Gellert, Martin 2000

Dr. Martin Gellert Oral History 2000

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Martin Gellert, Ph.D

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The interviewer is Dr. Buhm Soon Park.

Park: First of all, thank you very much for allowing me to have an interview with you.

Gellert: You're welcome.

Park: And I'd like to start with your education and what made you become a scientist and how, who or what influenced you to study science in college, and so I want to go back to your early family background and also your college years and graduate years.

Gellert: Yeah. Well, I mean, I wasn't born in this country. I was born in Czechoslovakia. And we left in 1938 to get away from the Germans. My family is Jewish. And I think they were business people, and probably if I'd stayed there, I would have gone into business, but being in a new country, I think I had a freer chance to choose a career for myself. And at about the time that I went into high school, I realized I was very interested in science. It was the kind of thing that stayed in my head easily and that I seemed to enjoy. I had at least one very good teacher in high school who recognized that I was more interested than the other students and sort of gave me additional material to read. And by the time I went to college, I just naturally assumed that this was what I was going to do, and I went to Harvard with an undergraduate major in chemistry, just nothing biological at all, just straightforward chemistry, and really took a fairly intensive program of courses. I mean, more than half of the courses I took in college were science courses even though you didn't have to take near that many in order to graduate. And then I realized that, among the science courses, what I really enjoyed was physical chemistry, and I went to Columbia as a graduate student and did my Ph.D. in, again, nothing biological, straight physical chemistry.

Park: Who was your advisor?

Gellert: He was a man named Ralph Halford, H-a-l-f-o-r-d, who was an infrared spectroscopist, and I did a thesis on infrared spectra of some liquid mixtures, which I began to see was a little bit of a dead end. And I had friends in graduate school who had gone into more biological problems, and also, in my senior year in college, I had the opportunity to do some research in the laboratory with Paul Doty, who had just gone to Harvard as a physical biochemist with a background in polymer chemistry and was now trying to apply this to proteins and nucleic acids. So, my senior year in college, in fact, I spent a tremendous amount of time in his lab. I was working on a problem having to do with the protein chemical properties of insulin and then dropped it and went to graduate school. But when I got out of graduate school, I thought I would like to take up the biological side of things again and I realized by then--this was in 1956--that there were many, many interesting things happening in biological science and probably a lot less interesting happening in physical chemistry. So I arranged for a postdoctoral fellowship that was in Bethesda but not actually at NIH, across the street, what was then the Naval Medical Research Institute, but it was a very strong group in physical biochemistry.

Park: I see.

Gellert: And I was working with a man named Manuel Morales, who worked on the properties of contractile muscle proteins, with the basic idea of trying to understand muscle contraction. So we were working on myosin and actomyosin and trying to understand its response to ATP in solution. I think this was not, I think, looking at it from the present point of view, not really an ideal project because the properties that are important for muscle contraction have to do with organized fibers of actomyosin, and by the time you have it in solution, it's probably been dispersed too far. But that wasn't evident then, and it was an interesting thing.

Park: Was there any other career options to your postdoctoral...

Gellert: Oh, yeah. I could have had a postdoctoral fellowship in, going on with infrared spectroscopy, and I was discussing that with somebody at the time but then decided to just decline that and try out this new possibility.

Park: Right.

