

This is the third in a series of oral history interviews with Dr. Ruth Lillian Kirschstein
10 November 1998

The interview is conducted in Dr. Kirschstein's office at the National Institutes of Health, Bethesda,
Maryland

Interviewers: Dr. Victoria Harden and Dr. Caroline Hannaway

Please Note: These Interviews Have Not been Verified for Accuracy

Harden: Dr. Kirschstein, when we ended our discussion last time, you had just been named Chief of the Laboratory of Pathology, and the Division of Biologics Standards had moved into a new building in 1960. We were looking at the NIH phone books, and we saw that, at this time, a number of changes were going on. I would like to ask you about a few of them. But, first, you had mentioned the move to Building 29, is there anything else you want to add about the move of the Division into this new facility?

Kirschstein: Let me first of all correct something. I was not named Chief of the Laboratory in 1960. It was maybe in 1961.

Harden: Was it? I did not realize that. We will correct this.

Kirschstein: Several things are important in that regard. When the Division of Biologics Standards was organized as a separate entity after the Cutter incident and it was separated from the then National Microbiological Institute, there were staff people of the old Laboratory of Biologics Control who were in Building 7, and there were some in Building 5. When I came on board in 1957 to do pathology, I actually was in Building 4 with Dr. Lillie's old group. At some point, probably in 1959, there was a sudden ability, because of money available, to build a building for the Division of Biologic Standards, and it had to be done in a hurry. So, rather than design the most ideal building, the blueprints for Buildings 2, 3, 4, and 5--all buildings that were basically identical and had been built at the same time--were resurrected and simply transformed into Building 29. It had a more modern veneer put on the front of it as opposed to the columns and so forth that are on the old buildings, but it was basically the same. When we moved in 1960, it was the first time that all the

groups were able to come together. I think that with that and the extra space, Dr. Murray decided there could be some expansion and some reorganization.

Harden : Within the laboratory?

Kirschstein: Within the laboratories and within the entire division. Then people began to devise names for organizational units that were better suited to the regulatory aspects of what they were doing. There was nothing dire or anything else in the changes. It was simply an evolution.

Harden: There was no sense at this time, in the wake of the Cutter incident, that Biologics was acting, as it always had done, as a regulatory body, and that the rest of NIH was not a regulatory agency.

Kirschstein: There was no sense then, and nobody really thought that it was inappropriate to do that. That came later. That came in the early 1970s, when the Division was finally moved to the Food and Drug Administration.

Harden: So the construction of the new building had nothing to do with that either.

Kirschstein: It had nothing to do with that. In terms of your comment about the blood bank, the Laboratory of Blood and Blood Products was one of the laboratories that had regulatory and research responsibility for blood, globulins, albumin, white-cell packs, platelets, etc. The blood bank was set up for the hospital. In the early days of the blood bank, because Dr. [Theodore] Ted Tripp was so knowledgeable about blood banking, he was given titular oversight of that blood bank, but he never did very much. By the time [Dr.] Paul Schmidt, who was really an expert, was recruited, the blood bank was separated off and became part of the hospital, which it still is.

Harden: Yes.

Kirschstein: So it was the official blood bank to supply blood and blood products for the hospital.

Harden: I have the names [Drs.] Alan Kleeman and William Bronson as having replaced Dr.

Schmidt, and then in 1962, it was...

Kirschstein: It may have been that on paper they remained in the titular control of Dr. Tripp, but when I was a resident in 1956 in clinical pathology, the hematology group there was headed by [Dr.] George Brecker, who was a world renowned hematologist, and we worked very closely with Paul Schmidt on a whole series of things. He was pretty independent, I could tell you. So it may have been purely paperwork. I must say, in those days, paperwork took forever to do, and if Murray did not get around to it, it probably just never got done. So it had nothing of significance to it.

Harden: Let me ask one other question here. You have already discussed how Dr. Smadel moved from Building 1 to the Division I presume the Laboratory of Virology and Rickettsiology was created because that was his research interest.

Kirschstein: That was exactly true. Smadel was here for a number of years with Shannon, and he was a remarkable curmudgeon, as I said last time. I think there was a feeling among the powers that be in the intramural program that he was apparently a little too militaristic for them. And Shannon relied on him very heavily. I think Shannon felt that the place to put Smadel was one where he could use his talents and watch out for that division that everybody was worried would get into trouble again. He was not going to put him as deputy to Rod Murray because that would be demeaning to Smadel. Smadel could gracefully leave this building [Building 1] saying, "I really want to go back to do research. I have been out of research for a long time." Smadel could do that, and so he did. Dr. George Hottle was in charge of the other laboratory of virology, it was the Laboratory of Viral Products. Smadel certainly could not have worked for George, and George could not have worked for Smadel, so they gave Smadel his own laboratory. He brought a whole crew of people who had been at Walter Reed with him. That was a very interesting phenomenon because he brought three women who were at the non-doctoral

level who had done a lot of research under him and who really ruled the roost. He brought the person who was probably eventually to lead to the downfall of Biologics being part of the NIH, and that was Dr. Anthony Morris, Tony Morris.

Harden: Tell us more.

Kirschstein: Tony Morris was a scientist who worked very well under direction from Joe Smadel and carried out the things he wanted him to do. He was difficult, and he got it into his head that Biologics was not serving its regulatory function very well. He would constantly make innuendoes to the effect that we had missed something, that there were tumor viruses in products, and he was doing little studies and so forth. Joe Smadel tried to keep him under control and actually did for a while. Then, finally, Tony got together with a consumerist lawyer named [James] Jim Turner, who had a law firm in the late 1960s—the consumer movement was getting going, and they began making serious allegations. Finally, I think the NIH decided it did not have to have this regulatory organization any longer. It could move it over to the Food and Drug Administration where it really belonged, and let the people in it just do regulation and never mind research. Many of us were very unhappy about this. That goes back to the late 1960s and early 1970s. I actually came over here to this office [Office of the Director] and asked [Dr. Robert] Bob Berliner—by that time I had a moderately good reputation, knew Bob well, and he knew I was a pretty good researcher—“If I found enough people from Biologics who were really interested in research, would they accept them in NIAID or one of the other institutes,” and he said no. He said that they could not expand and they did not have room and they did not this and they did not that. Many of us were deeply concerned because we predicted that eventually the organization would no longer have the balance of research that improved regulation and regulation that led to new research projects. It was really a very nice balance. Most of my research was based on that. I predicted it

was going to cause trouble. It did 35 years later. I had thought it would take much less time than it did. Rod Murray retired, and Biologics was moved to the Food and Drug Administration. [Dr. Charles] Charlie Edwards was the commissioner of the Food and Drug Administration at the time. He thought about who would be the head of the division, which quickly changed its name to the Bureau of Biologics. He interviewed me and he interviewed Dr. Harry Meyer. He chose Harry, and told me that he would make me Harry's deputy and that he did so because he thought that my background was broad enough that there might be other things he would want me for at the FDA. True to his word, about four months later, he asked me to come up there as deputy associate commissioner for science for the whole of the Food and Drug Administration. The associate commissioner was a wonderful man named [Dr.] Lloyd Tepper, a chemist, who was a good scientist and who was biding his time at the Food and Drug Administration, waiting for an appropriate industrial job. He spent most of the time I was there traveling and, in essence, I acted as the associate commissioner. I realized at the end of about a year and a half that it was fun. I had learned a great deal. I got very interested in some things. I took the Food and Drug Law Course at night, and told my husband that if I were 10 years younger, I would have gone to law school. Then I found that I missed NIH. And so.

