This is the second interview in an oral history with Dr. Ruth Lillian Kirschstein.
The interview is being conducted on 29 October 1998, in her office at the National Institutes of Health in Bethesda, Maryland.
Interviewers: Dr. Victoria Harden and Dr. Caroline Hannaway.
*Please Note: These Interviews Have Not been Verified for Accuracy*

Harden: Dr. Kirschstein, after we had finished our first interview, it occurred to me that there was one question that we had not asked you. You have kept your maiden name. This is a very common thing to do now, but it was not necessarily so common previously. Was there some person who inspired you or some reason you decided to do this?

Kirschstein: There were several reasons, one of which was very practical. I did not anticipate having the kind of a career I have had, nor did my husband, Dr. Alan Rabson. We both thought that we would probably end up practicing pathology in the same hospital and that it would be confusing to have two Dr. Rabson's. But, above and beyond that, was another reason. I was an only child, my parents were not wealthy and had found a way to support me through medical school. My father had never had a son. He had wanted to be a physician and he had not become one, and I thought it would be an honor to them to keep my name. For both reasons, I have been delighted that I did it.

Harden: Have you ever received any criticism or snide remarks about this?

Kirschstein: No. People have been confused by it. I had one very unpleasant experience, and the man who treated me unpleasantly this way knew exactly what he was doing. We went to a social event at the home of a well-known hematologist who had

trained me. When we came in—and he knew both of us very well—he went around the room and introduced us as Dr. Kirschstein and Mr. Kirschstein, and that did not go over very well. But other than that, I have had no problems.

Hannaway: Now we would like to start talking about your career in the Division of Biologics Standards. In 1957, you began working in the Laboratory of Viral Products of this division, and, in the previous interview, you told us about the application process and some problems you had with your civil service rating for your position. I would like to discuss your polio research in more detail a little later in this interview. But, first, was the expansion of the division following the Cutter incident a factor in how you obtained your position?

Kirschstein: Yes. The testing of the Salk vaccine lots produced before the Cutter incident was quite minimal, and was expanded for those starting to be produced shortly after the manufacturers went back into production. The individual in the then National Institute of Arthritis and Metabolic Diseases in charge of this had other duties as a pathologist and felt that he could not go on doing all of the work. He told the Institute he needed some help. The decision was then made that since the Division of Biologics Standards had become a separate entity, it would hire somebody who was on its rolls who would work in the Laboratory of Pathology of NIAMD on polio. The person would be taught by Dr. Louis Ashburn, a physician pathologist there. It was not until later, when the Division of Biologics Standards built its own building that I moved to be within the new building. That was about three years later.

Harden: Which building did you actually work in?

Kirschstein: Four. I was in Building 4 for three years. By either late 1960 or it could have been early 1961, but I believe it was 1960, Building 29 was opened. What happened was that at the very end of the year, in the appropriation, NIH got some extra money. Now the Division of Biologics Standards did not get its own appropriation in those early days. It was through the Office of the Director. A decision was made very quickly that they would build a building for the Division, and so they took the plans of Building 4, Building 2, and Building 3 and simply adapted them with a little bit of a modern touch and built Building 29 very quickly.

Harden: We will come back to that shortly. But we got out the old phone books, trying to get a sense of the structure of the Division, and it appeared to me that most of the staff were in Building 8, although Dr. George A. Hottle was in Building 5 at one point. So was the staff spread out?

Kirschstein: Yes, the staff was spread out. In fact, I did not get to know many of them very well in the first couple of years, when I was in Building 4. It was not a cohesive organization. What had happened was, it had grown out of a crisis. Dr. Roderick Murray had been appointed as a reluctant leader. He really did not want that job. He was a very introverted, shy South African, and realized, I think, in his own mind, that having that enormous responsibility was not something that he would either enjoy or wish for. He had been working for Dr. William Workman before. He was a commissioned officer in the Public Health Service, and they told him he

had to do it, and so he did do it. The staff was mostly in Building 5, because that was where the infectious disease people were. As they expanded, they put people in Building 8, and they put me in Building 4. Dr. Hottle had been at Fort Detrick. A lot of people here at the NIH, after the war, and even after the Korean War, came down from Detrick, and he was one of them. He was a newer employee because of that, so they probably did not have room for him in Building 5 and moved him into 8. It became clear that they needed this new building, and when they got this windfall of money, they built it in a hurry.

Harden: Do you have anything else to add about Drs. Murray and Hottle as scientists, their personal research, and how they were as supervisors?

Kirschstein: By the time I knew Dr. Hottle, he was no longer doing research. He was leading a laboratory and was a wonderful man. He was not a strong leader, but he was fine. Dr. Murray had had a very good career in the Army, working on hepatitis during World War II. There were outbreaks of hepatitis A primarily, some B, in Africa, during that invasion, and in Italy. He had worked on that and had actually done some work to try to inactivate blood, in one case, and some other things to prevent hepatitis, and had had an unfortunate experience. A number of people had died of hepatitis following his studies. He was a very fine researcher.

He was a consummate South African gentleman, everything that you expected of that apartheid society. He was an elitist and very proud. He had gone to Harvard, married a woman from Massachusetts who worked in the Cancer Institute, Barbara Murray, and was really quite a private person. I probably got closer to

him than almost anybody else because we worked so closely in the days of the live polio vaccine, not so much in the killed polio vaccine days, because I was in a different building.