Gellert: So, this was under the Navy, and about a year and a half after I came there, the Navy decided that they didn't want to support this physical biochemistry program anymore. There was a change in administration over there, and they thought, I think quite reasonably, that this was maybe enjoyable work, but it wasn't anything that had to do with the Navy. And this was at a time when, anyway, research was being, if you like, civilianized. During the war and for some years after the war, much of the basic research in this country was supported by the military. You probably know, the Office of Naval Research had a tremendous, by the standards of that time, tremendous research program, and I think this internal program over at the Naval Hospital was in a way analogous to that. But by the late '50s, other sources of research support were coming in, and the Navy decided they didn't want this anymore. So, basically, they gave us a year's warning and we all left in various directions, and I went with part of the group up to Dartmouth Medical School as an assistant professor and worked there for a couple of years, but then realized that, for somebody who was new in biology, as I was, this was a very isolated environment. It was a small place. At that point, there weren't even any good roads to Boston, so it was like six hours from Boston, and you just didn't hear about enough of what was going on in the outside world. So I talked to friends I had made down here, and in the end of 1959, I came back here. And at that point, the group that I joined was in the Mental Health Institute. It was a group that had been started by Alex Rich, who had left. It had at one point Gary Felsenfeld, who had left. It was then run by Sidney Bernhard, and David Davies was over there also. And after I had been there for about a year, Bernhard left to go to the University of Oregon. I had, anyway, my independent research project, and so I was attached to David Davies' group, and then rather soon after that, began hearing about Gordon Tompkins and his efforts to pull people interested in molecular biology into a single group in this institute. And I think although the lab started in 1961, as I remember, Davies and I probably didn't move over until 1962, but I could be wrong about that. And so we then joined this group. And, again, I mean, I had, to some extent, my own research, although David and I collaborated sometimes. And, in fact, one of the great things about the lab is that it made possible all kinds of very informal collaborations that would exist just for the purpose of one particular research problem, would then dissolve, and other collaborations would be set up. So, we had two problems that we pretty much collaborated on. One was a project that I started of trying to determine the orientation of DNA in bacteria phage particles, which was sort of leftover physical chemistry. I was doing this by flow birefringence. By accidental reasons, we had a source of T4 bacteria phage, which is a big phage with a long tail, so that it can be oriented in a flow field. There were people who were working on a lysozyme from the bacteria phage, and for them, these very large quantities of bacteria phage were a side product. So I just took what they were throwing away and purified it and then used it for these physical experiments on a scale that probably most other people couldn't have done because a single experiment might involve using and throwing away 10^{12} phage particles or something like that. And we actually got a fairly interesting answer out of that by the standards of the day, when one could do nothing very much detail. You could tell that there was some orientation of the DNA within the phage head so that it wasn't just stuffed in there randomly. It was in some organized way. And we published that. And then, the other project that he and I collaborated on was something that was presented to us by a colleague in another lab, Marie Lipsett, who accidentally found that if she cooled a solution of guanylic acid--now, not a polymer of guanylic acid, just the monomer--it formed a gel, and she brought that over and showed it to us and wondered whether there might be something interesting there. And so David and I went to work on it and found that, indeed, these gels had many properties that were like those of a nucleic acid, that an ordered nucleic acid absorbs less light than a disordered one, so-called hypochromic effect. And these gels have a hypochromic effect like a nucleic acid. They could be melted at higher temperature so that as you warm the solution from zero degrees to 35 degrees, you could see that it absorbed light. They had an optical rotation like an ordered nucleic acid. And then David discovered that one could pull fibers out of them and that they had a fiber diffraction pattern. And analysis of that fiber diffraction pattern showed that, in fact, what fitted best was a four-stranded structure. And so, David then made a model of how this would work with four guanines in a square bound together by so-called Hoogsteen hydrogen bonds, and this was really the first case of a four-strand G, what's now called G-tetraplex structure, a four-stranded structure. And it is so stable that it doesn't even require the covalent bonds along a nucleic acid axis to hold it together. Just the monomer of guanylic acid can form this four-stranded stack and be sufficiently stable at low temperature to gel. It's quite remarkable, and I think it took a long time for people to appreciate that that might have something interesting to do with real biological structures.

So, at that point, in terms of the lab structure, I started up another collaboration with Gary Felsenfeld. We were working on an inhibitor of RNA synthesis called actinomycin D, which, it became apparent to us, had some nucleotide specificity in the way it bound to DNA. And we spent quite a bit of time understanding the binding, understanding the basis for this nucleotide specificity. At that point there were not, as there are now, vast numbers of things that would bind to DNA and with some particular specificity. Now that's just sort of routine but at that point it was something very new and we thought it was worth the trouble to analyze it in quite a bit of detail. And we found that there was some specificity for binding to guanylic acid, but not entirely that. There was some probably more complicated site that invited a G and something else, so that as you went through a series of nucleic acids, when you got to those that were more G-rich, the actinomycin bound better, and we determined binding constants and wrote a fairly detailed paper about that.

Park: It's very interesting that you collaborated with other scientists without planning. It just happened.

Gellert: Exactly right. I mean, the intellectual life of the laboratory was at that point in the corridor. You know, anytime that you went out of your room, you could start up a conversation with somebody. And the laboratory was new, and I think people's ultimate directions were not so well fixed, and so there were many, many things that sort of happened as just informal conversation. I mean, I think back, and the lysine story was one of them, because we accidentally started reading some of the material on this, that it was an inhibitor of RNA synthesis and that there seemed to be something funny about the base preference of the compound. And so, within a week or two, we had recruited myself and Gary and Bob Martin to do various parts of this, and discovered that, sure enough, you could get inhibition of RNA synthesis from everything else except an alternating AT polymer as the template. If you used that, then RNA synthesis went ahead just fine. Therefore, that was the first strong evidence that there was binding to guanine, and we were just tremendously excited about that. And, unfortunately, then, a month or so later, a paper appeared showing us that somebody had already done this. But it made us realize that, you know, we had the potential here to form very interesting links between groups that could do new and interesting things and do them, sometimes, very efficiently and very fast. So that was, I think, one of the sort of immediate examples that set the style for the lab. I remember a couple of times sitting around a table with half a dozen of us all talking about different aspects of this actinomycin problem and realizing that we could move through it faster than practically anybody else could.

Park: When you came to NIH in the late 1950s, what was the reputation of NIH at the time among scientists? It was just one of the government agencies, or was it regarded as an emerging research institution that could provide a great opportunity for research-oriented scientists?

Gellert: I think somewhere in between those. I mean, it was clear that it was not a normal government agency. At that point, even the administration was relatively informal. It was a new place and it was quite un-bureaucratic, and some of the first generation of administrators had a great contempt for bureaucracy. On the other hand, I don't think it was particularly well known. It hadn't yet become the predominant funding source for university science and biology. That was just building up. And the intramural program was really just building up. There had been some very distinguished people here already, but they were in just very restricted areas. So it wasn't a broadly known biological community. For example, Arthur Kornberg had been here, and Leon Hepple in the same general area, polynucleotide metabolism, was here; and Bernard Horecker had been here. But these were people all from one tradition of sort of mechanistic biochemistry, and in that area, yes, NIH was very well known. But in many other areas of biology, it certainly was not. So, I think one of the things that interested me was that it was a place that looked as if it was very active, very energetic, and not yet very well known. And you can take as an example--and this is just a random example--when I, a few years later, started working on DNA ligase, the *Proceedings of the National Academy* was the best place to publish something if you were really excited about it because it would publish papers faster than anybody else. It was recognized to be the best place. But you had to find a member of the National Academy to submit a paper for you, and NIH was so new that there were practically no members. There were only like maybe three, four, or five, and at one point I got desperate enough that I actually got the director of NIH to submit one of my papers to the NAS because all the others happened to be out of town. But, you know, now you look in the index of the National Academy and there's something over 50 members of the National Academy here. That's the difference between an immature and a mature research institution.