Harden: We are going to come back to this in more detail, but go ahead.

Kirschstein: We should go back because this is an interesting story. Let us go back

Hannaway: Please tell us the story.

Kirschstein: I was looking about and thinking what I would do when the advertisement for the search for a director of the National Institute of General Medical Sciences came along. In the time I had been at Biologics, I had gotten to know a lot of people here, particularly in Building 1. Dr. Leon Jacobs was the associate director for Research Contracts, and he

wanted a representative from every one of the organizations to be on a coordinating committee on research contracting. He wanted Dr. Murray there, but he and Dr. Murray did not get along. Dr. Jacobs had been in Biologics for a while. So Murray sent me in the 1960s, and I walked into this room full of—have I told you this story before?

Hannaway: No.

Kirschstein: [a room] full of men, and I was the only woman there. At that time I guess I was called an associate director of the Division for Contracting, and for Research Contracts. Leon looked at me and he said, “Oh, Ruth, I am so glad to see you. You will be our executive secretary and take the notes.” I thought about it for a couple of minutes and I decided that I could say no and raise a fuss, but I would not. I would take the notes, write the minutes, and sign my name to them, not Leon’s, and I did. I got to be pretty well known around here as a result. So people knew me. When the job for the director of NIGMS came up—by that time I had had a moderate amount of administrative experience—I came back around Christmas time of 1973, I think, and went to see [Dr.] John Sherman, who was the deputy director under [Dr.] Robert Stone. I said, “John, I miss NIH. I would like to come back. Are there any positions open?” He said, “No, Ruth, I don’t think so.” I said, “You have an advertisement for the directorship of the National Institute of General Medical Sciences,” and he said, “Oh, I hadn’t thought of you for that.” It was perfectly obvious. So I said, “Well, think about it. Here’s my CV,” and I left. [Dr. Thomas] Tom Malone, who was associate director for Extramural Programs—and NIGMS was totally extramural—was chairing the Search Committee, and I was on the Grants Associates [G.A.] Board. Tom stopped me at the end of the meeting of the G.A. Board. It was about a week, or maybe two weeks, after I had given John Sherman my CV, and he said, “I need to talk to you,” so I said, “Fine, call me.” The next thing that happened was he called and he said, “Come for an interview very quickly.” So I went—Tom’s office was

where [Dr. Stephen] Steve Ficca's is now—and had a luncheon interview with the committee. A couple of people were missing. [Dr.] Thressa Stadtman, for one, could not make it. I went away feeling pretty good. Actually, before I went for the interview, I called up my friend [Dr.] Leo von Euler, whom I had known for years, and who was, I guess, the acting director [of NIGMS], because Stetten had left or Leo was about to become the acting director because he was deputy to Stetten. I said, "I need some pamphlets about NIGMS so I can learn more about it." He told me where to go over in Building 31 to get them. I drove down from the Parklawn Building one afternoon at about four o'clock and went up to where he told me, and the rooms were all empty. I said to myself, "Gee, these people go home early." I finally found somebody who gave me everything I needed. It was not until later, when I got the job—I will come back to that in a minute—that I realized that everybody on the staff of NIGMS was working in the Westwood Building, but that Dr. Stetten, who, of course, could not see and would not have left this campus for anything—this was his home and his abode, and what he wanted to do was to talk science all day long with people here—had asked for space on campus. At that time space was not at the premium that it is now, and so they had given him space on the fourth floor of Building 31 in the A wing, and his staff used to come over and visit him. But, of course, they were really working at the Westwood Building. It was not that they were a bunch of lazy people. They just were not there when I got there. So I read the material [about NIGMS] prodigiously, and therefore was pretty versed in it, and I answered all the Search Committee's questions. I went back to the Parklawn Building thinking, "Nothing ventured, nothing lost." About maybe three weeks later, Terry Stadtman called me in my office at Parklawn and said, "Ruth, I want to come talk to you." I said, "Sure, when would you like me to come down to the campus, and what would you like?" She said, "No. I am coming up there this afternoon to see you." At

that point, I realized they were serious. So she came up. We had a wonderful conversation. A week later I was attending a meeting for the FDA in Wilson Hall [in Building 1]. Bel Ceja was Bob Stone's secretary at the time, and all of a sudden she wandered in, looked around, and motioned to me. I went downstairs, and Bob said, "I would like you to take the job." So it was really quite exciting.

Harden: I will bet.

Kirschstein: Very exciting. But that is getting ahead of the story, too, a little bit.

Harden: We will come back and probably revisit some more of that. I have only one more Biologics question, and then we will move into polio. My question is about the researchers in the Biologics Division who never left the campus. They are still here.

Kirschstein: That is right.

Harden: Did no one ever suggest that they should be moved to Parklawn?

Kirschstein: Yes. Many people thought about it. But they were still doing research. It was not until fairly recently, as I said, that people have begun to question, more because of difficulties with finances than anything else, whether they should continue to do research. And the scientists, there was no question, even Harry Meyer, who was the director for quite a while and had been a researcher, realized that there was an enormous benefit to being on a campus with other good researchers. Harry made an agreement with, I guess, Stetten, but probably the agreement was between him and [Dr. Robert] Bob Marston, that his intramural program, that is, the researchers, who did some regulation, had always been thought of as research staff. In order to keep up the scientific standards, he would attend the meetings as the scientific director from Biologics. To this day, that has been happening. The director of what is now the Center for Biologics Evaluation and Research is [Dr. Kathryn] Kathy Zoon and she is the scientific director who attends [Dr.] Michael Gottesman's scientific directors' meetings. There have been small blips of time

during which people have said, “You should concentrate on regulation.” It was not until the money got very tight that this happened. When [Dr.] Frank Young was the FDA commissioner, he actually was able to persuade [Dr. James] Jim Wyngaarden to let him build a third building. By the time I left, there were Buildings 29 and 29A, and then 29B came along. Wyngaarden had planned it. It actually did not get finished until [Dr.] Harold Varmus and I came to this building [Building 1], and I went over there and helped them dedicate that building

Harden: Now, let us see if we can drop back in time to polio.

Hannaway: We have already talked a little about the Cutter incident on and off during part of our discussions, but the incident had called into question the safety of the Salk vaccine. Now, in response to this, the NIH changed the manufacturing requirements for the vaccine. We would like you to comment on the statutes that were governing oversight of vaccine development before the Cutter incident, and what changed after it.

