NIH so I tried to contact my other offers. Suddenly, the mail came from NIH, one after another, so it was back to here. So, I came here in 1971.

PARK: What subjects did you start working on?

BOON CHOCK: As a person who's interested in mechanism and genetics, I was trying to solve the ,,, catalytic cycle from the mechanism point of view. So that was my project.

PARK: In the beginning, you mentioned that you are a chemist and having not much background in biology. Was that a very—did you have any difficulties in working with the biochemists or biology-oriented scientists?

BOON CHOCK: Not at all, actually. I think everything went very smoothly and also, I had a lot of help and a lot of the people in the lab are extremely helpful. In particular Earl Stadtman spent a lot of time with me. I also got help learning to set up the instruments and to take care of our own instruments.

I remember when I was in Germany, we'd heard about the work of Robert Berger, he could measure a very fast reaction. He was very helpful as well to set up our system. It allowed us to measure the … low millisecond range.

PARK: Could you tell me a little bit about the work on the glutamine synthetase cascade and what part you contributed to and how things? Many years have been spent on that project and how things were progressing step by step.

BOON CHOCK: Actually, when I came here as a biophysical kineticist, it reminded me of at the time there were not much computer facilities. I [asked] is there any computer I can use for compilation? Stan told me, he said, computer? You must be kidding. So, all his compilations is done with a slide rule he's hiding in this drawer.

[Inaudible section.] Earl and I thought differently so we built a model, we finally formulated the model and revealed the cyclic cascade; how cyclic cascade mechanism works and the advantage of it.

PARK: Could you continue?

BOON CHOCK: Based on the work we had done on the modification of glutamine synthetase regulation, we formulated a cyclic cascade model to try to think of why nature would adopt such a regulatory mechanism. Based on our formulation, we found this mechanism is involved with an enormous signal amplification, actually. Rate amplification, sensitivity, and flexibility. These advantages cannot be obtained by simply … direction because of the kinetic constraints. To obtain such a result in signal amplification and rate amplification, reversible … modification is required.

Based on the advantages we found, it's not surprising that nature adopted such a mechanism to regulate these enzymes. It's not surprising that you can see the many reversible modifications take place in nature.

For example, … phosphorylation, food …, acetylation, and so on. Although there are very few involved in … which is what we found originally in glutamine synthetase. But by studying the glutamine synthetase system it provided us a very detailed picture of how these reversible modifications of protein function as a regulatory mechanism.

PARK: Could you comment on other scientific achievements in this lab; the Laboratory of Biochemistry?

BOON CHOCK: In the Laboratory of Biochemistry? The Laboratory of Biochemistry, I was told, started as a Laboratory of Cell Physiology. At the time, Chris Anfinsen was the lab chief and Earl Stadtman was made lab chief of the Laboratory of Biochemistry in 1962.

Earl stepped down and I took over in my 1994. However, the Laboratory of Biochemistry, I think has made significant contributions based on their work and also training of post-doctoral fellows. The work on the cellular regulation using the cyclic cascade system, I think, has made a major contribution. The work on selenium biochemistry, which is done by Terry Stadtman, where they've identified and purified many enzymes and also the seleno derivatives, which are important in the biological system. Such as selenophosphate synthetase.

In addition, this laboratory also pioneered the research to investigate the role of reactive oxidase species and free radicals in the biological system that included signal transduction, and impacts on the disease, aging. Nowadays, this field is very popular but it was initiated in this laboratory almost 20 years ago.

PARK: Could you talk briefly about your current research project and the size of your sections and how many staff members and the post-doctoral fellows and what research topic you are pursuing these days?

BOON CHOCK: At the moment our lab is concentrated on trying to find out the mechanisms by which free radicals are reacting off the species … system and also … or signal transduction and disease. For example, we recently demonstrated that superoxide radical … seems to be playing a major role in signal transduction.

[A largely inaudible section.]

And trying to support this free radical argument, we built this instrument shown over here. I think Dr. … could probably tell you more about this instrument because he's the one who built it. This instrument is used to show that it could provide a very efficient way of making holes on the membrane on the cell.

[Another largely inaudible section.]

PARK: Do you know why this room should be dark?

BOON CHOCK: Because we always joke that scientists always work in the dark. But in reality, most of the work is sensitive to light and he's monitoring a very weak fluorescent signal so any light would overcome the signal.

PARK: Thank you very much.