Park: Right. The Laboratory of Molecular Biology was created in 1961, and at that time the field of molecular biology studies is blossoming, especially after the discovery of the DNA structure in 1953 by Watson and Crick. And also in Paris, the people are showing a lot of new discoveries, and here in the West, they just created what is a place for young researchers coming together and doing very exciting things. Did you feel any kind of competition with other research groups in the world? Did you feel that you, this group is a group that can compete with others in the world who already made great discoveries?

Gellert: Oh, I don't think we regarded ourselves as in competition with other groups. I don't think we looked on ourselves, in fact, as being particularly important. I mean, you know, we were just getting started and trying to find interesting things to do. There was work going on, clearly, on regulation. Some of it was in this lab. I'm sure that, for example, Bruce Ames, who was here, must have regarded himself as being, to some extent, in competition with Jacob and Monod and I think probably to some extent for a while, he was not very well recognized because they were very well known and he wasn't. But in many ways the problems that we were working on were not the same problems as were being worked on elsewhere, so I don't think, you know, we regarded ourselves as saying, "Oh, my God," you know, "we'll never make it. There's this group in Paris that's doing all these fantastic things." We had, to some extent, other interests, and we weren't trying to march in on exactly the same things as they were. Now, competition in science develops quite naturally when you don't necessarily anticipate it. In the middle 1960s, after some conversations with friends, I started working on an enzyme, looking for an enzyme, what joined the ends of DNA molecules, now DNA ligase. And I was at that point still attached to David Davies's group, and I was basically working entirely by myself. I didn't have any postdocs, I didn't have a technician. And the beginning of 1966, I got this actually to work on extracts of *E. coli*, and for the next several months I sort of happily pursued it. And in the fall of '66, I then finally submitted a paper on this, and at that point it became public knowledge that this was a possibility. And at that point, all kinds of people started in on the problem. So I went from being in a completely noncompetitive situation to being all of a sudden in a highly competitive situation, and not because I had gone looking for a competitive problem. Rather, I thought I was looking for something where nobody else was working, and I think they weren't working until it became obvious that this was something one could do.

Park: It's very interesting that you just didn't follow the existing problems, trying to explore something new, and then it leads you to something very important.

Gellert: Yeah. That was sort of a funny situation because I had no training in the real discipline of biochemistry. I mean, I hadn't ever had a course, even, in biochemistry. I had no lab experience in purifying proteins or in following the methodology that one would. And so, you know, for a while I was really learning at a tremendous rate. And one thing, again, in the way of informal collaborations, I set up a collaboration here with Steve Zimmerman upstairs, and for the first two or three... Well, after the first paper on ligase, we then started intensively collaborating, and for the next two or three years we were working very hard together. And he had been a student of Arthur Kornberg's and he was really a very skilled and very disciplined biochemist. So I would come up with some idea, and he says, "Well, that's probably not the best way to do this," you know. "What we should do is so-and-so." And he taught me a lot about how to approach a biochemical problem over the next couple of years.

Park: Have you ever read Horace Judson's book, *The Eighth Day of Creation*?

Gellert: Yes.

Park: It covers the history of microbiology up to the 1970s, I think.

Gellert: Yes.

Park: From its beginning.

Gellert: Yes.

Park: In one section, he describes, especially the section that deals with Marshall Nirenberg's contribution, and he describes that Nirenberg was not a member of the phage group led by Max Perutz, and kind of outsiders.

Gellert: Max Delbrück.

Park: Yes, and Marshall Nirenberg was also kind of an outsider coming into that problem, and then... And I was told that Marshall Nirenberg didn't like that description and things. How do you think about that, the kind of phage group out there and the NIH scientists?

Gellert: I think it was an interesting example, because everybody in the field recognized that the genetic code was a central problem, and some of the people in the phage group had, in the first place, set up elegant mutational experiments that tell them some general properties of the code. But they didn't have yet any way of telling exactly what the code was. And they had plans for doing it in a very, very methodical and long-range kind of way. In looking back on it, the way that they were trying to do it would have taken probably five to 10 years, even with good luck at every stage of the way. And Marshall Nirenberg basically just bypassed all of that and shortcut it by doing direct biochemical experiments and doing them in a way that I think at first nobody expected them to work. I mean, nobody expected a synthetic polynucleotide would actually code for production of a polypeptide chain that you could recognize. And so, I think there was, no question, at first a certain degree of irritation. And there was also--there were some people in the biochemical community, for example, Ochoa [Severo Ochoa], who thought that they had some sort of right to that problem and were not very kind to him for the first year or so. But, on the other hand, it was obvious that he had the real story and other people didn't, and I think there was a fair degree of realism in science. I don't think that after--he did this in 1961. By 1962, I don't think that there was much doubt that he was already very much accepted. And I think that was also an interesting example in the way the NIH worked back then, because all kinds of people pitched in to help him. Maxine Singer helped him make oligo polynucleotides of the fine composition. Bob Martin was helping him at one point. So were many other people. So he went from being essentially this very small operator with one postdoc to having the resources of a considerably larger group and all their experience in working with polynucleotides. So this enabled him to move a lot faster than he could have done on his own, and I think people did this very selflessly because, you know, they just didn't want him to get scooped. And so they decided they would put their efforts to pushing his research forward as fast as they could, even if it didn't do anything for them.