Kirschstein: They were not actually statutes, and that was part of the problem. They were regulations. A statute is the law, and the law said there shall be regulation. Each product was regulated through a series of written regulations which quote the initial statute, and then went through a process of describing requirements. Some of the regulations were not prepared in a timely fashion. That was another thing that led to the demise of DBS and to some of the lawsuits. But we will come back to that another time. The regulations quoted the statute and then the writers went through a number of drafts, and people were asked to look at them and to comment. Then, finally, DBS went through the formal process by which one makes regulations, which is to publish a notice of proposed rule-making and get a period of comment—three months, six months, whatever seemed appropriate. You then go through, analyze all the comments, and write a long dissertation that again gets published in the *Federal Register*, saying, “Twelve comments

were received from a variety of people”—the people would be listed at the beginning or the end—“on the means of testing for potency. This was the general gist of their comments, and this is where we agree with them and this is where we do not. The regulations have been modified to take that into account.” If the regulations were not modified, you said so and why, and you just went through them. They were enormously thick and very ponderous documents. Manufacturers read them very carefully. After a while, consumers began to read them very carefully as well. So they were done through regulation. I am not a 100 percent sure whether actual written regulations were put together for the Salk polio vaccine before the licensure, because things were so rapid. There was such a demand for the vaccine that I think probably there may have been a draft, but I am not sure it was ever finalized. After the Cutter incident, people began to realize that there were going to be problems with making the vaccine because if there truly were live virus in these clumps they would have to do something about it—did I talk about that last time?

Harden: No, not at all.

Kirschstein: When Jonas Salk did his experiments that showed that formaldehyde could inactivate polio virus, they were based on the use of formaldehyde to inactivate influenza virus and the making of flu vaccine. Flu is a very different virus than polio. Salk started with a very high titer of polio virus. He added formaldehyde and let them interact for a long time. Then he took measured points hours afterward and looked at the decay curve in which he could find live virus. It went down steadily, and he got to about three or four days—I do not remember exactly—and he extrapolated that the decay would go to zero. It did not. It tailed off. The reason it tailed off was that, among the things that happened when the formaldehyde was used, was these tiny, tiny virus particles began to clump together.

Hannaway: Yes. This is mentioned in the accounts, but no one has explained to me what the

significance of this was.

Kirschstein: The formaldehyde did fine in inactivation, except for the virus particles in the middle of the clumps. Salk knew that there were going to be clumps, so he suggested to the manufacturers, though he did not realize this early on—he would never admit that he did not, but he did not—and it was a very traumatic time for him and for everybody else, that they provide a filtration step, and that would presumably take out the majority of the clumps, but it did not take out all of them. Whether or not it was solely something about that filtration step in the Cutter manufacturing process or not, I do not know. I do not think anybody ever will know. But my own personal view is that, but for the grace of God, all the rest of them might have had trouble too. Cutter had made most of the vaccine lots, and it had been extremely aggressive in selling the vaccine out in the California, Arizona, and New Mexico area, so we will never know. So everything stopped. They went back into production, because of Jim Shannon's persistence. I told you that he became director, and, of course, everybody else was fired. He brought Smadel over because Smadel was a virologist, and he put him here in his Building 1 office to give him advice about polio. They decided the vaccine needed a second filtration step. So, manufacturers did a second filtration step. It did cure that problem, but it also took out a lot of the antigenic mass. So the potency and, therefore, the efficacy of the vaccine was not as great as it had been before.

Hannaway: It was diminished.

Kirschstein: Yes. So a lot of effort was put into starting with a higher titer, maybe doing some things, maybe using different types of filtration, and finally it got to the point where it seemed okay. Now, the other thing that was done was they had to prove that virus clumps had been there. This was even before I came and before [Dr. Samuel] Sam Baron came. Sam became a very important part of these studies. He was recruited and he came in July of

1955 from Thomas Francis's laboratory, where he had worked on polio. Actually, Sam Baron and my husband had been together in the Francis lab, so we had known him and we did not realize that he was coming until we both arrived here. I went to work a year and a half later for DBS. Sam and I and several others then began to do all sorts of studies together and write paper after paper. He developed some things to increase the potency. He developed a sensitive test for potency using chick red cells.

Before he came, several people, virologists, had looked at the Cutter vaccine and had been able, on a not very reproducible basis, to cause polio in monkeys with the Cutter samples. But it was very hard for them to figure out what had happened, and it was very hard to repeat the work reproducibly. They began to say, "Maybe we need to inoculate monkeys in several parts of the brain and in the spinal cord and intramuscularly. We need to give them cortisone because it reduces their immune response," and so forth. Actually, that test, the safety test, was changed as well in order to have a monkey safety test. That is where I came in. I was going to read the slides and I got curious about how the test was done. As I told you last time, it was very boring reading the slides. I went over—Sam was there by then—and I said, "Let's see how you do the test." I looked at how they did the test and realized that it was not very precise. I said to Sam, "Let's start devising some experiments, using"—we had supplies of the Cutter material that had induced disease—"and let's see if we can figure out what is going on here." We actually did, and we found that the most sensitive method for inoculating the monkeys was into the spinal cord, in the lumbar enlargement. That probably was all that you would need, you probably did not need the cortisone, or the intramuscular injection. But there was such fear that we could never persuade anybody to drop these other procedures. The test worked and there was no point in arguing. But these studies taught me about the pathogenesis of polio as a virus, a wild virus that causes disease in monkeys. You could

take Mahoney Type 1, which was the wild type, and you could feed it to monkeys. If you fed 20 monkeys enough virus, you would probably get a couple of them to be infected. We know that that is the way humans get infected. But humans are always infected naturally, by the oral-fecal route, from fecal contamination of water to having dirty hands and putting them in one's mouth. And the epidemic spread that way. Rhesus monkeys could not be reproducibly infected orally. You could get an occasional case.

Hannaway: It had to be injected?

Kirschstein: It had to be injected, and the most sensitive place to inject it was the spinal cord. Now, if that was true, then would that be a reasonable place to look at for how to test the attenuated viruses that were coming along? In point of fact, it seemed to be a reasonable place but, actually, it was too sensitive. Every monkey would get pathologic lesions of polio at the site of the lumbar spinal cord where you inoculated the virus. The neurons had receptors on them, and every virus particle would cause disease. So the question was, would you ever be able to use these attenuated viruses at all? No monkeys, at least in the small numbers that Sabin and some of the other people used could be infected with the attenuated strains orally. Now, if the monkey was not a perfect animal to test the wild most virulent virus, then you certainly could not rely on their response to oral administration to say a virus sample was safe, and you had a problem with the lumbar enlargement being too sensitive. That was when we began to test the attenuated strains. Intramuscularly, a couple of the strains could infect monkeys and give them mild paralysis, and you got polio lesions. We showed that the virus traveled up the peripheral nerve because we actually did some experiments that showed that if you cut the peripheral nerve and then inoculate the virus in the muscle that the cut peripheral nerve enervated, and you would not get disease. That was not going to help for an oral vaccine, however. In the brain, would it work or would it not? We had nine virus strains to test.