I do not remember the date but it was in the early 1960s that Dr. James Shannon, as director of the NIH, brought to the NIH as his deputy director for science Dr. [Joseph E.] Joe Smadel, from the Walter Reed Army Medical Research Institute. As shy and introverted as Rod Murray was, Joe Smadel was just the opposite. He was the brashest, rudest, most profane, difficult person I think most of us had ever met. And he worked here in this room [Dr. Kirschstein's office] for two or three years. I do not know what happened, whether there was a problem or whether they thought that somebody needed to watch out for what was going on in Biologics, but Smadel was sent over [from the director's office] to set up a second virus laboratory. I guess it was called the Laboratory of Virology and Rickettsiology, something like that. Smadel clearly was running DBS behind the scenes, for the years that he was there.

Hannaway: He was a behind the scenes director?

Kirschstein: Yes, I think so. He did talk out loud and handle things when there were committee meetings and so forth. He let Murray, ostensibly, lead, but nothing really was done without Smadel's direct okay, and he clearly was still very, very close to Jim Shannon through all of that.

Smadel did know science in a very real way, and he had many ties to the people at the Rockefeller [Institute for Medical Research] through his time in the military

and to the people who were supported by the National Foundation for Infantile Paralysis. Again, it was this fact that many vaccines were developed as a result of the needs of the Army, and he was a very big force at the Armed Forces Epidemiological Board. He brought with him three women who were his "gofers." They were very high level technicians, and he told them what to do. They would bear his messages, and so we would all get, "Dr. Smadel says to do so-and-so." A couple of times I got pretty angry about it and said, "If Dr. Smadel wants me to do something, let Dr. Smadel tell me," and then he would. So he was an interesting man.During the war, he had been an officer in the Army. When World War II was over and he went to Walter Reed, he became a civilian, but he sure acted like he was still an officer.

Harden: He is one of the very interesting characters who has come up in a variety of ways. Dr. Margaret Pittman described him as a giant of medical science. Dr. Stetten thought, as you had said, that he was the rudest, crudest human being I think he had ever met. So, clearly, the man inspired strong feelings.

Kirschstein: Yes. You have to remember that Margaret Pittman had worked at Rockefeller.

Harden: That is right.

Kirschtein: I do not know whether she knew him from there or not. In some ways he was a giant, but he was a giant who knew exactly what he wanted to do. He could inspire people. There was no question. There were friends of mine at Tulane Medical School, one was a classmate, the other one was a year ahead, who married and came to Walter Reed for a while. Then he sent them to Thailand to

work on one of the rickettsial diseases, scrub typhus or something of the sort, and they were deeply devoted to him. The man, Dr. Bennett Ellisberg, was one of the gentlest people I ever knew, and yet he was deeply inspired by Joe Smadel.

Harden: Let us talk about pathology at the NIH when you arrived. You had said that were three concentrations of pathologists, the one in DBS, the one in the Arthritis Institute, and the one in the Cancer Institute. We will come back to the one in the Division in a minute, but let us start with Dr. Ralph Lillie's Laboratory of Pathology and Histochemistry in NIAMD. He was nearing the end of his career when you arrived.

Kirschstein: Yes, but he was still as sharp as he could be.

Harden: I would like for you to talk about him. I ran into him when I was doing my book on Rocky Mountain spotted fever because of his publications on the pathology of spotted fever. Could you describe him as a person and the work of his laboratory?

Kirschstein: Dr. Lillie was a giant in those days. He had been here for many, many years. That is how he did the work on Rocky Mountain spotted fever. There is, if I am not mistaken—and you need to tell me if I am right or wrong—a paper by Joseph Goldberger and Ralph Lillie. I am not absolutely sure of that, but they did know each other. I know that, because Goldberger worked on infectious diseases. And Dr. Lillie left for a while. He developed a good deal of histochemistry during its early days. He had very specific ideas about what he wanted to do, and he was not particularly interested in this group that came down from Boston to set up the Cancer Institute. One of the people he particularly was not interested in was Dr.

Harold “Red” Stewart, and Harold Stewart was not interested in him. They did not like each other at all. So one of the interesting things is that when the hospital [Clinical Center] opened, the question was who was going to do pathology for the hospital? Neither man would give in, in terms of who was going to support what and who was going to provide the money, and that is how the Laboratory of Pathology, the Anatomic Lab, got to the Cancer Institute, because Stewart had more money than Ralph Lillie and he was not going to share it with him. And it is still there today in that form.Now, clinical pathology was always in the Clinical Center, under, first, Dr. George Williams, with whom I trained. Dr. George Brecher was there.

Harden: Yes. So that was yet another laboratory, clinical pathology.

Kirschstein: It was not uncommon in those days, in the middle 1950s, for there to be pathologists--particularly the old school of pathologists who believed themselves to be experimentalists studying the pathogenesis of disease, and they did it by studying stained histologic sections and then used histochemistry to determine whether an enzyme or some other chemical was present. They were a separate entity, particularly in academic hospitals, but also even in private hospitals, from clinical pathology, which was the laboratory tests. Today, it would be almost unheard of. It began to change late in the 1950s. I would guess that the group that was most influential in that regard were the pathologists who first were at the Mayo Clinic, and then populated Detroit and many other cities. So it was not surprising that in 1953, when the hospital was about to open, there would be these

two separate units. I guess in some ways you could say it is a little surprising that they are still separate, but it is the tradition now. The two groups of pathologists talk to each other more than they ever did before, and particularly in terms of hematology, they collaborate, but do not necessarily join together.

The Laboratory of Pathology at DBS was a late phenomenon. From 1957 through probably 1965, I was under Dr. Hottle, first as just a pathologist in Building 4, then as chief of a section of pathology, and, then, when Dr. Murray decided that I was pretty independent and I could function on my own, he established the independent laboratory.