BOON CHOCK: In addition, with respect to the contributions in terms of training biomedical scientists in this country, the Laboratory of Biochemistry has trained approximately 250 post-doctorate fellows and about 90 of them currently are holding professor, director, [or] research director [positions] either in a university, research institute, or pharmaceutical company.

Ten of the alumni have been elected for member of the National Academy of Sciences and two of them have been awarded the Nobel Prize in physiology and medicine. One of them was the CEO of Merck Pharmaceutical Company.

This is Dr. Ephrem Tekle and he's the one who built this instrument shown over here, based on trying to validate the idea of how energy-driven fluctuation oscillation and make the biology system do work. Ephrem, do you want to explain?

EPHREM TEKLE: One of the things that we do in this laboratory is to see how external electric fields affect cellular function. This is possible because of the geometry of the cell and so on. Very small

electric fields are enormously amplified across the cell membrane. This amplification could range by 45 orders of magnitude. The strength of the electric field across a membrane could range into, very easily 400 to 500,000, per centimeter. This enormous electric field is going to, in one way or another, affect how the stability of the membrane. And also, to some extent, how proteins in other receptors embedded in the membrane are affected by this.

A very small potential difference across membranes is very much amplified across a membrane to an order of 4 to 500,000 … per centimeter. In order to study this general effect, we've essentially built up an equipment here that could give us any number of waves that we would like to generate. We can stand down from very small microvolts generating system up to very high amplitude generating system. We can go up to several thousand kilowatts per centimeter fields that could be generated.

This system is integrated with the microscope system so we can study what happens at a single cell level. The microscope is integrated with our computer system so that we can image what happens as the field is applied; what happens to the membrane or other signals that we follow in real-time.

One of the things that's important in this study is that some events happen very quickly and we are able to resolve with our system in the order, we can pick frames up to 500 frames per second that gives us a resolution of a few milliseconds in capturing events that have occurred at the cell level.

Once these images are captured then we have the analysis on a computer system that you see over here. Much of the analysis is done off-line because of the time requirements the analysis takes. We can make—you can see here an example of an imaging system that is done off-line and this is a signal generated from … signaling in one of these experiments. This is a very long experiment but compressed over a time of one minute to show us what's happening.

This is the data collection and imaging section of our instrument. Right here is the microscope system that picks up and the camera system that picks up the instrument. The camera is underneath so that we don't lose as much light as we would have had it been up on the other side. The left side of the equipment here is for generating the various field strengths and wave forms that we would like to apply during these experiments.

PARK: This is Room 110 of Building 3. I'm here with Dr. Lin Tsai. Thank you very much for having an interview with me. Could you tell me about your educational background and when and why you came to NIH?

LIN TSAI: I grew up in Hong Kong and I went to university in … ; that's during the war time. When I finished my bachelor's degree there, that's about the year before they had the war, and I came to this country in 1947 after I had … in the Beijing University.

I went to school in this country and finally I got my Ph.D. degree from the Florida State University in Tallahassee, Florida. After that I went to Ohio State University in Columbus, Ohio and did post-doctoral work for three years.

And after that I moved over to Worcester Foundation for Experimental Biology because at the time I was very interested in the chemistry of steroids. I stayed there as a scientist for two years, then I heard about the opening in Stadtman's laboratory in NIH.

PARK: How did you hear about it?

LIN TSAI: I have an old colleague who was, at the time, in this laboratory and he recommended me to Dr. Stadtman so I took the opportunity to come and work in NIH because I heard very good reputation about the chemistry in this institute at the time. I started here in February of 1959.

PARK: You came as a post-doctorate fellow or staff scientist?

LIN TSAI: I came as a visiting scientist because I was not yet a citizen then. When I became a citizen, in 1962, then I was converted into a staff scientist in the laboratory.

PARK: Did you have a plan to go back to your home country or you wanted to stay here?

LIN TSAI: At that stage I planned to stay because earlier I planned to study and go back to the country and it happened to be the worst time since the Communist government took over China in 1949. That's why I hated to go back right then. As a result, I could obtain naturalization in this country and decided to stay and make my career in this country.

PARK: What kind of a research did you start from 1959?

LIN TSAI: I did all kinds of things. In 1959, came in as an alternate chemist of Dr. Stadtman's laboratory. At the time he was very interested in doing the bacterial degradation of compounds. So, I collaborated and did the chemistry investigation of the courses of the bacterial degradation of riboflavin. And then later on we also started another project together, also with Dr. Stadtman, on the anaerobic degradation of nicotine acid. This occupied most of my time in the first almost 10 years in this laboratory.