We had the three from Sabin, the Type 1, Type 2, Type 3, from Lederle that were really developed by [Dr.] Herald Cox. And then we had the three from [Dr.] Hilary Koprowski, who had started his work at Lederle. Lederle had hired these two people to both work on polio, putting them in competition with each other. They fought all the time. They each complained that one was getting more money and more support and more salary than the other one. Finally, Koprowski left. By the time we got to worrying about his strains, he was at the Wistar Institute, and so we never actually tested his strains from Wistar. But he developed at least two of the three, and I cannot remember whether it was all three, while he was at Lederle. And Lederle was glad to have him go. By that time they were betting their money on [Dr.] Herald Cox. Bad mistake. And the question was, were all the strains going to be the same? What were we going to do? How were we going to differentiate them? So I said, "We know the spinal cord is too sensitive. We tried and we could not differentiate among all of these strains. Giving them intramuscularly is not going to work, orally will not work. Is it possible to inoculate them into a specific area of the brain, by which we could differentiate?" Now, we had been inoculating into the brain, the lumbar cord, and intramuscularly for the Salk vaccine for a very long time. The inoculations into the brain were done based on some very crude anatomical markings on the skull, and we never knew until we looked whether we got it into the right place or not. In the spinal cord, you could tell if you inoculated it properly into the lumbar enlargement, because there was a reflex action of one of the legs of the monkey, either on the right or the left side. It depended on which side you were on. So you knew when you missed the spinal cord. At this point, I was there for all of the work on the monkeys directly. I decided I needed to get somebody to work for me who knew more about the neuroanatomy of the brain than I did. I went back and I read a lot of the material from [Dr.] David Bodian, who had been in on some of the early work, and I visited David

Bodian. David Bodian was a neuroanatomist. I got somebody to work for me, [Dr. Ronald] Ron Clark from George Washington Anatomy Department. He came out and did his thesis with me on this and wrote it up. The place that we had been trying to get into approximately by these very crude anatomical markers on the skull was the thalamus. So I said, "Let us see if we can be sure that we can get it into the thalamus, but not with a big hemorrhage," which very often you got if you used a fairly large needle. "Let us get a very fine needle and develop some ways of doing it very carefully." We developed a very simple bar, a metal bar with holes in it that Ron had actually worked out stereotactically to be sure that we were above the thalamus, and we did it with electrodes first. The electrodes did go into the thalamus. With a very small needle, we were able to inoculate so that the way you got what you needed was something that simply had two linear scars. There was a little bleeding, but nothing else. We cut brains and watched and studied them. Very quickly we were able to show that the three Cox strains were more virulent, with the development, in some cases, of paralysis in monkeys, than were the Koprowski strains. But all three of the Koprowski strains were more virulent than were the Sabin strains. Now, there were differences in the Sabin strains, and we can come back to that a little later. But the Cox and the Koprowski strains were more virulent; they caused more polio and they caused paralysis. We quickly developed the statistical information to say that the number of animals out of a group that became paralyzed, and the number that showed lesions, could differentiate reproducibly these differences. Now, Albert Sabin did not believe us, Herald Cox did not believe us, and Hilary Koprowski did not believe us. So we went and looked at how they were doing their studies, and they were not doing the inoculation with the neuro-anatomical precision that we were. Also Herald Cox's polio vaccine was used in trials in South America, and we were able to correlate what we were seeing in monkeys with the children who were getting polio as a

result of that vaccine. Subsequently, Hilary Koprowski was doing his trials in Poland, and there was a similar correlation. We presented this first at a meeting in Copenhagen and then at two Pan American Health Organization meetings—Herald is dead, Hilary is still alive and he still fights me about this--in 1959 and 1960, I think. So the advisory group that had Bodian and many other people on it came to the conclusion that the Sabin strains were the correct ones to use. At about the same time, with the SV-40 story which we talked about last time, the Sabin strains, and probably the others as well, were found to be contaminated with SV-40. So here everybody was sure that there was going to be the possibility of a really good live virus vaccine and the country and the United States government were committed. Here we were with vaccine strains that were going to be given to the manufacturers, and, in fact, were being given to them to make small lots to get ready for real clinical trials, and the viruses had this extraneous virus in them. We had tried to prevent extraneous viruses every which way. Not only was SV-40 an extraneous virus, but it was an extraneous virus that was possibly causing tumors in hamsters. There was, I do not know, meeting after meeting after meeting of how were we going to do something about this. Sabin had derived his strains by various passages from seed stock that had come from many people, and he had saved every little piece he had. So you went back and you looked and looked. Finally, there was one free of SV-40. Then Sabin began to try to passage again through clean monkey cells that were absolutely free of SV-40 to get to a passage that was still attenuated and still worked and did not cause problems. It took long periods. There was no problem with Type 2; not a terrible problem, though some with Type 1; and finally with Type 3, it was very, very difficult. When he finally did it, the virus was less attenuated than the one that had SV-40 in it. Now, whether or not that was because of the SV-40, I do not think we ever determined, and I am not sure it was. It was something about the passage. Now, it was still pretty well

attenuated, but that was going to be the seed, and they would have to make at least one that was going to be the master seed. Also they were going to have to make at least one seed stock beyond it and then the lots, and it took a long, long time, with all sorts of temperature controls and so forth. It always was slightly more virulent, and we had to reject lots. That was when we came to the rule of five-lot consistency. No lots of final product to be used in humans could be released unless they were part of a series of five that had passed every test, including the monkey tests, in the manufacturer's hands and the tests in our hands. If the lots did not pass, then they had to go back to the seed and start again. It really was a horrendous job. Another question was, if this is an oral vaccine, what will the virus that is being excreted in the feces be like in terms of becoming more virulent. People, particularly children, varied considerably in the time they shed the virus. The purpose of the attenuated virus was to multiply, to replicate in the gastrointestinal tract, set up a gastrointestinal immunity, pass into the bloodstream, set up humoral immunity, and yet not go from the bloodstream into the brain or spinal cord. So the virus had to be attenuated for the central nervous system, but able to infect the gastrointestinal tract. For some people, that occurred within three days, but they continued to shed for longer. For some people, they shed for only three days, and who knows why. Some people shed for a long time, particularly young people. There was reason to believe that they might, and that the virus might change, and so stools were collected. [Dr. Frederick] Fred Robins did a lot of that, and we inoculated the stool material into monkeys and studied the brains and spinal cords. There was some reversion to virulence. The question was, how much? That was seized upon by the people who thought they got polio as a result of the vaccine. In point of fact, there were some cases, but very, very few. There were meetings at the CDC [Centers for Disease Control] and the acceptable rate was one in something like a million people, in three million in one

other set of data. What made the use of the vaccine in the United States possible finally was that Sabin went to Russia and did an enormous trial. Nobody believed that the Russians knew what they were doing, but [Dr.] Dorothy Horstmann, who was the professor of epidemiology and virology at Yale, a remarkable lady, was sent over to study the situation, and she came back convinced that it had been safe there. Then things took off from there. We tested every lot the whole time that I was at Biologics. I do not know whether they do it now.