Harden: So you were a free-floating pathologist, as it were, to start with, providing services, rather than a part of a larger group of pathologists.

Kirschstein: That is right. Now, what happened, and it is an interesting phenomenon, is that while I was the pathologist who was being paid by DBS but was in the Laboratory of Pathology and Histochemistry of NIAMD, I participated in some of their other activities. One of these, started by Dr.Lillie, was surgical and autopsy pathology for the Indian Health Service [IHS] hospitals, which were scattered all over the country. The IHS was not part of our department [DHHS, previously DHEW] but part of the Bureau of Indian Affairs in the Department of the Interior. The hospitals very often could not afford or could not find pathologists to do their work. We did mail-order anatomic pathology for them. They would send specimens for both surgicals and some autopsies, but mainly surgicals, in formalin into the Laboratory of Pathology at NIAMD, and people took rotations. It was

wonderful for me, because I kept my hand in in regular pathology. Even when I went to DBS, I went back one week a month and did the histologic pathology for them.

Harden: Do you have any idea why the Indian Health Service sent the specimens there instead of to the Armed Forces Institute of Pathology?

Kirschstein: First of all, the Armed Forces Institute does not do diagnostic pathology on a routine basis. It studies interesting and unusual cases, and it was not as ecumenical then as it is now. It was strictly for Armed Forces personnel. The Public Health Service does participate in the AFIP now. Second, I think Ralph Lillie knew that he could get people who wanted to keep their hands in. Third, there were a lot of interesting specimens. I actually collated and studied some of the trends in pathology among American Indians. I do not think I published a paper about it, but there is certainly somewhere in the files a report that talked about the incidence of gall bladder disease in American Indians, for example. And the rate of tuberculosis was incredible. There were lots of lungs with tuberculosis. Now, sometime maybe in the late 1960s, the Indian Health Service was moved and was established as part of the then Public Health Service, which we do not have anymore. Or we do not have it as an entity exactly the same as it was before. We still have the commissioned corps. They were able then, for all sorts of reasons, even using contractors or their own personnel, to set up their own pathology laboratories, and they stopped sending material here.

Hannaway: The other pathology group, that you already mentioned, was with Dr. Harold

Stewart, and your husband was with that group.

Kirschstein: Yes

Hannaway: Would you talk about Dr. Stewart and your husband's work?

Kirschstein: You really ought to talk to my husband about him. But Dr. Stewart was a wonderful man. He just died very recently.

Hannaway: Yes.

Kirschstein: We were getting ready to think about having his hundredth birthday party. He died at 99.

Harden: Yes. He and Dr. Pittman sat on an NIH Alumni Association committee about 10 years ago, and he was supposed to give us some pictures. His family is planning to do so.

Kirschstein: His daughter, Janet Stewart [Rowan], is a nurse in the Eye Institute.

Harden: We have talked to her. My memory is that Dr. Stewart too was a larger-than-life figure in so many ways.

Kirschstein: He was a larger-than-life figure. In some ways he had some of the same characteristics as Joe Smadel, but he was a nice man. Stewart could be a little vindictive, but he was a nice man. He was very gregarious. He had, for years in his office, a brown bag lunch every day, five days a week. Anybody who wanted to come from his laboratory or any other part of the Cancer Institute or any other place could do so, and occasionally I would go. Al would go every day to the brown-bag lunch, and they would talk about everything, anything, a lot of pathology. He would bring guests in. He was world-famous. Now, Ralph Lillie

was world-famous too, but Ralph Lillie was coming to the end of his career. Dr. Stewart's career went on for considerably longer. He had established his reputation in carcinogenesis at Harvard first, with that great group that came down here, and he was very internationally minded. He had people who would come and study in his laboratory. Dr. Thelma Dunn was with him, and she was remarkable. She became the world's expert on mouse leukemia. And he had a number of other women who worked with him as well. His wife was a nurse who worked with [Dr. Robert] Bob Chanock and others at Junior Village of D.C. on the respiratory syncytial virus [RSV] and other childhood viral infections, and so it was sort of a family venture. She was a wonderful patrician woman, and she took care of him beautifully. It was remarkable. Stewart brought people from all over the world and had a remarkable reputation. Now, he knew that he could run that laboratory of pathology and get those autopsies and surgicals done. Ralph Lillie was in the mode of "my research comes first," and Stewart's research came first [too], but he got the pathology specimens done. When they opened the hospital, a lot of people were doing the autopsies and surgicals, and they began to realize that they needed a training program, and Al was their first resident, just as I was the first resident in the clinical pathology department. He had one year to finish, as I had. Dr. Stewart liked the idea that Al had had some training as an epidemiologist, because he was very interested in studies that would look for carcinogens from an epidemiologic point of view. There was a study that he was interested in as to whether, as reported by some people, dark roast Louisiana

coffee, with chicory in it, caused bladder cancer.

Hannaway: I have heard this somewhere.

Kirschstein: He asked Al to join him, first of all because Al had some epidemiology background, and [also] because Al had been in New Orleans for a year. So they found a wonderful woman who helped them with the study down there [in Louisiana], gathered the patients, and did everything. They used to go there at least twice a year. They used to have a wonderful time because they worked very hard, but they went to every good restaurant in town, and I was very jealous. I was home with the baby.

Hannaway: You wanted to dine out too.