Park: It's very interesting that when something exciting is found. Then many people have it materialize, and then how to credit both finding or doing things were distributed or shared.

Gellert: Mm-hmm.

Park: Because it's a very important aspect in sharing intellectual credit among university scientists.

Gellert: Sure.

Park: Was there any problem of sharing credits? For example, you mentioned that you did collaboration with Dr. Gary Felsenfeld.

Gellert: Mm-hmm.

Park: Was there any issue of who should be the first author or, you know...

Gellert: Oh, I think the way we settled it there, you know, it was a little bit arbitrary. I think on that paper, I was the first author, he was the last author, and a couple of his postdocs were in the middle. So, you know, I think he was the last author because he had already a research group, and I was basically just by myself. But, on the other hand, I had done a very large fraction of the experiments myself, so I was the first author. So that was fine. No. I think within our group, we never really had any problems that I recognize about assigning credit. Relative to the outside world, we had all the normal problems, among them being that, you know, analogously to what happened with Marshall Nirenberg, we were unknown, we were sometimes going into areas where there were people who were much better known and who didn't necessarily like all of a sudden having somebody come in and play on their turf. That certainly happened to me with the DNA ligase. I mean, even though I was, by a few months, the first person from the real orthodox nucleic community--Arthur Kornberg, Bob Lehman, etc., etc.--for some years I didn't get very much credit. And, you know, they rearranged the referencing to emphasize their own work. And what I found entertaining then was that, after I found another enzyme, which was DNA gyrase, then I guess they had to recognize that I was in the field to stay, and then the structure of the references for the older work on the ligase suddenly changed and my name started appearing. So, some of that is just plain survival.

Park: So, could you tell me the year when you discovered ligase?

Gellert: Well, the year I did it was '66, and the paper appeared in January of '67. And then there was what I'm sure was an independent discovery also by Charlie Richardson. I was working on the *E. coli* enzyme, he was working on a parallel enzyme from T4 phage--he was maybe two months later--and then a whole bunch of papers from Bob Lehman, from Kornberg's group, from Jerry Hurwitz, but were really not independent because they had the information both from Richardson and from me. But the way that this has become established in the literature is that there were five independent discoveries, and isn't this interesting. Well, it's not all that interesting. I know, in the case of my paper, that I had actually started thinking about this project when I was on sabbatical at Stanford for eight months with Buzz Baldwin, and so when I finally got it all written up, I sent the preprint of the paper, and the journal club was given it, and I think it was at that point that Lehman's and Kornberg's groups became very active in that area.

Park: I see, I see. And when was the gyrase…?

Gellert: That was in 1976, and that was also an interesting collaboration because that involved Mizuuchi, who at that point was a postdoc in my lab, and a collaboration with Howard Nash. And that was something that we didn't go looking for that we found kind of accidentally. So, Mizuuchi was interested in working on site-specific recombination, and Howard Nash, at that point, was just getting started working on the site-specific recombination of lambda integrase. And I suggested that Mizuuchi maybe collaborate with Howard Nash, and I kept them interested in what was going on. I suggested a different kind of assay than what Nash was using, and he and Mizuuchi set that up, just looking for changes in the restriction enzyme pattern that would follow recombination. And as this work was going along, they had--at that point, one did not yet have convenience plasmids, so they were still doing recombination less conveniently in an old lambda-phage molecule. And the lambda phage had two sites between which recombination would take place, and when it did; the piece of the DNA would be deleted. And although this recombination was taking place within a single molecule, it turned out, for reasons we at first didn't understand, that the structure of the molecule made an enormous difference. Now, do you know about lambda DNA, that it has cohesive ends? Okay? So lambda DNA is linear, but it has 12 base pair ends, single-stranded and complementary, producing from each side. So it's very easy to make those ends cohere and make a circular molecule. And it turned out that if we cohered the ends first, then the recombination went pretty well in a crude extract; but if we left the DNA linear, it didn't work at all. So, there's a puzzle. Right? The reaction is in the middle of the molecule, but the structure of the ends, kilobases away, is important. Well, why should the DNA have to be circular? We started thinking maybe it was that the ends have to become actually joined into a covalent circle by the ligase. And so, at a certain point, we made some circular DNA--I think I made it--and tried that. That's now covalently circular all the way around. And, sure enough, that worked much better than just the DNA with the ends cohered. Well, why shouldn't that be a requirement? And at a point, we started wondering about whether the reason why it had to be covalent, the joint, had something to do with supercoiling. At that point, the reaction required ATP. Again, at a certain point in time, I think I made supercoiled DNA, and that was a good substrate. And then we found that when we started with the DNA supercoiled, we no longer needed the ATP. That was very interesting. What it made us think was that, okay, if you start with covalent circular DNA that isn't supercoiled, you need ATP. If you start with supercoiled DNA, the ATP requirement drops out. Maybe what's happening is that there's some ATP-dependent reaction that supercoils the DNA. So we went looking for an activity like that and, sure enough, it's there, and that's the DNA gyrase.