Hannaway: From every manufacturer?

Kirschstein: From every manufacturer. We taught the manufacturers from all over the world how to do the test.

Hannaway: Did they come to the NIH?

Kirschstein: They came here to learn how to do the testing. We only tested the lots from the American manufacturers and those companies in Europe that wanted to be licensed. Pfizer England wanted to be licensed, and so they came and learned how to do it. Albert Sabin, to the day he died, never believed the importance of stereotactic placement of the virus. I presented papers all over, and I have pictures of the little lines of inoculation. We allowed no paralysis in monkeys and one in ten animals with minimal lesions in the thoracic enlargement, but not spreading all the way down to the lumbar enlargement. If it spread there, the lot was rejected. We probably rejected more lots than we had to, but Cutter had taught us all a good lesson. We taught people all over the world how to do this test.

Harden: Were there ethical concerns that people talked about in doing the trials of the attenuated live virus vaccine in foreign countries, and, if so, were they similar at those about the AZT trials in Africa.

Kirschstein: No, I do not think so. It may be that we should have thought of things like that. In fact, I

will add something that I did not say before. Even long after the Sabin strains were licensed, the original trials of measles vaccine that Harry Meyer and Paul Parkman did were done in the Ivory Coast of Africa. That was problematic at the time, but, nevertheless, they were done there. But to go back to the polio, the concerns that we had were how were we going to prove that the vaccine was efficacious and worked, and how were we going to show that people developed antibody as a result of getting the vaccine in a population in the United States in which the majority of people had been immunized with Salk vaccine and therefore already had antibody. And the numbers that needed to be used were very large, the number of people to be immunized. So the proponents resorted to going elsewhere. The Lederle Company had ties to a number of South American countries, particularly Nicaragua, and they did a number of studies there. Hilary Koprowski had ties to Poland, because he had come from Poland, and also to Czechoslovakia. There were people who were studying the virus in Finland. The British had not used as much Salk vaccine as we had, so the Pfizer England Company—Pfizer Ltd., it was called—did many of their trials in England, but also some in other countries. Finally, as Albert Sabin was trying to prove to everybody that his vaccine really was the one that could give immunity to vast populations without any danger, and because he had contacts in Russia, he went there and worked with a number of virologists and health ministers to do a very large trial of probably several millions of people in Russia.

Harden: And you were saying people came here too?

Kirschstein: People came here to study how to do the tests. We taught people from all over the world how to do the tests. Many of them came and stayed for weeks at a time. We had Russian visitors who came, Professor [M.P.] Chumakov and his wife, Professor Voroshilova, who were in charge of the Moscow Institute for Polio Research; Professor Smorodintsev, and others. There was a meeting here around Christmastime, probably 1964-1965, something

like that. Chumakov and his wife came with a number of other people, including two young women, one from Latvia and one from Lithuania. Professor Chumakov had a crippled right arm. He had been infected with Russian spring-summer encephalitis virus during the war, I think, and his wife had to take care of him. She was a very plain lady with braids on top of her head, and dressed very plainly. The two young women, Latvian or Lithuanian, were lovely. Most of them spoke no English. They asked could they go shopping. So I took the women shopping to Woodie's [Woodward and Lothrop] down at Wisconsin and Western, and as we walked into the store—it was just before Christmas—there was the Salvation Army lady ringing her bell. I had the worst time with the interpreter explaining this to them. They had never heard of charity and what this was all about, and they could not get it into their heads. Then we went in, and I was shocked. Voroshilova had a sheaf of money such as I have never seen, and she bought stockings and shoes—she was a heavy woman—dresses, lipstick, all sorts of things. The two young women did not have much money. Each of them had a daughter at home, and they bought the prettiest dress they could buy for the daughter. It really tore my heart apart. It was a very fascinating event. The next morning Voroshilova appeared in her new dress to give her speech with thick lipstick on her lips. But one of the other things that was interesting was that each time the Russians would come, when they left, a CIA agent would come to ask us what the visit was like. We got to know the man. In fact, one day he got in the elevator of Building 31, and I greeted him, and he looked at me like, “What are you talking about? I do not know you.”

Hannaway: Did the Russians have the equipment to do your test, or did you provide equipment?

Kirschstein: Yes. We provided the equipment. The equipment was very simple. The equipment was this little thing that probably cost \$30-\$40. We showed them how to make the slides and we showed them how to test it. This was true for everybody, all the foreign and domestic

scientific visitors. We gave it to them. We did not need X-rays to confirm the results.

Hannaway: You did not?

Kirschstein: The stereotactic studies were done with electrodes to prove we were getting into the right place, until we made this very simple little bar that had two holes in the right places. And we used a very fine drill to get through the bone and then used the syringe and needle. This apparatus probably, in the original form, cost about \$40. It probably ended up being about \$10 or \$15 apiece. We made them and gave them to everybody to use. But we told them they had to do the test right, and we taught them how to do it. I presented a paper in Munich, Germany, in probably 1967, 1968, 1969—I do not remember which—in which we again told everybody they had to do the test right, and there were people who argued with us, but we proceeded.

Hannaway: And the Russians had supplies of laboratory animals?

Kirschstein: Yes. But, of course, you have to remember that the Russians primarily imported the vaccine from here.

Hannaway: So it was American manufacturers who were making the vaccine?

Kirschstein: Yes, probably. Not all countries did that. Many of them made their own.

Hannaway: Because the figure of 77 million people being vaccinated in Russia is mentioned.

Kirschstein: Yes.

Hannaway: That is a huge number, and obviously involves a lot of vaccine and a lot of testing.

Kirschstein: Yes, that is right. A lot of it came from here. Vaccine was made in very large lots eventually.

Harden: We have noticed in many meetings that the debate between the partisans of Salk and the partisans of Sabin has hardly abated at all, and that recently there has been a decision to return to the use of Salk vaccine. I wondered if you would comment on how this decision got made and what factors went into it.

Kirschstein: I will to the best of my ability, but I do not know all of them because it was done over in Biologics, and I was not privy to any of those discussions. The debate was hot and heavy, and there probably is no doubt, as I said a few minutes ago, that improved Salk vaccine could have eliminated the vast majority of cases, and could have prevented epidemics. The incidence was very low before the Sabin vaccine was used in large numbers of children. The issue was the gut immunity, and also, once people realized that you could use a sugar cube or a pill rather than an intramuscular inoculation, number one, they preferred it, number two, it was cheaper in terms of giving the vaccine. It was not cheaper to make, but it was cheaper in terms of giving the vaccine. And, three, there was a sense that the gut immunity was probably important. Now, on a very personal note, I was always concerned about the few cases of polio that did occur and felt that, in the best of all worlds, ideally both vaccines should be used. In fact, by virtue of the particular age of my child, he got both, and, frankly, I would not have let him get the Sabin vaccine if he had not had the Salk first. At this point we now have no polio in this country, and only the possibility--until it is eliminated from the world, which is apparently taking a little longer than anybody expected--of getting wild virus from immigrants or on the borders or from people coming in for some reason or another who are carrying the virus. The danger, then, of an occasional case with the Sabin vaccine exceeds that of the danger of not having gut immunity. I believe the recommendations are to go back and finally do both, but I am not sure of that. You would have to check that with probably Kathy Zoon or Carolyn Hardegree over in Biologics. I have not read much about it, but I believe I read that.