PARK: Did you do research primary in collaboration with Dr. Stadtman and other scientists or did you initiate your own research?

LIN TSAI: I have some of my smaller projects but my major intention to come to NIH was I like to collaborate with biochemistry. I wanted to make use of biochemistry to study biochemical problems. So, I had to make various collaborations and later on with Dr. [Thressa] Terry Stadtman and other biochemistry.

PARK: Is this room was yours from the --

(END OF INTERVIEW)

PARK: When you came to Building 3 as a scientist, is this room is the place that you started working? Or did you have another room before having this room?

LIN TSAI: When I first moved in this building, this floor was offices.

PARK: The first floor was offices.

LIN TSAI: It was all offices for the Heart Institute. We had a laboratory in the basement in the first of the two-level basement. I have a lab in the first basement. I stayed in that lab while awaiting this lab for the laboratories.

Actually, this whole room is my design because it has to fit working of an organic chemist whereas all the other rooms are for biochemistry work. So, you can see the difference in this room and the other rooms. I moved into this room in 1962 and I've been in this room since.

PARK: Can you describe a little bit of the differences of this room from others; the characteristics, peculiar features of this room?

LIN TSAI: For one reason, I have to have a very powerful and large cruet. This is very important for doing organic chemistry reactions. And all these tabletops, they are stone slate and they're resistant to acid and base whereas the other labs, they all use plastic, which will not last.

PARK: Do you remember other floors? Are there any interesting things that we have to have on record, say on second or third or fourth floor?

LIN TSAI: The fourth floor I remember it was all animals.

PARK: What kind of animals?

LIN TSAI: I don't remember. I think a lot of times they were dogs. I think they were practicing open heart surgery on the dogs upstairs in those days. Of course, when you have to do the surgery, they have to shave the dog and our problem with them upstairs is that they flush so much of all the hair that they shave down the drain. And they plugged up our drainpipes. That's the first thing we do when the drainpipe blocks; we go upstairs and ask them to look at their drainpipes.

PARK: Until when were the animals there?

LIN TSAI: I don't remember. Early and mid-'60s, I think. Early '60s, yes.

PARK: And the second or third floor?

LIN TSAI: The second and third floor originally were offices, but they also renovated them and they became laboratories then.

PARK: How was your relationship with the scientists? Did you find the scientists here very supportive? How was your impression?

LIN TSAI: It was very good. I enjoy myself very much working here because we are all very cooperative and we are very friendly.

PARK: Could you comment on Dr. Earl Stadtman's style of collaboration in doing experiments?

LIN TSAI: We are very liberal in that sense because we say that he—a certain amount organic chemistry requires to understand the process and I just go ahead and do it any way I want. Then, of course, I don't understand enough biochemistry to question his experiments, so we just write the paper together after we've got the results.

PARK: Did you meet other scientists outside NIH? Social interactions, did you have many?

LIN TSAI: A lot, yes. I don't know how many. Easily about 20 or 30 other scientists I've got very friendly with and we talk about our work. It was a very good atmosphere.

PARK: May I ask you about how you keep—do you speak Chinese at home?

LIN TSAI: Actually, I'm single. But I do have a niece here. We do speak Chinese. I'm Cantonese but I speak more of an alternate northern dialect as well.

PARK: You are devoted to science; married to science. While you are staying in Building 3 for many, many years, did you recall any or some changes in terms of the building itself or in terms of social interactions between the people, in terms of atmospheric things or the science the people are pursuing?

LIN TSAI: Yes, there is some change but mostly this is very gradual, and the laboratories become bigger and bigger and more and more people come in and people come and go all the time. That essentially is very gradual. There's no dramatic change in that sense. But on the other hand, we get older and the people who come, they get younger. So, the gap between myself and the newer arrivals post-doctoral are much wider and we have to adjust to that.

PARK: When you came to NIH in 1959, were there many Asian scientists? Nowadays there are many Asian fellows around here.

LIN TSAI: There are just a few, not that many. There were a few Chinese and then there's a few Japanese. I got very friendly with a Chinese, Dr. [Joe Hin] Tjio, because he's Chinese but from Indonesia; that's how the name's spelled. We had become friends. There were only a handful of Chinese or Japanese at that time.