Kirschstein: Yes. But that was all right. I would not leave the baby for anything. Dr. Stewart and Al worked closely together. I am not sure anything really came out of the study. You would have to ask Al that. Stewart kept his laboratory going. I think probably he, like Margaret Pittman, had to retire at age 70. She had to. I cannot remember whether Stewart reached 70 at the point where you still had to retire or not. But he stayed on as pathologist emeritus, moved over and set up the cancer registry. He had Umberto Saffiotti working with him and several other people. We used to see him regularly. We would have parties. And [Dr.] Louis Thomas took over the Laboratory of Pathology for a while. When Lou retired, Al took the Laboratory of Pathology and kept it, even when he became scientific director of the Cancer Biology Division, until somebody said they thought that was not a good idea, and then he recruited somebody else.

Hannaway: You have already mentioned Dr. Ralph Lillie and Dr. Murray. Did you have any other mentors in the division whom you would like to tell us about in particular?

Kirschstein: I do not think they were mentors, the people I have mentioned to you. They were colleagues.

Hannaway: They were not mentors.

Kirschstein: Margaret Pittman and I became colleagues later. She brought some nice young people there, and there was a wonderful woman who came. She was a pediatrician who came shortly after we moved into Building 29, and who is still there, named [Dr. M.] Carolyn Hardegree. Carolyn had gone to the University of Minnesota to train in pediatrics. Like me, her husband was coming to NIH to be in the Neurology Institute, as part of a doctor draft, and so she came too. She was interested in bacterial diseases, particularly cholera, and so she set up a laboratory. We had a decision that we all made and stuck to in Building 29, that, because we were working with infectious diseases, it was not a good idea to eat in our laboratories. Some people violated that, but most of us did not. There was a conference room, which was at the back end of Building 29, with tables, and we would all meet every day for lunch down there. We had some wonderful, lively discussions, and Carolyn and I became very good friends and still are today. There were others as well, a wonderful man who studied hemophilia and clotting factors, named [Dr.] David Aronson, in the Blood Division, who is no longer there and has retired. He left and went to George Washington [University]. He would be one of the group. There were a large number of people. Carolyn and I

were probably the closest.

Harden: So there would not be anybody, then, that you would see as a mentor the way that you might have when you were in college or medical school.

Kirschstein: Not really.

Harden: I would like you to talk a little more about Dr. Pittman.

Kirschstein: Did you get anything from her before she died?

Harden: I have all kinds of things from her. I have an interview with her and I have some photographs. Many of the women who came early to the NIH were in Biologics Standards. I got the sense that they were *put* in Biologics Standards to some extent—not to denigrate Biologics Standards, but that somehow chemistry?

Kirschstein: No, I do not think so.

Harden: Chemistry was more macho? I do not know.

Kirschstein: No. I think it was not because *they* were put in, but because women in that era did microbiology. They did not do chemistry.

Harden: Thelma Dunn certainly was in the Cancer Institute.

Kirschstein: Yes, and Dr. Stewart and Thelma Dunn and [Dr.] Lucia Dunham and Katherine somebody, and then [Dr.] Wilton Earle.

Harden: Katherine Sanford?

Kirschstein: No. Sanford was in NCI with Earle.

Harden: You are right.

Kirschstein: It was another Katherine. And Wilton Earle had two women with him. Arthritis probably did not have very many people. Ralph Lillie did not exactly like women.

He probably had more prejudice than most. I think it was because the women were microbiologists, and they were good microbiologists. Many of them had probably started out as technicians and had gone on to earn doctorates. Now, one of them was a physician whom I knew, but she had retired by the time I got there: [Dr.] Sara Branham.

Harden: Yes.

Kirschstein: Margaret Pittman introduced me to her. Sara actually got me to join the local chapter of the American Medical Women's Association, but then I got too busy to go to the meetings and dropped out. She probably was busy with it after she retired. She worked on meningitis. Margaret worked on pertussis. I do not think it was that they were dumped in Biologics at all. Now, Sarah Stewart was in the Cancer Institute.

Harden: That is right.

Kirschstein: [Dr.] Bernice Eddy, again, was a microbiologist. I think that when they were busily putting this organization [DBS] together, which they had to do almost in a crisis mode, they pulled everybody who was doing anything that related to the microbiological products to be in DBS. Then they pulled in a man to run the blood group, Ted Tripp, and George Hottle was there, and there were a lot of other women. I do not know whether there were a lot of women left—there probably were not—in what became NIAID, but there were some. But Margaret Pittman was one of the most remarkable women I have ever known.

Harden: She came in 1937, I believe it was, with an international reputation from the

Rockefeller Institute. I cannot believe that it would have taken 20 years for a man with those sorts of credentials to become a laboratory chief.

Kirschstein: You are absolutely right. She came in 1937, which was still in the Depression, and I remember her telling me that she came to work for something like $3000 or $3600 a year. She was used to all sorts of adversity. She was a very spartan lady. She grew up in Arkansas. Did she talk to you about living in the country; her father would drive them down to the city so that the daughters could go to Hendrix College [Conway, Arkansas] and get a good education every winter, and then go back. She rode a horse and she knew how to shoot. She used to shoot alligators.

Harden: She was very resourceful.

Kirschstein: A very amazing woman. I agree with you. I do not think it would have taken a man that long to become a laboratory chief. She did not push. She did not care. She wanted to do her work.

Harden: That is right.

Kirschstein: That was what she was dedicated to, and I think, that if she had not had to make a living, she probably would have done it for nothing, because she really was that dedicated. When we made her retirement party—maybe I told you last time that I made her retirement party for her. She had to retire at the age of 70, and I put on the party. We had it over at the Officers' Club, National Naval Medical Center [Bethesda, Maryland], and people came from all over. It was amazing that they came, because it was the snowiest January night, and I could not figure out how

everybody was going to get there, but they did. And she came back to work [at the NIH] the next day as a volunteer.

Harden: Yes.