Harden: But there was nothing that you know of with respect to trying to eliminate polio in Third World countries that might have to do with the ease of whether something had to be refrigerated or not refrigerated, or the ease of using it.

Kirschstein: The ease of using it in Third World countries, there is no question. You could not eliminate polio in the world with inoculation. It would just be horrendous to do that. So you are going to have to use the Sabin vaccine. I am talking about this country when I say both vaccines. They are very close to eliminating polio. The predictions are for about the year 2003. The World Health Organization is working on this now. Whether they will succeed or not, I do not know. You have to believe that they will, because they were able to do it with smallpox, which is a scarification, but that took great effort.

Harden: So, then, the actual emphasis would be to use the Sabin vaccine in the Third World?

Kirschstein: Yes, and both vaccines in this country. I think so, but I am not absolutely sure. I do know that, over the years, the Connaught Laboratories in Canada, which actually is owned by some other company now, was making both vaccines. We used to go up to Canada and we taught them how to do the test too. The Connaught Laboratories is a very fine laboratory. They are associated with the University of Toronto Medical School, and they had some of the best scientists around in the business. They probably use both vaccines in Canada, in some populations, and Connaught was making a very good and very efficacious Salk vaccine, which has now been reaffirmed and relicensed in this country, so I know it is being used. But I do not know the details. I have long since moved away from that area.

Harden: When you mentioned your child growing up, all of the people in Biologics were living in the community here. Did the school system seek your counsel as parents who had special knowledge?

Kirschstein: No. Actually, I think it would have been unethical for us to do that. We were involved in control, regulation. It was the Surgeon General's responsibility to talk about such things. I had opinions, but.

Harden: Okay. It is always interesting to inquire about a scientist's view of the public/private

relationship.

Hannaway: In the discussions over starting to use the Sabin vaccine, Dr. Shannon seems to have been involved in saying that there should be a delay in the start because of this problem with the Type 3.

Kirschstein: I did not think Dr. Shannon was here then.

Hannaway: He is quoted in newspaper articles of the time, and then later he talks about this.

Kirschstein: It could be. I do not remember that.

Hannaway: I was just curious if you had known about it.

Kirschstein: I do not remember that. Joe Smadel was one of the members of the Advisory Committee to the division and to the Surgeon General. It was Smadel and [Dr.] John Paul and [Dr. Alexander] Alex Langmuir and [Dr. William] Bill Hammond from Pittsburgh, and Bodian, and a couple of others, I guess. But Shannon would have relied on Joe very heavily. I do not think Shannon understood anything about this at all.

Harden: I noticed that in a paper that you published in 1960, paper 6 in your bibliography—this is really a broader question than the paper itself—it is one you co-authored with [Dr.] Paul Gerber, you determined that RNA from Type 1 polio virus carried the genetic information which determined the degree of neurovirulence.

Kirschstein: Yes.

Harden: Now, what intrigued me about the paper was the fact that you did this study at this particular time. You said in the paper that the method to extract RNA from viruses was only two years old at that time, and in 1960—this is the period when Marshall Nirenberg was working on the genetic code and using RNA. I just wondered how much interaction there was on campus with this group.

Kirschstein: Paul Gerber was both a superb virologist and biochemist, and he may well have talked to Marshall. I do not know. Paul developed, as soon as he could, techniques to study RNA.

He was interested in the RNA of many viruses, and probably the DNA too, but RNA was easier to work with, and polio virus is an RNA virus. So we were very anxious to do that. There were a whole series of people who were trying to prove that naked nucleic acid was infective. Paul had done it first in cell culture and had written some papers on that. Then he asked me to work with him to inoculate and study the monkeys. So that is what we had done. I do not know. I am sure that he worked with and talked to a lot of the scientists in the rest of the place.

Harden: Do you recall any other special things about the beginnings of the understanding of DNA and RNA and how the genetic code worked and what it might mean for virology?

Kirschstein: The only thing I remember is that Marshall Nirenberg and his wife lived in the apartment house here, as did Alan and I, and we knew them a little bit. Marshall was a very quiet, unassuming individual, and when we heard what he had done, we just could not believe it. It was the most marvelous thing in the world. He is a lovely human being.

Harden: In the virus B studies that you did, too, the virus had many names, and I gather it was a simian herpes virus.

Kirschstein: Yes.

Harden: What is it called today?

Kirschstein: Herpes simian B.

Harden: Okay. Is there any comment about it that you would like to make?

Kirschstein: It is a very interesting virus, because it was discovered by [Dr.] Albert Sabin. Somebody else had actually discovered it too, and called it W, as I remember. But Albert found this herpes virus in monkeys, was not sure of how dangerous it was, and luckily did not find out. Just as all of us humans are probably infected with herpes simplex, since it is a latent virus that has been around forever, herpes virus B is also the simplex virus of rhesus monkeys. You can actually see in a few monkeys some funny brain lesions with

inclusions in them which clearly are due to herpes B. But that did not matter so much. They clearly were carrying the virus in their mouths, in their saliva, not dissimilar to humans. The real danger was monkey bites. And working with monkeys is very difficult. We had a whole series of animal caretakers and laboratory technicians who used, in those days, the most crude methods to catch the monkeys in the cages. They had a long metal pole with a canvas brown bag sewn on a hoop. Monkeys were usually caged together; two, at least, together, sometimes more. The bag was thrown in. They would get it over the monkey, then open the cage just enough to get the animal out, slam the cage door closed, and throw the bag down on the floor. Then two of them together would sort of feel around where the arms were, catch the monkey's arms inside the brown bag, and lift the bag up and finally get their hands on the arms themselves, take the animal out of the brown bag, and control it. They put the monkey down on a wooden board which had two metal things at each end that you could wind rope around and tie around the ankles and around the wrists. The monkeys were either on their stomachs if you were going to inoculate them in the spinal cord or brain, or on their backs if you were going to draw blood from them. Blood was drawn from the femoral vein. Most of these were men were absolutely wonderful. A few were not. One of them, George Rusten, that I told you about before was absolutely marvelous. None of them had more than a high school education; some of them had less than that. Inevitably, they were going to get bitten, and they were. We knew during our work that there had been people who had been bitten and people who had died of B virus infection. By the time we started the Sabin work, there probably were 12 deaths, maybe more. All we could do was lecture the men about being careful and scare them into being careful. We had no idea whether anything would work, but it was our routine that if they got bitten, we sent them to occupational health, where they got a very large dose of immune gamma globulin. That is human immune gamma

globulin. I am sure it had no antibody to B virus. But, on the assumption that it had herpes simplex antibody, we gave it, and, in addition, it was not very pleasant and they were more careful for a while. We had nobody, in the time that I was there, who got bitten and who got the B virus. We also did some experimental work on hepatitis trying to transmit it orally quite late in the period, just before I left. We were holding the monkeys' mouths open with a stick and then moved the stick from monkey to monkey to monkey and spread the B virus throughout the monkey colony. We were in the middle of the experiments, and I had everybody gowned and masked, including me, and we finished the experiment and we got away with it. How we did, I will never know, but we did.