Park: Did you create the name "gyrase"?

Gellert: Yes. Created it over beer at a Gordon conference with a few friends where this was the first time I talked about it. It was, I think, in June of '76. It was a biopolymers Gordon conference, and I got myself attached to the program at the last minute, and I was in the session with a rather tough-minded guy who gave me two minutes. You can do a lot in two minutes. So people said, "Okay, but what you need is a name. You need a name that people will remember." So we sat around and we started thinking about rotase, porase, and then somebody said, "Well, how about gyrase?" Okay, gyrase. Why not? So that's what it became.

Park: Sounds good. How about ligase? Did you create it yourself?

Gellert: No. That was not my name. I just called it, I think, a polynucleotide joining activity, and then some of the biochemists named the ligase because there was already a tradition of calling things that linked molecules together as ligases.

Park: When I interviewed other scientists, they mentioned Dr. Gordon Tompkins as a wonderful person and a great musician and a great scientist and encouraging collaboration. What can you say about his legacy during the 1960s?

Gellert: Well, I think he really established the style of this lab. He was always interested in discussing any new finding, any new problem. He thought that really, this lab could attack anything it found interesting, and he was willing to encourage you to do that, and to begin with a creative idea, not to begin with experiments, and I think, you know, that sounds fairly obvious. But it wasn't necessarily the style of the laboratories. I found when I went to Stanford, for example, that you were only considered to be active in research if you had a test tube in one hand and a pipette in the other, and since I was on sabbatical and I was trying to generate ideas, I would sometimes spend a fair bit of time during the day reading, reading journals. And I had a couple of times the experience of somebody coming in, looking at me reading and looking puzzled, and then saying, "Oh, that's right, you're on sabbatical." Well, you know, that was never the way it was here. I mean, the notion was that you could discuss something intensively and that you had no advance way of telling what would turn out to be interesting. So just start, do something, and the interest will become apparent in the work. Now, I have to say, I mean, that has been a very effective style also, but it was never ours. I mean, we wanted to have a clear-cut idea before we went marching in to do the experiments, and that, I think, was Gordy's main contribution. You could go to him with some very unformed idea and, you know, he would listen and he'd say, "Oh, actually, I saw a paper that might be relevant," and reach into this unsorted stack and say, "Have you seen this?" And then you'd look at it and say, "Well, maybe that's not quite the direction, but it's more like this," and he'd say, "Oh, I see," and we'd go off in a new direction for a while. And other people would come along and join in the conversation, and there was never any feeling that you had to be doing an experiment every moment of the day or you were wasting your time. And I think that, and also the feeling that he gave us that we were as smart as anybody else in the world and that any problem that anybody else was thinking about, we were entitled to think about, and also, if we wanted to work on it. So, and also, he wasn't so much a working scientist. If you had a technical problem with an experiment, he wasn't the person that you would go to, you know, to tell you how to do a centrifugation in a better way or exactly how to purify a protein. There were lots better people at that. But for dealing with scientific ideas, I think he was unparalleled. And that was the wonderful thing about the laboratory in the early days.

Park: And you inherited this lab, his section?

Gellert: I inherited... Yeah, I guess I did. But, I mean, that was just a convenience because, you know, it happened that it was time to promote me to section chief just about the time that he left, so I inherited that section with the name of it and with the one other senior person, Elizabeth Maxwell [sp.], who did not move with him. And so for a while Liz Maxwell [sp.] and I were the only two senior people in the section, and then after she retired, it became mine alone.

Park: For a while, you worked just by yourself, and after that, you just had a couple of postdocs, not many, and probably not more than five or not more than 10.

Gellert: Oh, never even up to 10. No.

Park: Yeah. And it's quite contrasted with the professors in the universities.

Gellert: Yeah.

Park: They have Ph.D. candidates and postdocs and post-postdocs. I mean, usually an established professor has many researchers around him or her, and kind of directing research rather than doing all the research. And does having a small number of researchers around you have any implications on your scientific research or research productivity, or did you ever miss having more people around you?

Gellert: Yes. I mean, I think that this is something else we should talk about that is another reflection of the style here, which was different from other places. In a university environment, it's very, very hard for people to continue doing laboratory work once they have a faculty position. A lot of their time is used in raising money, grant applications, fellowship applications, etc. A lot of their time, a certain amount of their time, goes into teaching and into academic affairs. They're on all kinds of committees. And basically, they don't have the time, they don't have the concentration to be very active in lab work. Here, we didn't really have many other obligations. We don't have to raise money, we don't have to write grant applications. All these other committee things are not so much part of the environment, though as we get more senior, we tend to get more. So it was perfectly possible for me to go on doing lab work myself, Gary Felsenfeld also, David Davies also. We've continued pretty much through our whole careers doing some of our own lab work. And if you do that, then the attraction of having a big group is maybe not so great because you can still be pretty effective with a smaller number of people. I mean, after all, if you've been working in the lab for a while and you have some experience, you can be very efficient.