I wouldn't think there was any Korean. I'm talking about back in the early '60s. Later on, this changed a lot. I think a lot more Japanese come toward the end of—around '60s and early '70s. Especially the laboratory over in Building 4 where they do a lot of organic chemistry, they have quite a number of Japanese organic chemists come through. And we have very good interactions in those days.

PARK: Did you have any other collaborations besides Dr. Earl Stadtman? For example, did you work with Dr. Terry Stadtman and other people?

LIN TSAI: I did, yes. I worked with a number of other people later on, yes. Even people outside NIH.

PARK: How did that collaboration come about?

LIN TSAI: I usually—we'd know each other when they were here briefly and then they went back to their own country and then we'd keep up a collaboration. Not very extensive but we'd just enjoy doing things together.

PARK: As an organic chemist, what are the major instruments you are using for your research?

LIN TSAI: That's the difference between organic chemistry research and others like the biochemistry field. We do everything. We have anything that determines the physical and chemical property of a compound. So, I use all sorts of instrumentations.

Spectroscopy, all kinds of spectroscopy, and for separation we use all kinds of high-tech separation processes like high performance liquid chromatography and gas chromatography and all this sort of thing. So, there's not one thing. I couldn't even do it in one room. I rely on my colleagues in other labs; they have certain specialties I don't have here, and I go to work in their lab or their special process. Like if I want a spectrum of, the nuclear spectrum, with a compound, I go to my colleagues who have the big instruments.

PARK: Could you tell me about your daily routine; what time you came in and how long you stay here?

LIN TSAI: In the early days, I come here almost any time and stay any day as long as the experiment lasts. When I get older, in the past 10 or 15 years, I am more limited in my activity. But originally, we were almost any time of the day, any day of the week. But now I usually come in fairly early; I'm an early person. I usually get here before 8 o'clock. I stay around here until about 4 o'clock in the afternoon before I go home.

PARK: And when did you retire?

LIN TSAI: I retired about more than a year ago. I retired in 1999, July. But I hardly left the lab, I just stayed on and continued what I was doing.

PARK: As a volunteer?

LIN TSAI: As a volunteer, yes.

PARK: Could you describe a little bit about the position of volunteer?

LIN TSAI: It is considered a member of the laboratory, but they have to take care of my expenses working here, that's all.

PARK: But you are pleased to continue to work here?

LIN TSAI: Yes. I have the support of the laboratory administratively.

PARK: Thank you very much. It's been a pleasure.

PARK: Today is March 9, 2001. I'm here in Room B-207, the room that has high-tech instruments like EPR (electron paramagnetic resonance). I'm here with Dr. Moon B. Yim, who is in charge of this laboratory. Good morning.

MOON B. YIM: Good morning.

PARK: Could you tell me a little bit about when you came to NIH and how you came to NIH?

MOON B. YIM: Yes. I came to NIH in the beginning of 1988. One day I had a phone call from Dr. Boon Chock, who is now the current lab chief of our lab. He called me one day and informed me that the Laboratory of Biochemistry in NHLBI intends to build a new EPR, the electron paramagnetic resonance facility. At that time, they were having a nationwide search for EPR spectroscopists working in the biological system. That became the occasion and I thought it was a good opportunity for me, so I came in 1988 and the instrument arrived the end of October of 1988. At that time, we had one instrument, which is the big instrument over there in the back side. A couple of years later we had another small instrument come. At that time, I was at the University of Chicago.

PARK: Since you came to NIH, what kind of research did you work on?

MOON B. YIM: The first work we had after we set up this instrument was the manganese complex with bicarbonate and amino acid system. That system had been worked by Dr. Stadtman and Boon Chock for a long time and it sort of involved free radicals.

That was the first experiment that we had done here. Then after that it led to the enzyme system which is superoxide dismutase, which contains copper and zinc. It extends onto removing superoxide dismutase, proportionate superoxide dismutase to hydrogen peroxide. But in certain cases, we found that the product—the hydrogen peroxide—can be a substrate for this enzyme system and generate hydroxyl radical and other free radicals. So, we have done that. That led to the study on the mutant which is associated with amyotrophic lateral sclerosis, which is called Lou Gehrig's disease. That Lou Gehrig's disease involved the mutation of this enzyme. So, we cloned this mutant and studied that. So, it's quite a productive. At the same time, we are doing what you call the glycation reaction, which is this product is accumulating with aging and it involves diabetes mellitus.