Harden: Let us continue on that line.

Hannaway: Just to complete this, I was going to ask, what numbers of animals are we talking about that you had tested?

Kirschstein: Oh, my goodness. For the Salk vaccine, we used 20 animals per test. For the Sabin vaccine, we used 20 animals intra-thalamically, five animals per dose intra-spinally, and we used at least three doses, so that was 15. We were using 35 animals per test. We were testing vaccine sometimes six days a week. The test went 14 days, and then the animals were autopsied. We had men working overtime, Saturdays, Sundays. I would go in on Saturdays and Sundays. It was a horrendous time. We worked very, very hard. Because once we had promised people we were going to give them the vaccine, we had to get it out, and we wanted to be sure it would be safe.

Hannaway: Right.

Kirschstein: So we did thousands and thousands and thousands of monkeys. They were all, at that time, being imported from India, some from the Philippines. There are four types of Old World monkeys. Old World means where they came from, not necessarily what is the Old World and what is the New World. The reason they are called Old World is because

they are from Africa, India, and Southeast Asia. New World is this new world.

Hannaway: The Americas?

Kirschstein: The American world. New World monkeys—squirrel monkeys, marmosets, etc.—cannot be infected by polio virus. Only humans, chimpanzees—I have no idea about gorillas and orangutans, but I would assume that they might be—rhesus monkeys, which are from India and Pakistan, cynomologous monkeys, which are from the Philippines, vervet and red patas—vervets are the greens (*cercopithecus*) and patas are the reds, which are called *erythrocebus*--can be infected. But the vast experience was with rhesus and cynomologous monkeys, and even then mostly rhesus. So they were being imported by the thousands from India in the most crude conditions—dirty, filthy, infected with everything known to man, including tuberculosis. While we were lucky and never had any B virus infection, every monkey was skin-tested for tuberculosis. They were put in quarantine for a period of time when they got here. They had been put in quarantine first by the company that sold them to us. We did not trust their quarantine procedure, so we put them in quarantine again, and used them only after they passed the quarantine. Any monkey that was tuberculosis positive was destroyed. Some of them tested negative, and they were still found to have tuberculosis when you finally autopsied them. We did have some men who developed tuberculosis—not many, but a few—and it was really terrible.

Harden: The NIH Animal Farm at Poolesville apparently raised a number of animals. Was it impossible to raise these monkeys?

Kirschstein: You could not raise them at that time in the numbers needed. Now they are doing it. There was a colony that was being set up in Puerto Rico. There are a couple of others. [Dr. Mortimer] Mort Lipsett and the people in the Child Health Institute were trying to figure out how you could increase the fertility of rhesus monkeys. It is not easy. They used all sorts of things. I did a number of studies on newborns, trying to see if we could

infect newborn monkeys with some of the so-called tumor viruses. We did a few studies with some of them. Mostly Al [Rabson] was collaborating on that. But you could not raise a sufficient number of animals then, in the 1950s, 1960s, and 1970s, for the thousands and thousands of monkeys you needed to do testing of polio vaccine. The monkeys are pretty clean now, and although I do not know for sure, I think they are raising them. It is a different era. But you could not do it then. You could not afford to use chimpanzees at all, and, besides, they are impossible to handle. Chimpanzees were used, and still are being used, for hepatitis and AIDS. The monkeys also, as opposed to dogs which can be trained, cannot be trained. They are incontinent. I mean, there are people who talk about having pet monkeys and they keep them in diapers, and so forth. I do not believe it. They are filthy creatures. They really are. And they smell. The men were very good about trying to keep the cages washed and cleaned, and the monkey was a very difficult animal to work with. But we did.

Harden: You published a paper in 1970 about the NIH Quarantine Unit. It apparently had been established in 1955. This paper struck me as similar to your paper about how to inoculate the monkeys for the safety test, that it was either a part of your job or you felt it was necessary to instruct people to pass it along so that they would do it right. Tell me about the development of this quarantine unit and what you were doing.

Kirschstein: I cannot remember. Let me see the title of the paper. There was a meeting in either Switzerland or Germany—I cannot remember—and I was asked to attend and talk about our work. It may have even been in Israel, if I am not mistaken, now that I think about it. [Dr.] Amos Palmer actually had developed the program; he was a veterinarian who was working with me. Again, it was very important to make sure that the monkeys would be as clean as possible and as free of any viruses as possible, and so we developed a program for testing them. Again, the other thing was to try to make the test as

reproducible as possible, and that was the basis of the program. It was not so much about quarantine as about how to develop the program with animals that were as healthy as possible in order to have reproducible testing.

Harden: It was something that NIH, I guess, had done.

Kirschstein: Yes.

Harden: And that maybe other people did not know about.

Kirschstein: That is right.

Harden: It reminds me that, on several fronts, the NIH has had to educate people as well as do research in terms of these things.

Kirschstein: Yes, and most of the development of the testing for any vaccine and some of the parameters of the vaccine, all of them were developed at the NIH. For instance, Dr. [Margaret] Pittman's work on pertussis, Carolyn Hardegree's work on cholera, the work on measles and mumps—all of this was to find the best way to do things to teach this and then export it to the world and to other companies, other countries, and other scientists along the way.

Hannaway: Would you tell us a little about your interaction with the World Health Organization just to wrap up your polio years?

Kirschstein: The WHO had groups of expert committees that met to set up standards of how vaccines or drugs, if it were drugs, should be made. In the early stages, Dr. Murray went to those meetings. He was not as cognizant of the details on polio, so he asked me to go. I went two or three times, particularly for discussions of live polio. There were considerable differences among countries, and we had to adjudicate and be very diplomatic. The Russians wanted to be in charge. WHO was an interesting organization at the time, and it got worse for a while and now is getting better again. It was very concerned about the big gorilla, the United States, and wanted to be sure that we were not inordinately

powerful. So one had to be extremely diplomatic in what one said and did. We worked very, very hard. We would arrive early in the morning in Geneva time. They never sent you anything in advance. At your hotel, you found a stack of papers this high which you were expected to read by the next morning, and you kept falling asleep. So then we started working. It was an interesting time, an interesting set of events. I probably did not enjoy it as much as some people did because I did not like being away from my husband and my son, but I would go and I got to know some people very well. I became, again, friendly with the two Russians, Chumakov and Voroshilova. The last time I went to WHO—I do not remember what year that was—there had been a change in the Russian dictatorship, and Professor Chumakov who had been in with the former dictator was not in anymore—I do not remember if it was Khrushchev or beyond; it was probably Khrushchev—and he was not allowed to come. His wife, Marina Voroshilova, came, and cried and cried about how awful their life was and was there anything we could do to get them out. Of course, there was not. It was very sad.