Kirschstein: She worked until about three years before she died. I also cannot believe it took them that long to name a lecture after her.

Harden: Even so, as you said, my experience of her was that she focused intently on the science. It was all-consuming.

Kirschstein: Absolutely.

Harden: Is there anything else that you think remarkable about when you first met her or how she went about her activities, just for the record, that you can say?

Kirschstein: She was in many ways a very private person. She lived alone. But she mentored and took Carolyn Hardegree under her wing and made Carolyn what she is today. And Carolyn will tell you that. You asked if I had mentors. By the time I got to know Margaret, I was pretty well established. I guess I just *grew like topsy* and never particularly had mentors. I had teachers, but not real mentors. I do a lot of mentoring of young women as well as men these days because I enjoy doing it, and it always amazes me but it never occurred to me that I needed the same thing. Margaret was an extremely proper individual. She had very strong ethical and moral standards, and she kept to them. She believed firmly in what she was doing. There were people who were concerned that there clearly were problems with the pertussis product that was being made and thought they were rather slow in finding out what it was, but she doggedly went ahead and finally figured some

things out.

Harden: In reading your 1950s and early 1960s publications, I have identified several major lines of research. I am not sure I got them all right. Here is my categorical list, with your papers numbered as they are in your curriculum vitae. I saw the 14 papers on polio, then the virus cancer work and the virology work, especially with respect to vaccine production, immunology, and biologics control administration, research techniques, the Food and Drug Administration, and finally some miscellaneous studies like poison ivy. One or two of these papers seem to overlap. I put them in both fields. We would like to explore each one of these lines of research, but to vary it, we want to talk a little about your virus cancer work at the beginning and then move into polio, if we can.

Hannaway: Would you like to tell us about general thinking on the relationship between viruses and cancer in the late 1950s?

Kirschstein: I actually got into virus cancer work in two different ways. One was because it was something that Al was really interested in, and we collaborated on some things. The second was because the polio strains were contaminated with SV-40, which was found to cause tumors in hamsters. I described my basic activities within Biologics, other than the absolute testing of vaccine, as studies of viral pathogenesis, of which the induction of tumors was a part. So those are the two ways I got into it. The other thing I did—and that is personified by papers two, three, four, as a starting point, and there were others as well—was to collaborate as a pathologist with many investigators who needed that kind of collaboration.

Now, there are a fair number of people who believe that if you look at a slide, that is not collaboration. You are doing a service for them. That is probably true. What I tried to do, and I think I succeeded, was to convince these people that they would be better off and the work would be done better if, instead of their doing their experiments, doing the autopsies on the animals, putting a piece of tissue in formalin and getting a slide and then coming and asking me to read it, or even asking me to have it made into a slide, we could talk about it from the beginning and plan the studies accordingly. I was pretty successful at that.

Harden: Let us begin with paper two, which describes the difference between lesions caused by a virus infection itself and the neoplasms that are caused by viruses. This must be a very interesting kind of a problem to try to figure out what the difference is.

Kirschstein: It is. Actually, the last author is the person who really was working on these viruses. It was [Dr. Lawrence] Larry Kilham. Larry was an amazing individual, a physician who was also a naturalist. He became interested in unusual animal tumors, unusual animal infections, and needed some help in studying them, and Al and I provided him help and coordination. A sidelight: Larry Kilham's brother was a very prominent architect and designed the National Library of Medicine building.

Harden: Very interesting. I was most intrigued in this paper by this quote about tissue culture: "Now that tissue culture and other precise methods for the study of viruses are readily available, investigations of the mechanisms by which viruses

induce cellular proliferation may be possible." What was that referring to? What things were especially exciting in that time?

Kirschstein: Animals are to some extent unpredictable. Although you can get some end results, you have to use a lot of them. You have to be sure that they have all been raised the same way. That is why we use—and I notice you have some questions later on about this--inbred strains of mice. Some of the viruses are very recalcitrant and are difficult to work with. Fibroma virus is one of the recalcitrant ones. What we were hoping was that in an animal study one could precisely measure the amounts of virus which would cause an infection, the infectivity endpoints, as in a in a cell-culture system that supported the growth of the virus, and that would then get correlated with some of the animal work. For fibroma viruses, that was never found to be true. Fibroma viruses were totally recalcitrant to growth in cell culture.

Harden: That is very interesting.

Kirschstein: The interesting thing about this, though, was something rather different. Fibroma viruses produced a tumor of the connective tissue, and it was basically a benign tumor of the connective tissue of the rabbit. The lesion in the squirrel, under the skin, was also the same. At that time, people were starting to do work in newborn animals, particularly mice and hamsters. [Remember] Sarah Stewart and Bernice Eddy's work on polyoma virus. The three of us, Larry Kilham, Al, and I, got the idea that it would be interesting to study the fibroma virus in newborn rabbits, and in newborn squirrels. Now, newborn rabbits are fine. You can breed the rabbit in

the cage and you can get the babies and study them. All you got out of that was fibromas, tumors under the skin. Newborn squirrels are another thing. These were wild squirrels. The animals were obtained by having the Montgomery County people trap squirrels so that they would not destroy tulip bulbs and everything else in the garden. If you did that in February, a certain number of females—it was pretty hard to tell whether a female was a female or whether a male was a male—were pregnant, and they were vicious. So Larry would put on gloves up to his elbows, and as soon as the babies were born, he would get them out and we would give them the virus. We got lung tumors, pulmonary tumors that, for all the world—I will never know what it really means because we could not pursue it; we never could get enough of them to do anything—looked like a disease that occurs spontaneously in sheep in Iceland called jaagziekte. It is a mucinous pulmonary adenoma, and we really wanted to study it because the sheep disease was also known as a virus-induced tumor. But you just could not get enough squirrels to do it. So it was an isolated paper. We talked about some provocative things to do, but never went on [to pursue it]. Larry left the NIH shortly thereafter. He was also a cantankerous person, although he was wonderful. He went back to Boston, and that was the end of that, unfortunately. But it was quite an era of trying to catch the squirrels, and get them out of the cages without the mothers clawing you to death. It was really something.