Park: Right.

Gellert: Now, looking back at my own career, I probably should have expanded my group somewhat more, somewhat earlier. Until the middle 1980s, I really never had more than two postdoctoral fellows and a technician, and that was in an area where there were considerably larger groups. And, you know, I think our work maybe was better controlled and was very well done because there was a small group and we were all in daily touch with each other. But it didn't go as fast as it could have. And it was only when I started working on V(D)J recombination in the 1980s that my group really started to expand because there were quite a lot of people who wanted to do that and I could see that now, since we were dealing with eukaryotic cells and everything was a little bit slower and more complicated, there was simply no way to work effectively in that area unless we were a larger number, and so the group grew to perhaps half a dozen people beside me.

Park: Did you ever miss teaching?

Gellert: Yes. I do a little bit of teaching here. For a while, I was sharing a course with Lederman, who was here, and then, after he left, I took it over and drew in a couple of other people, and we had this course on DNA replication, recombination, and transcription, mainly in bacterial systems, which went on for quite a while. You know about these informal courses. And now I'm co-chair of the Biochemistry Department in the FAES School, so I still have an involvement there. And I do a little bit of teaching in other people's courses. I teach one lecture in an immunology course and another lecture in a special topics in molecular biology course. I wouldn't at all mind if I were giving, say, 10 lectures a year or 15 lectures a year. Beyond that, it would get to be a pretty heavy commitment and I'd just as soon let somebody else do it. But I think what I miss more is not having graduate students, because graduate students are a little bit freer intellectually than postdocs. Postdocs are already very career oriented. Many of them are not willing to take chances on a speculative problem, so they want and, to some extent, they need something that gives them assured professional success so that when they go out looking for their first independent job, they have a respectable bibliography. And if they take on something that's more speculative, you can spend a year and maybe not get anything back for it. So, my work for the last several years has involved V[D]J recombination, and we were the people who managed to get the specific steps of that working in a cell-free system. But it took us several years to be able to do that, and it was difficult for me working with postdocs. What I had to do was encourage a postdoc to do that, but only for several months, and then, if it didn't work, as indeed the first few times it didn' t, to then push them to switch to a different problem that would be more immediately productive and have somebody else take up that problem again. And, you know, about the fourth or fifth time, we began to know enough about the system so that it actually began to work, and then everybody was able to join in on that aspect of it.

Park: I see. When you have a new postdoc does she or he have his or her own agenda or research topic, or do you give or suggest research topic to the postdoc?

Gellert: We usually do it by discussion. I mean, people come here because they know the general area that I work in. But then, you know, I generally talk to them about the directions where I see interesting problems and the kinds of approaches that one might take and then ask them to go and think about this, and then come back and talk to me about what kind of approaches seem reasonable for them. I mean, I don't generally have postdoctoral fellows of the kind who are just good to do experiments and not really very independent thinkers. I look for people who are able to think independently, and I've been pretty lucky in finding them. And when you have people like that, they want to do it. They don't want you to be telling them, you know, today you do this, tomorrow you do that. They want to have their own creative input, and they work much more efficiently when they do. So, that's the way we operated, and it actually worked out, I'd say, quite well. The work has gone well and the people come out with confidence that they're able to run their own research, and many of them have now gone on to university careers. So, I think it's not entirely a question of training at all. It's also a question of having chosen people who were suitable for that kind of life.

Park: Let me go back to the 1960s.

Gellert: Sure, sure.

Park: And the 1970s. I looked through the annual reports of NIDDK, the former NIAMD, and I read a report which is kind of a general description of a situation of NIDDK in the early 1970s. It's written by, I think, Dr. Ed Rall [?], saying that these days, NIH has felt a lot of pressure from society regarding accountability. NIH spends so much money, and what did you produce? And at the time of when America was involved in the Vietnam War and everybody was in a different situation at NIH, spending so much money. And so Congress pressured NIH to cut something or to reduce some budget or be more accountable. And so, it seems to me that, at least on the administrative level, they are concerned about dealing with that problem. And I'm wondering whether the lab-bench scientist like you and others felt that way. Did you really feel a great pressure from society as the United States experienced?

Gellert: As far as the operations at our lab went, I would have to say no. I mean, we were all part of the society. We recognized that there were tremendous pressures in the society that the war had generated, among other things, a great distrust of government and of the things that government did. And we also could see, even in other parts of NIH, that there was very great political pressure for more immediate results, for example, the war on cancer, which really turned the Cancer Institute upside down. And the Cancer Institute, because of the diseases they work on, has always been very much even more under political pressure and has, also, I think, tried more to respond on a year-to-year basis to that pressure. And I think people in the Cancer Institute would tell you that, yes, research there, the direction of research changed quite repeatedly as a result, in part, of these pressures that were coming from the outside world, not just where they saw scientific opportunities. And I think if you looked at the general structure of this institute, you would see the same thing. After all, the fact that the name has changed so often is largely a reflection of those political pressures, that there were groups in the outside society that felt that their particular interests were not being well enough represented, and so from Arthritis and Metabolic Diseases, diseases was then focused particularly on diabetes, and then the name changed again to digestive diseases and kidney diseases. But in terms of the way we live here, there was never any pressure in any of those directions. The pressure was only that we had to show that we were doing creative, independent, and productive research and that we were producing excellent basic research, and that was enough. There was never any pressure to say, you know, "Gee, it would be awfully nice if we could do something on diabetes." Nobody ever even made that suggestion. It was just understood that the institute had more medically directed research and some basic research, and that the basic research would probably do best if it was pretty much left to be self-directed, and we certainly were.