Harden: As you were finishing up the polio work, you began working with Paul Parkman and Harry Meyer on the rubella vaccine. Is there anything special you would like to say about your contributions and what happened there?

Kirschstein: As a matter of fact, I was not in a sense finishing up the polio work. The situation was that the testing of polio had become more routine. They needed someone to work with them to see whether rubella vaccine, made from an attenuated rubella virus, was going to be neurovirulent or was going to cause any problems. They basically asked me to help them, and I worked with them. They were fairly gracious and included me on their papers. Harry Meyer and Paul Parkman were Joe Smadel's protégés, particularly Harry. Harry had been an Army officer at the Walter Reed Army Medical Research Institute and had worked with Hope Hopps and Betsy, whatever her last name, and Nancy, whatever

her last name was. And Joe brought Harry to the NIH. Then Harry, who was trained in pediatrics, in turn brought Paul Parkman. When Joe became ill and stepped down, Harry took over the laboratory from him. By that time, George Hottle was gone and Harry was really in charge. I had my own laboratory and I was doing a number of other things. But we worked together. Paul Parkman is still around. Harry has retired and is living out in Seattle now. They just simply asked me to help them, and I did. The rubella vaccine was an interesting story, because they were working on the attenuation of rubella at the same time as a number of other people were. There was a race, which I think was equally won by two groups, and I have never been quite sure who got the credit for it. I cannot remember the other group. I think it was up in Boston, [Dr. Thomas] Tom Weller's group, but I am not sure. They had learned their lessons pretty well from Joe Smadel. Harry had many of Joe's characteristics.

Harden: Dr. Parkman does not strike me, however, as being like Dr. Smadel.

Kirschstein: Dr. Parkman is a lovely, charming, delightful human being who, when he decided he wanted to do something for somebody, did it without questions being asked.

Harden: Interesting.

Hannaway: Would you speculate, if you feel like it, on why so few additional vaccines have been developed since 1968?

Kirschstein: Because of the liability. The lawyers learned that they could get enormous sums of money for people who claimed they were injured as a result of a vaccine. It is probably a child, or a mother who has just had a baby, or something of this sort, so it tears at juries' heartstrings. Making vaccines is very expensive, and you do not make the profit on them, or at least manufacturers did not think they made the profit on them that they did with drugs. You have a population that is of a more limited size. After all, there are millions of people with hypertension that you can give a drug to. There are millions getting a

vaccine only once, and then a small population continues to get it. So the liability is the problem. Every one of the developed countries in the world, except the United States, back in the 1960s, had indemnification programs for vaccinations. They required vaccination, and then if somebody had an adverse reaction, they simply indemnified them. We did not have that for a very long time. We do now. But also it is not, from what I gather, enormously successful because, although there was a trust fund established, there were enough pertussis cases that they ran out of money. I do not know whether they have set it up again or not, but the fund has always been short of money. It is similar to how we handle health care in this country compared to the way they do it in the rest of Europe, Canada, England, and so forth.

Hannaway: Do you think that better education of the public about vaccines would help people understand that there is always *a* risk?

Kirschstein: Yes, but we are a litigious society in this country, much more so than our European brethren are, for example, and manufacturers do not want to take a chance. Now, what will change this is federal support for the development of new vaccines. The most wonderful thing is [Dr. Albert] Al Kapikian's rotavirus vaccine. He worked 20 years on it before it got approved. AIDS is clearly going to have to be solved at least partially with a vaccine. [Dr. Richard] Dick Krause said, when he was director of NIAID, that one of the reasons he became less interested in that directorship and left—you need to confirm this with him, but I think I have heard him say this—was that with the advent of antibiotics, and with vaccines for the major viral killer diseases in this country--though we are beginning to see reemerging ones and newly emerging ones--he could not get people in the Congress interested in infectious diseases. So his budget did not go up when all of the other institute budgets were going up. To some extent that was true, but that was before AIDS and before the recrudescence of tuberculosis. The really amazing

thing is that it has been so difficult, compared to the rapidity with which antibiotics were found, to find really good antiviral drugs. They are coming, but they are very slow to appear. The anti-reverse transcriptases, and the new anti-nucleases, and so forth, are making these things happen, but they are slow and it has not been a real growth industry. There is renewed interest in vaccines now, but it will have to be the government that will spend the money. The manufacturers will not spend the money.

Harden: When you were talking about the numerous monkeys that you had to use, I thought about how expensive a process this was. The manufacturers were not paying for any of this directly, were they?

Kirschstein: Oh, yes.

Harden: They were?

Kirschstein: They paid for the tests that they used in order to obtain their licenses. But they did not pay for the testing that the government did.

Harden: When you were doing the tests here on the campus, you were testing the manufacturers' lots and were going to approve their licenses.

Kirschstein: They had to test them, too.

Harden: Yes, but the work done here at the NIH?

Kirschstein: They did not pay for that. The government was paying for it.

Harden: We are about to move into discussing your larger administrative career at this point in the series of interviews, and before we stop today, I wondered if there is anything else that you want to comment on about particular research projects before 1965.

Kirschstein: I remained active in a laboratory until I left Biologics. I became a laboratory chief, and then I became an assistant director and I continued all the work in the laboratory. I just added the new duties onto everything else.

Harden: At some point you made a comment that when you became a laboratory chief, you started

to have a different view.

Kirschstein: I was being involved in more and more of the regulatory things. Rod Murray, interestingly enough, began to rely very heavily on me. It is fair to say, I guess, in those last years, he was not well, and he began to rely more and more heavily on me. So I did a lot of administrative things for him and was in on almost all the decision-making for many products.

Hannaway: So you were really having training in administration for the next stage of your career.

Kirschstein: Yes, but I was self-trained, because Dr. Murray was not a very good administrator.

Harden: At the point when you were named laboratory chief—this is not an easy question to answer—did you have a sense that your promotion came because of your long line of work primarily, or was it more a reward for the safety test for polio?

Kirschstein: Partially each of these, and partially a sense that pathology was going to be more important in all sorts of testing of biological products. We were beginning to worry about preservatives in vaccines and other products, and I did a study on preservatives. We were worried about tumor viruses, and so we needed to look at various animal testing to see whether there were things that would cause tumors. It was both a realization that pathology was more important, a realization that I had reached a stage where Rod Murray wanted to use my advice and did not see any reason to go through other people, and most of it was a reward.

Harden: Very good. I would like to stop here for today and say thank you.