Harden: We do want to talk more about the animals. I have some more questions for the next time, but we may come back to the topic because of the whole situation of

animals in the research process.

Hannaway: But we could maybe talk more about the tumors.

Harden: I was going to jump back to cell culture. Let me ask you a cell culture question. Then we will move to Bernice Eddy and Sarah Stewart. [Dr.] Harry Eagle and Wilton Earle were both working on tissue culture, and Dr. Eagle had made his famous medium and the support things, and Wilton Earle was growing those cultures in that wonderful glassware that he had. Apparently there was some problem between them, some tension or something, and I never quite understood what was going on. Do you know anything about it?

Kirschstein: No, I do not. I knew Harry very well. I barely knew Wilton Earle. Alan might know. I would suspect that it was—and this is a suspicion without any evidence—that Wilton Earle had spent his life developing this very meticulous, remarkable way of somehow growing cells in culture. It was almost a mystique that it could happen. Along comes the rest of the world, of which Harry Eagle is the prime example, and you can just grow the cells any which way with some medium. You get some contamination, but you stop it and you just go on and you do it. Of course, this way, the way John Enders did it, is what led to being able to do the big technical things that allowed vaccines to be made. Earle was studying the cells in culture in terms of their physiology, their metabolism, why they were tumor cells, why they were not. This is truly a guess, and I think you would have to talk to some other people, but that is what I think probably happened. There was a certain natural tension between them. Harry was another larger-than-life

figure. He became larger than life even more after he left the NIH. Of course, it was Harry Eagle who, along with a couple of other people, helped the first company in this area to be able to do these things, Microbiological Associates. He helped found Microbiological Associates. He could not own it, but he helped found it. All of that was able to make these things grow in a very real way. You also know, of course, that Harry had done all sorts of other things in microbiology. There is the Eagle test for syphilis.

Harden: No, I did not know that.

Kirschstein: It was a standard test for syphilis that he had developed. He was over at the Navy [National Naval Medical Center] at the time. So Harry was a microbiologist of major proportions. He left here—I do not remember what year—to go to Albert Einstein Medical School, where he eventually became the dean and really made that school. He was a remarkable man. He took a bunch of very good people with him when he went.

Hannaway: Was he a New Yorker originally?

Kirschstein: I do not know, but I think so.

Harden: Now we can move on to Bernice Eddy.

Hannaway: You wrote your paper three with Bernice Eddy and Sarah Stewart, so we are interested in knowing a little more about your collaboration with them and what they were like.

Harden: And their polyoma work. You have written about it and talked about it, but I would like to get it on the record.

Kirschstein: Sarah Stewart was in the Cancer Institute for a long time. She had a conviction that viruses caused tumors. She had no evidence, no anything, but she had a conviction. She was working on passing tumors from mouse to mouse to mouse, and sometimes she would get tumors and sometimes she would not. She would work on supposedly cell-free extracts, and very little would happen. She felt that nobody was taking her seriously because she was a Ph.D. scientist. So she picked herself up and went down to Georgetown Medical School and got an M.D. degree, and was very distressed that they still did not take her seriously enough. Bernice Eddy had a Ph.D. degree, and she worked in Biologics. The two [women] became natural allies because they both had very creative, intuitive minds. I like to think of both of them as intuitive scientists. They were creative and they were bright. But they did not know, or else they got so excited about what they were doing—and I do not know which it was—that it was absolutely crucial to have meticulous data. If you wanted to prove that a virus caused a tumor, for the purists who did not believe that that was true, you needed to make sure that the preparation that you inoculated into the animal could not possibly have even one tumor cell in it, because one tumor cell could proliferate. And the work was not done with that precision by them. They were not alone. The other person who was among the first was Dr. Ludwig Gross at the V.A. Hospital in the Bronx. He had exactly the same sort of personality and method of working, and he received as much scorn as they did, and they all turned out to be right. Now, these tumors finally were accepted by everybody as having been virally induced. Al will tell you this story,

and I do not know the details--but there was a point at which Sarah was banned from this campus, and was told she could not work here. They sent her somewhere else to work. Finally, she came back. She never received the honor that she should have. But Al gives a lecture on tumor virology in which he talks about both of them in really hushed tones. Sarah and Bernice wondered whether the polyoma virus, which was a mouse virus, which also infected hamsters--we had done a lot of work on that--could cause malignant tumors in other animals. So we did the rabbit experiment, and the tumors were not malignant. They were benign fibroma type tumors. So that was that work, and they asked me to work with them on it, and I did. The interesting thing about that--you should find a reference to this somewhere–it is not in my bibliography–is that Bernice found—this is skipping ahead a little—that the fluids from monkey kidney cells that grew polio had something in them that caused tumors in hamsters and she insisted it was a virus. Again, the same questions about how careful she was came up. Did I tell you this story last time?

Harden: No.

Kirschstein: She was working on polyoma virus in the laboratory, in the same area where she was doing this work on the monkey kidney cells, and she came to me. I had an associate with me then named Dr. Gerald Borman, who is on a couple of these papers. I had trained him to do pathology. She came to me and asked me to look at the tumors, and we looked at them. They were very similar in histology to polyoma tumors in the hamster. I was deeply concerned that she had

contaminated her materials. Gerry kept his name on the paper but I refused to keep my name on the paper. It was a classic paper. It was the first paper that showed that SV-40 caused tumors in animals.