Park: So, you didn't really expect immediate medical results out of your research.

Gellert: We weren't working in that direction. Sometimes, as has happened without our really anticipating it, I think that gyrase was really a prime example of that, that very soon after we found that enzyme, we started looking at what kinds of things might inhibit it, and we realized that gyrase was probably involved in DNA replication. And there were two families of DNA replication inhibitors that were known that did not have an identified target, and we found that both of those families worked on DNA gyrase, one-on-one subunit, one on the other, and in the case of one of those families, the quinolones, there was already an active effort at a number of drug companies to develop new antibiotics in those families. And when it became apparent that gyrase was the target, I think it became much more efficient for them to go faster in developing those antibiotics. So, quinolone antibiotics are now a big business, and these are antibiotics like norfloxacin, ofloxacin. They all have related names. They all work on gyrase. And they're a billion-dollar business.

Park: Did you get something?

Gellert: Zero. But, I mean, you know, probably... I don't know. I could, I suppose, have had the use of gyrase as a screen for better antibiotics, but the fact is the companies were already working on the antibiotics. I mean, even without knowing what the target was, you know, you can just keep looking for things that kill bacteria more effectively. So, we shouldn't have the credit for discovering the antibiotics. And, in fact, at that time, in the 1970s, we still didn't really think of anything. It was a different time. Nowadays, I think if we realized that a new protein was the target for some interesting family of drugs, yes, we would find our way to patent it and--though, in that case, the money, whatever money there is, comes back to NIH. Only maybe a little bit comes back to the investigator, but sometimes quite a large amount comes back to NIH. And we've come back to the laboratory for research.

Park: You mentioned a little about collaboration within the lab. And did you have any collaboration with the people outside the lab within the NIH, like the Cancer Institute, the Heart Institute and others?

Gellert: Yes. So, I mean, I already mentioned our collaboration with Howard Nash.

Park: Right.

Gellert: Who's in the Mental Health Institute. That went on for a number of years. Both Mizuuchi and myself. And part of that work also involved Bob Weisberg, who is in the Child Health Institute. And we sometimes started things with people in other institutes that didn't necessarily lead to a published paper. But we've always gotten a lot of help. And I've found that NIH is a very, very good place in the way that people are often very willing to help you. And my feeling is--I don't know; I couldn't say this for sure because I haven't worked in a university--that it's probably easier to get help and collaboration here than it is in most universities, partly because professors in universities have large research groups and partly because their fund-raising depends on their reputation to a greater extent than ours does. They tend to be a little bit more separated and stand-offish and to maintain the integrity and separateness of their own research group. If you go to Harvard, for example, you are supposed to be *the* world's authority on some particular topic. And if you're the world's authority, it's not easy to go down the hall and ask somebody else for help. Whereas here, the style has always been, we're all working scientists, we're all in this together, and if we can help each other fine, let's do it. And that's one thing that I like very much about the NIH.

Park: How was the kind of collaboration initiated? I mean, just an informal network or...

Gellert: Very much an informal network. I mean, a number of our collaborations have come about through the medium of one seminar series that has existed here since the 1960s, which became known as lambda lunch, and lambda lunch became a forum for prokaryotic biology. I mean, it was first involved in understanding regulation of lambda phage, regulation of bacterial systems generally. Then, as some of us got more interested in recombination, it was regulation and recombination, and I think it's probably spread out even more. But this is a weekly seminar where many of the people with our shared interests come and where what's more important always is the discussion than the actual presentation. And sometimes the speakers get very frustrated because they get only five minutes into their talk and this tremendous argument breaks out, and they don't have a chance to get much further. But it's always entertaining, and sometimes you learn a lot. And that was how our collaboration with Nash and with Weisberg started. This was sort of a precursor of what now is more formally known here as interest groups.

Park: I see. So at that time, the lambda lunch was not as formal.

Gellert: No. It was something that just started on its own, and, you know, I think it was at that time, back in the 1960s, it was probably quite unique here because it did draw in people from many different institutes, many different labs, and sort of group of unexpected relationships between what people were doing.

Park: Did you ever have research associates or clinical associates to fulfill their military obligation to spend the postdoctoral years here, or just, do you have your postdocs or fellows from the universities, whether Ph.D.s or... Did you ever have M.D.s?

Gellert: I've had M.D.s, but later if there was any problem with draft obligations. So, M.D.s only started coming to my lab in the 1980s, and I guess I've had three or four of them. They were generally M.D./Ph.Ds., and most of them, in fact, were from a single source which was already inside NIH. They were people who were in the pathology residency program, and that program is a four-year program, but the last two years of it are not so intensive, so the people are encouraged to go and find a research lab to work in. And so I had first, under that program, Michael Lieber, and then he encouraged two other people who were pathology residents to come over to this lab also after he left, and so this was a very effective source of getting interesting people. My work is sufficiently over on the basic side so that I would not generally get M.D.s from the outside world applying to come here. The ones who are here already find it an interesting environment.