So that also involved the free radical reaction. So mainly what we are doing is anything involving free radicals in biological systems.

PARK: Could you say a little bit about the history of this instrument: how old it is? It is being used for studying biological systems? And the basic principles of the EPR?

MOON B. YIM: This EPR was actually discovered in Soviet Union. The first experiment they did is on the metal system. The EPR instrument was mainly developed by physicists and then it went to chemists.

PARK: Do you know when approximately it was first invented?

MOON B. YIM: Around beginning of 19th century; 1910 or 1920.

PARK: Before NMR?

MOON B. YIM: No. NMR was first invented and then later EPR.

PARK: I think then maybe after World War II or around that time.

MOON B. YIM: Yes, around that time. So, it's not 1910. But anyway, it was developed mainly by physicists. It came to chemists who used this EPR instrument for free radical reactions in organic chemistry and also for essentially taking the theoretical result from quantum chemistry.

So, whether their molecular … calculation is correct … experimental result so that's what they used. Then of course the biological enzyme contains a lot of metal ion in active site so they used EPR for structural or functional—structure/function relationships of the enzyme.

Recently, the free radical reaction in aging and a lot of disease is known for—it's a burst of studies occurring in biological science about using EPR to detect the free radical involvement in disease and aging. So, what we are trying to do is the free radical detection.

PARK: Are there many EPR instruments at NIH and in the United States?

MOON B. YIM: In NIH this kind of instrument, this is the only one we have. So, NCI has one lab which has a different type of EPR. But this type of instrument, this is the only one we have in NIH.

PARK: Could you comment on the procedures for buying this kind of instrument at NIH? Is it very difficult to order a new instrument and getting approval? Some kind of procedures.

MOON B. YIM: NIH is very generous. Actually, NIH is generous to buy new equipment. They encourage us to buy the new instrument, set-up the new instrument, and apply an existing problem—to solve an existing problem we can approach in many different ways. One of the ways is, for example, if we need this instrument and justify why we need it, usually they approve it. The only difficult thing is the personnel to work with. But the instrument device is not really—the only thing is that you justify.

PARK: Could you give me an approximate price for the small EPR and the big EPR?

MOON B. YIM: This EPR is, it's not really a set price for the instrument. If you put an accessory, you buy first the basic instrument and then you acquire a lot of accessories. So, if you put one by one, it varies; the price range is very different.

But for example, the instrument which we buy, at that time what they called the ESP-300, which is just the EPR unit, that probably cost about $200,000. Then you add the endo, which is called electronuclear double resonance spectroscopy, accessory, which is detecting essentially animal signal from EPR experiment. That cost another one. And then we have the pulse facility, which is sort of a time domain

measurement that cost a lot of money. Altogether, our lab chief is always saying, Dr. Boon Chock, he says that this lab costs about $1 million right now.

Because the technology's changing so much, we have to upgrade this instrument. So, we upgraded this EPR instrument last year. So essentially, except for magnet, it's essentially a new set-up again. So total, so many times we added and so I don't know exact amount. But always our lab chief said it cost about $1 million.

PARK: Are you excited about moving to a new building?

MOON B. YIM: Yes and no. Yes, in a sense that if I move to a new building I will join with our group. Actually, I am the only one in the sub-basement and our lab people are all in the second floor and first floor and sometimes you're lonely.

And also, as you can see, that the space is very small, so the arrangement is very hard to put in. But when we move to our new building, I will have a little more space so the lab will be a little better and at the same time I can join with our group on the second floor.

But also, that thing is the Building 3 is very cozy. As you know, historically it's a very significant building and you work here all the time you're reminded of the people who passed by here who accomplished so much. So, sort of you are leaving this building is kind of sad in a sense.

So it's bad and good.

PARK: Could you explain how you operate this machine?

MOON B. YIM: The basic principle of EPR is that, first of all, EPR is detecting signals from free radicals. Free radicals which has unpaired electron. The principle is when you put the unpaired electron into the magnet, there is a splitting. In that splitting energy level, you give a certain frequency of energy wave. In this EPR there's a microwave range. So about 9 GHz. So, we have the source of the microwave, which is what we call the microwave ridge. That connected to the sample—the resonator, which is what we call the cavity. We will put a sample in and then that resonance of this energy transition is detected and then shown in the scope here.