Hannaway: This was the paper that she was not allowed to publish for a year?

Kirschstein: Right. Was I a fool? Maybe.

Harden: But it raises a whole question about the nature of evidence.

Kirschstein: That is right, and about what precision means. Not precision, accuracy. I just could not bring myself to do it. I have not really been sorry because having that kind of standard has stood me in good stead, and now I am a scientific research integrity officer. If it had been an error, my career might have been finished. Bernice was at the end of her career anyway, more or less. But it was an interesting phenomenon. We then later went on and did all sorts of work with SV-40, Al and I, and never published with Bernice.

Harden: In the literature, one of the things they wrote about [Dr.] Julius Axelrod was that he had the "let's try it" way of working, the intuitive model that you are talking about. Yet, when you get right down to it, you have to have that very clean and compelling evidence.

Kirschstein: And he did. There is no question.

Harden: But it is a fine line, is it not, between intuition and accuracy.

Kirschstein: Yes. Actually, I would say that Bernice probably—talk about mentoring—had never been mentored in this kind of thing. We did not do that in those days. She also had a feisty personality, which did not help. Sarah loved to fight with

everybody. But they did make their mark, and they deserve all the credit. There is no question.Now, SV-40 was discovered by several people. At the same time Bernice was doing this, there was a group at Merck that had found the virus as well. It was Joe Smadel who would not let Bernice publish [her discovery], and he told Rod Murray not to let her publish that paper, because he did not believe it. Yes, it was that paper, and the paper simply said that there was a virus in the fluid of the cell cultures from monkey kidney cells that were being used to make polio and test polio vaccine. The group at Merck found it. The director of vaccine research at Merck was [Dr.] Maurice Hilleman, who has probably done more for viral vaccines than anybody in the world. He had worked with Joe Smadel at Walter Reed in the Army, and then he went to Merck. Hilleman came down to NIH and brought Joe Smadel the evidence that they had found, and Joe suddenly realized that it was true, and then the papers all got published. There was a woman at Yale named Edith Hsiung--who worked with Dorothy Horstmann and with Bob Stevens. She worked with red monkeys, *Erythrocebus patas*, and had found it also. She never looked to see whether it was a tumor-inducing virus. She talked about contamination. So there were a lot of leads. Nobody wanted to listen. There were lots of monkey viruses. There was a man named Hull at Eli Lilly who in the Salk vaccine days began to realize that there were viruses in the monkeys, and named them simian viruses [SV] and it was SV-1, SV-2, SV-3, SV-4. By the time we got to this virus, it was the fortieth. So people knew it. Yet the desire to make that vaccine was so great. What happened was that people went

back to the inactivated virus, so that even with the formalin, you could find SV-40 in some of the vaccine lots. That led to the epidemiologic study that [Dr. Joseph] Joe Fraumeni of NCI did some years later, following a whole group of children in Cleveland to whom [Drs.] Fred Robbins and Martha Lepow had given as newborns large doses of regular Salk vaccine and to some who had been given very large doses of Sabin vaccine, which clearly had SV-40 in it. The study followed them for years and did not find anything. Just this week, I got this proceedings, which was from a conference that was held by what is now the Center for biologics Evaluation and Research [CBER]. I chaired a session. There are people now who are insistent that they are finding tumors in humans that they think are induced by SV-40. I do not personally think the evidence is very good. There are human tumors, human viruses that are similar to SV-40. You are welcome to borrow the volume. I will not have time to read it for some time.

Harden: I just wanted to read it into the record so that the transcriber would get this, that Dr. Kirschstein has showed us a book, a conference publication called *Simian Virus 40 (SV-40): A Possible Human Polyoma Virus*, edited by F. Brown, A. M. Lewis, Jr., and it was published in Basel and New York by Karger in 1998. But it is a very interesting volume. Now, I want one more follow-up on this whole thing, and that is to pull in the AIDS story. When the question came up, that, maybe, if there was all these contaminants, that is where AIDS came from. It was the polio vaccine and the retrovirus. Do you remember when this came up in AIDS?

Kirschstein: Yes.

Harden: There was an article in [?]

Kirschstein: The *Village Voice*. Yes, and I think I have it somewhere in the drawer.

Harden: What was your initial reaction when you read that, and did you think it was a possibility, or did you think absolutely not.

Kirschstein: No, I did not. One of the reporters for the *Village Voice* called me. I talked to him a little bit. I did not think it was a possibility at all. The whole symptomatology just did not seem to fit. Now, if you ask me whether I believe that the HIV virus is a mutated form and jumped from monkeys or other primates in Africa to the human population, I think that is very possible. We do know about another virus that we learned about some years later called the Marburg virus, which came out of African green monkeys, as I remember—Marburg is for Marburg, Germany—in a monkey colony and infected humans. Not only did it infect and make humans sick, but the humans passed the virus, spouse to spouse, in a couple of cases, and through the family. It did not seem to last. It seemed to be one batch. Maybe the monkeys all died off somewhere. We have all been looking for something like it for a long time and have not seen anything else that I know of, but I do not follow the literature in those areas very much anymore, so I do not know. I do not think I felt it was a possibility.

Hannaway: Just to come back to the SV-40, the claim was at the time, as I understand from looking at newspaper clippings and so on, that the techniques were not available until about 1960 to know that this SV-40 was in the monkey kidney cells that were used.