Park: I was told that in the 1960s, and also in the 1970s, there was no problem in communicating with other people in other specialties, like Dr. Davies in x-ray crystallography can talk on genetics, and other physical chemists on other, and spectroscopy. Everybody seems to understand what others are talking about. But these days, they are more specialized and there's a little bit of differences from the early days. When do you think that happened?

Gellert: Oh, I think it's been happening steadily, and I think it's still moving in that direction. I mean, biology has been, in a way, too successful for its own good. The amount of information now is enormously greater than it was in, say, the early 1960s. At that point, the problems that people were concerned with were, you know, pretty well defined and covered only a relatively small part of what we now recognize as biological research. These days, if you are a developmental biologist, for example, the amount of specialized knowledge you have to have before you can even talk intelligently about it is so great that somebody coming from another field has a very, very hard time even following the conversation. That's one thing that's happened. The other thing is that also, within the context of this lab, when we got started, we were all young, we all had small research groups. We therefore, we did not live within our own research groups. We talked to each other very intensively. As we grew up and became more successful, our groups got bigger. Inevitably, then, you spend more time talking within your group, you spend less time talking among the groups, and so it becomes more difficult to keep track of what people, even in your own laboratory, in the other research groups are doing, and it's just the way the world has developed. So for both these reasons, yes, I think it's absolutely true that, you know, we each had a much better idea of what our colleagues were doing back in the 1960s than we do now. But I think that that's, as you go to universities, the problem is even worse in that realm. The dispersion of biological research is tremendous, and it's only going to keep going in that direction. I mean, there's just an overload of information and interesting material, and one simply will not be able to focus on more than a relatively narrow area.

Park: Looking back, your career at NIH and your life at NIH, do you have any regret? How could you comment on that, your life as an NIH scientist? And generally, you mentioned a lot of things on your science and your interaction with other people and the characteristics of this lab at NIH.

Gellert: Well, you mean, do I have regrets about staying at NIH rather than going somewhere else, for example?

Park: Yes.

Gellert: I've thought about it a number of times and considered other jobs. It isn't that there was any shortage of other job opportunities. But when I looked at the way people lived in universities, just how they live on a day-to-day basis, I felt that I would really rather continue here. I mean, I think that there's a tradeoff. There's no question that for a given level of accomplishment, you probably get more recognition if you're in a university than if you are with NIH. There's some kind of residual bias against government laboratories, and there's also the fact that, you know, if you're in a university and your career depends on your fund-raising abilities, to some extent you have the whole university publicity apparatus helping you and pushing you. And, you know, you notice, for example, that universities are very well organized about nominating people for awards, and the NIH people tend not to sometimes get organized in that way, and if one suggests it, they say, "Oh, yeah, I guess you're right. It would be a good idea to nominate," but they won't get to it on their own. So I think there's a tradeoff in some ways. I do wonder whether my life would have been very different, whether I would have been a more effective researcher if I'd gone to a university. I think there's no way to tell. I think it was not an unreasonable choice to stay here. I think some of the jobs that I could have taken, that, looking back on them, I would have been very unhappy with, and some of them might have been fine. It's, you know, you only have really one life, and you can't figure out how it would have happened in other environments.

Park: That's right. And are you involved in the professional society?

Gellert: Yes, not so much right now. I have been. I accidentally became president of the American Society for Biochemistry and Molecular Biology.

Park: A high position.

Gellert: They called me up at one point and asked whether I would run for the presidency, and I said, well, I didn't really want the job, but, why? And they said, "Well, we have one candidate and we'd like to have another one." And so I saw an opportunity and I said, "Okay. Who's the other candidate?" And the person who was the head of the nominating committee said, "Well, I shouldn't really tell you that." And I said, "Look, you know, I really don't have to run, so maybe I won't unless you tell me." And so he said, "All right, I'll tell you. It's Bruce Alberts." And I said, "Oh, okay, that's safe enough. I don't have to worry about that." So I said, "Sure, put my name on the ballot." And sure enough, Bruce Alberts won, and then two months later, Bruce Alberts accepted the job as president of the National Academy, and so they came back to me and said, "Well, are you...." So I put in a year as president of the society, and it was interesting. You learn some things, and maybe I got a little bit accomplished, not a very great deal, but, on the other hand, the societies are pretty much self-organizing, and so there wasn't that much to be done. I suppose, in the year, it took maybe three weeks of my working time or something no worse than that. And I occasionally organized meetings. I'm in the middle of organizing one for next June right now. And I'm on the editorial boards of journals and I do a lot of refereeing. Refereeing is actually by now a pretty major part of my work. I think I referee something between 60 and 80 papers a year. That's a lot.

Park: That's a lot. Do you have anything to tell about your lab, your section?

Gellert: Oh, I think we've done a pretty good job. People who shared equally in the administration of the lab, that all the decisions involving personnel, involving space, would be made by that group together, that there wasn't one person who would have the power to make those decisions; that that forced us into a more collegial style, I think, and it was a very valuable part of the scientific culture of this laboratory. If I think of anything more, I can get in touch with you. I'm sure you're going to be pursuing this for a while.

Park: Right.

Gellert: And if you have any more questions, you know, I'll be around. You can come back to me.

Park: Okay. Thank you very much for your time.

Gellert: Thank you.

End of transcript