So, for example, this signal is obtained from hydroxyl radical trapped by what we call the spin trapping agent DNPR. From this EPR spectrum we can monitor two types of parameters. One is a number of lines and at the same time the distance between the lines, and at the same time the center part of the called G value. which gives this four-line signal which identified the number of lines and then the distance between what we call the … lines. If you have different types of free radicals trapped by this same spin trapping agent, then the number of lines as well as this splitting will be different. So, by this kind of EPR signal we can analyze to find what type of free radical was generated.

And on the basis of this intensity we can follow the kinetic, we can get the kinetic measurement so that— Right as well as kinetics, the formation of the free radical generation. This free radical reaction sometimes is not only one type of free radical. As you know, free radical is very reactive molecule. So, one free radical generated and it can react very fast with other type molecules around there. It can react with other substrate or protein or any kind of thing that's an environmental thing. So, the first free radical is generated and that hit another molecule so that another type of free radical generates. It's just cascading.

So, not only the simple one free radical, but you can see the whole sort of free radicals mixed together.

We measure this spectrum with a time course and then, plotting from this the time course measurement, we can get some kinetic parameters, which is the formation constant and those kind of things. Then at the same time we can monitor the reaction schemes, the cascading mechanism. The free radical reacts with the surrounding molecules of proteins and solvents. So that also generates another free radical.

So it's a sort of a cascading free radicals.

We have two EPR spectrometers. This small one is called the EMX model from Bruker Instruments. Every EPR spectrometer consists of mainly three parts. One is magnet and microwave bridge, which generates microwave source, and then of course there's the signal, once we obtain the signal is the signal processing unit. There is a resonator inside between the magnets. The wave generated from microwave bridge is transferred through the wave guide to the resonator where the sample is located. So resonance occurred in there and that will be processed in this unit console and obtained in EPR spectrum over there.

This instrument is called an ELEXSYSTM E 580 from Bruker Instruments. The function of this instrument is much more than what we explained on EMX. In addition to the frequency domain EPR, this one can measure time domain EPR information. So it's what you call the pulse EPR instrument.

This EPR spectrometer also consists of the same three components just as I explained the EMX. That is magnet and microwave bridge, which generates microwave, and then signal processing and the control system console is here. That processed signal is displayed in the computer. So, compared to the EMX, this one contains more functions so that it has more panel here. Mainly it has a pulse microwave facility so that we can measure time domain information. So that's the difference between the EMX and the ELEXSYSTM E 580. It can do what you call the electron spin double resonance, which is called endo, and another one is called ESEMI, electron spin echo envelope modulation information. Most of the time when we use this instrument, we need liquid helium temperature. We put the helium in here, so it involves quite a bit for using this instrument.

PARK: Dr. Yim, could you comment on how your basic research has clinical implications or how your research can help the patients in certain diseases like Lou Gehrig's disease or diabetes as you mentioned?

MOON B. YIM: Yes. These days I think the information transfer obtained from a basic research is very rapid and it has a great affect. It's not only one way from basic science to the clinical but there's also clinical information can come to basic science and then we've got transfer back.

For example, it's around the 1995 that Lou Gehrig's disease was found to have a mutation of a superoxide dismutase. It's called a gain of function [mutation] because of that mutation you have these Lou Gehrig symptoms.

So when we read that paper we already had done this free radical generating function. So we go ahead and then mutate the enzyme and over produce and then look at the function of—the free radical generating function of this mutant compared to normal.

We found that the mutant generated more free radicals than the normal. The patient which has a certain mutant has a certain amount of surviving years after the onset of the symptom. So we looked at this kind of different type of mutant and found that there is a correlation between free radical generating function and patient survival or years. We studied just the basic research and then later on in a few years it has a significant impact on how you treat this patient for a longer survival.

And also we are doing the glycation, which usually it appears as atherosclerosis in diabetic patients. So it has this kind of enhanced glycation. It's found that not only there but in food science also that when you add this glycated protein in solution, you generate more glycate reaction.

So we studied that and found out that this glycation is essentially generating kind of an active site just like an enzyme and it deposits on the arterial wall and stays there and it keeps generating free radicals by catalyzing one electron oxidation reduction reaction.

And those kind of things are also quite important in atherosclerosis and diabetic patients mellitus and survival. So always you have the back and forth, clinic to basic, basic to clinic and back and forth.

And it improves a lot of patient care.

PARK: Could you comment on NIH in terms of having mutual benefits for basic research and clinical research?