Kirschstein: That is correct. But in the early stages, when Bernice thought there was something there, she wanted to get things done. She wanted to stop what she thought was dangerous, and nobody would listen. It is not a terribly pretty story, because although I doubted it considerably, I think we probably failed to do as much as we should have done to at least make sure we checked it out. Now, we did not get ourselves into terrible trouble, but it is another way of saying that we did not take her seriously, and there were reasons we should not have, yet at the same time we probably should have. You have a balancing act.

Harden: I want to ask you two questions primarily with respect to techniques. Looking at papers four and seven in your bibliography, in paper four, you determined that the intracerebral route of inoculation of mouse sarcoma 180 in suckling mice was about a thousand times as effective as the subcutaneous route. What was the purpose of this kind of research?

Kirschstein: Everybody was struggling to determine whether, if you believed that there were tumor viruses and other ways of transmitting tumors from animal to animal, were there ways to inoculate animals, were there areas that were particularly sensitive? Now, we already knew that for polio [virus], the brain was particularly sensitive. [Dr.] C. P. Li was a renowned Chinese scientist who had worked with [Dr.] Morris Schaefer. He, in fact, is the person who adapted type 2 polio virus to mice, and it was a derivative of his strain, LSC Type 2, that Sabin used. Dr. Li was interested in looking at the inoculation of viruses into the brain. Other people were as well. We also knew that there was a blood-brain barrier, and so if you

inoculated most infectious agents, particularly viruses, which were small, peripherally, you could not get brain disease. However, that did not always turn out to be true. So there was a lot of interest in putting things into the brains. We also knew that both newborn humans and animals are more immunologically suppressed than are adults, plus the fact that if you were going to try to inoculate something into the brains of small animals, you can do it very easily in a newborn. So Dr. Li persuaded me to work with him on the passage of sarcoma 180. He was hoping that we could make it more virulent and find a virus. We did not. But that, plus the way we were studying polio, set us on the trail of what we would do to begin to look at the viruses that we did know were tumorogenic. So Al and I designed experiments with newborn hamsters. The newborn hamster is an interesting animal to work with, even more so than the mice. The hamster mother is very protective of her young unless they are deemed to be a threat to her. You can handle newborn mice with gloved hands and put them back with the mother. She will accept them and she will nurse them. Sometimes she gets upset, but not very often. The hamster mother, to protect herself, will eat them. It is a protective thing. She is going to go on and produce more.So I did all the inoculations. I had a wonderful animal caretaker who would let me know when the newborns were born. I used to go in Saturdays, Sundays [if necessary]. It was easy to breed them. What we did was we took long forceps, wrapped them in gauze and tape, and then got them as dirty and as ugly as possible in the cage material. We would take the mother out and put her in a separate cage, and then take the babies one by

one, inoculate them, and put them back. Sometimes it did not work. Sometimes she would eat the whole lot, and we would have to start again. But the dirtier, the better. We got more skillful. You had to try not to let there be bleeding, because that would upset her too. We got these remarkable intracranial malignancies with the polyoma virus. That led us, when SV-40 was clearly a tumor virus, to do the next step, which is paper 17, excuse me, 18 and 19. There we found what was really something very different than polyoma. Sarcoma of the brain of a human is practically nonexistent. But an ependymoma is not an uncommon human brain tumor and these are the tumors in hamsters. So you began to wonder a little and we did a lot of studies on that. That was the first time anybody had ever induced—it made me feel slightly vindicated for making a mistake with Dr. Eddy—a brain tumor from brain cells that was a correlate of a human brain tumor.

Harden: There are some papers here, too, about the first time you had produced a true glioma.

Kirschstein: An ependymoma is a glioma. Ependymal cells are glial cells.

Hannaway: What building were you in, conducting this work?

Kirschstein: Twenty-nine. Al was in 10, I was in 29. I stayed in 29 until I left to go to the Food and Drug Administration.

Harden: Maybe we should end with this last question that I want to ask you, talking about paper seven. The particular thing I was most interested in in this paper were all the different NIH people you cited in your notes as having developed techniques. I just wondered if there were a lot of people working on the same thing, or if there

was some reason you had this explosion in interest.

Kirschstein: The hottest thing around, once the Eddy-Stewart notion was acceptable, was the worry about whether viruses caused human tumors, and that led to the explosion of interest. Also molecular techniques were beginning to come along. Stewart and Eddy could not use such techniques. But the great virologists got interested in this. [Dr.] Karl Habel, [Dr. Robert] Bob Huebner, [Dr. Wallace], Wally Rowe, [Dr.] Janice Hartley. All of these people were really going to work on those things. Then, out of that came the war on cancer, a study of viral tumorogenesis.

Harden: On the next page, you had a whole group listed.

Kirschstein: Yes. Rous. There was the Rous leukemia virus and the Rous sarcoma virus. [John] Moloney, [Frank] Rauscher, and Lou Sibal all had viruses named for them. Sibal is still here. The field just exploded. But at the same time what exploded was that everybody was trying to find the human virus, and there was not anything to find.

Harden: So a lot of this early virus cancer work that you were doing preceded the great explosion.

Kirschstein: Or, actually, preceded it and then it kept going.

Harden: Yes. K

rschstein: Now, people had known that Rous sarcoma virus caused tumors in chickens by 1911, and that the avian leukosis viruses existed. But there began to be cell-culture methods; there began to be hemagglutination tests; there began to be sensitive immunologic tests; they began to tease apart the genes, the SV-40 T-

antigen, and so forth. These were people who knew things that I did not know at all, but I collaborated with them. It made for wonderful times.

Harden: How exciting. We shall we stop here for this second interview.