MOON B. YIM: Yes, it's the best place to work for those kinds of things. In NIH, actually you have to be open-minded. So, you get ideas in both ways. Clinicians give lectures and you go. You don't know what's going on and you sit down, and you get the information and ideas. And also, of course, probably the clinicians will get information when the basic scientists talk, which sometimes is very tedious. But it's kind of going in both ways. NIH here provides those kinds of atmospheres and is essentially the purpose of NIH, I think.

PARK: Thank you very much.

BARBARA BERLETT: Hi, my name is Barbara Berlett. I was working down here about 16 years ago and I'd like to show you the fermenter and the fermentation facility that we have. This here is our current 500-liter fermenter. When I came 21 years ago, this is not the fermenter we had. This is a much newer model. But essentially it does the same thing. It's the same size and it's used to grow large scale cultures of bacterial suspensions in order to purify enzymes, whatever particular enzymes the researcher's working with. In the case when I first came, they were working with glutamine synthesize, which is an important enzyme in nitrogen metabolism.

We would grow 500 liters of the *e. coli* and from that we could purify maybe a milligram of glutamine synthetase; that's why they needed the large volumes. That's changed through the years. They have organisms now which will over-produce whatever enzyme they're looking for, so we don't quite need the large volumes for most things.

But anyway, we would start with a seed culture from the scientists and scale it up. These are the seed tanks—they're 10 liters—that are then transferred to the big 500-liter fermenter. Over here is the high-speed Sharples centrifuge, which we then use to harvest the 500-liter fermenter.

The culture flows through and the ball spins collecting the cells which are then scraped off and frozen in liquid nitrogen and then they're broken up and processed to purify the enzyme. These are other various pieces of equipment associated with growing the cultures and harvesting them.

When I first came, they were working with glutamine synthetase and an enzyme and nitrogen metabolism. We had an *e. coli* strain and we would grow 500 liters of *e. coli* and we would get about a kilogram of cells out of that. From purifying the enzyme from the kilogram of cells we would get maybe one gram of glutamine synthetase.

And then while I was here, we were lucky that we got an engineered strain, which over-produced glutamine synthetase so we didn't need 500 liters anymore. We mostly used 10 liters and we would get 50 grams of glutamine synthetase. So it was quite an improvement.

We started growing smaller scales now that they've engineered bacteria that will over-produce certain things that they're looking for and we can harvest them with these smaller Sharples Super Centrifuges.

These are various equipment. These are pumps and over here, these are the smaller Sharples for harvesting smaller volumes. They're high-speed centrifuges, these green things over here, and these are the pumps for transferring from the culture vessel to the centrifuges.

This is just a spectrophotometer so that we know when we reach a certain cell density, that's when we want to harvest the cells. That's about it over here. As I mentioned before, this is a newer, more modern version of what I had to work with.

Everything I did was manual where you had to open the steam and open the water and time it with your watch and take samples out to check pH or foaming. In this one, everything is automatically added. It has foam sensors and pH sensors and CO2 sensors, oxygen sensors. It's all microprocessor controls so nobody has to do anything manually or very little. This is the microprocessor control cabinet. I don't know how to run this, but they just push buttons and tell it what to do now. I think that's it.

PARK: This is B2 or sub-basement for Building 3. Here there are different rooms: a fermentation room (B-201), animal room, NMR room (B-204), and also there is a washing room.

This is B1, basement floor of Building 3. Here there is an office of Dr. Edward Korn, who is the chief of the Laboratory of Cell Biology. And there are also the laboratories of Dr. Evan Eisenberg and Dr. Richard Hendler and Dr. John Hammer, all of whom are the section chiefs in the Laboratory of Cell Biology.

This is the first floor of Building 3. There are laboratories of Dr. Sue Goo Rhee, who is the lab chief of the Laboratory of Cell Signaling and also there are labs of Dr. Rodney Levine and Dr. Thressa Stadtman, both of whom are the section chiefs of the Laboratory of Biochemistry.

This is the second floor of Building 3. Here is an office of Dr. Boon Chock, who is the lab chief of the Laboratory of Biochemistry, and also there are laboratories of Dr. Earl Stadtman, who used to be the lab chief of the Laboratory of Biochemistry and is currently a section chief in this lab. And there is also a laboratory of Dr. Ann Ginsburg, who is the section chief in the Laboratory of Biochemistry.

(END OF INTERVIEW)