

This is the fifth in a series of oral history interviews with Dr. Ruth Kirschstein, Deputy Director of the National Institutes of Health. The interview is being conducted in Dr. Kirschstein's office in Building 1 at the National Institutes of Health.

2 February 1999

Interviewers: Dr. Victoria A. Harden and Dr. Caroline Hannaway
Please Note: These Interviews Have Not been Verified for Accuracy

Harden: Dr. Kirschstein, I wanted to start this session by talking about some general events that occurred in the 1970s and 1980s. During the mid-1970s, there was an expansion of the Freedom of Information laws, making information more accessible to the public. Do you recall this, and can you describe how it affected NIGMS?

Kirschstein: It probably affected NIGMS somewhat less than some of the other institutes because, in the activities related to grants in the basic sciences, we had always had a policy of dealing with the grantees and giving them information. The concerns that I had before things began to loosen up were related more to the summary statements that were written after the initial review of grants. We had a policy at the NIH at that time of interpreting what was said but never giving those summary statements to the investigators. That was one of the things we changed when we began to implement the recommendations of the grantee study. And we worked through them. I have always been a great proponent of letting people know what is thought [of their applications] and being fair to people by letting them know things about themselves. But there was not a terribly big impact on NIGMS in that regard.

Harden: Storm Whaley told us the story about how much easier the new laws made it for people to submit frivolous inquiries. For example, there was a man in California

who thought that the NIH was sending out a beam to persecute him, and so he requested floor plans of all NIH buildings to try to locate this nefarious beam..

Kirschstein: Yes, I remember those letters.

Harden: What about the tightening of regulations on both human and animal subjects of research, especially in light of the human subjects issues that came up after the public revelations about the Tuskegee syphilis study? Did these have any impact on NIGMS?

Kirschstein: Again, NIGMS did not have a large clinical program. We did have some clinical centers related to burn and trauma research, and also anesthesiology research. I do not think we had any real problems in making sure that those regulations were followed. I had taken a great interest in the Tuskegee situation from the days when I was involved with vaccines, and I knew all the people at the CDC who were involved. Just as a sideline, you may know that we had a conference last November or December [1998] down in Tuskegee that related to the ethics of science. The whole event was related to the issues surrounding the President's apology. Dr. Gorman's [Myron D. Gorham?] office put it on, and a group of us went down there. I gave the closing remarks at the conference. But, in terms of NIGMS's actual activities, I do not think it had a profound effect.

Harden: What about with regard to animal research?

Kirschstein: With regard to animal research, I think we had to be sure that things were done properly, and that we did make sure our animals were cared for. Originally, the animal activities were more related to dogs and cats and primates, but it gradually

became such that one had to do something—and should have done—for rodents as well. We made sure that that happened. It was not a major problem.

Harden: Do you remember any demonstrations by PETA [People for the Ethical Treatment of Animals] or other groups?

Kirschstein: Not for NIGMS. NIGMS was primarily at the Westwood Building. I also had an office in Building 31, and the PETA people demonstrated there several times. There began to be problems. I do not even remember the date of the explosion and the chaos that occurred up at the University of Pennsylvania. We read and talked about these things. Dr. Murray Goldstein, the then director of the Neurological Diseases Institute, had a real issue related to some monkeys and the studies done on the monkeys that ended up in a lawsuit that prevented...

Harden: The Silver Spring monkeys?

Kirschstein: The Silver Spring monkeys—that prevented him from being able to destroy those monkeys. Several of them either still are, or were recently, living down in the Delta Regional Primate Center [Tulane]. That was pretty hectic.

Hannaway: “Early in 1974, a seminar was held by NIH officials to examine and appraise the peer-review system and the use of peer-review or public advisory groups by NIH for the rapidly expanding grants program.” I am quoting from the introduction to the report of the Grants Peer Review Committee, a committee of which you were the chair. Would you tell us about the circumstances that led to the creation of this committee and your appointment and activities as chair?

Kirschstein: That is an interesting story. There had been a seminar [on peer review] before I ever came to the NIGMS position. It was actually during the time when I had

that short interim period up at the FDA. Somewhere like six months after my appointment as director of NIGMS, the phone rang on a Friday afternoon quite late, maybe 4:30 p.m. or 5:00 p.m., and it was in my Building 31 office. The entire staff of NIGMS, except for the director, was in the Westwood Building, and Building 31 was the building from where Dr. Stetten ran the place. He could not get around easily, and the staff came to him. That was not my style. My practice was to drop in at Building 31 in the morning and see what was what, then go to the Westwood Building and spend the day, and basically come back in the evening and check again on whether anything had happened here. We kept one part-time secretary in Building 31. Everybody else was over there. The phone rang. I was alone in the office. I picked it up, and it was the deputy director of NIH, Dr. [Ronald W.] Lamont-Havers. He said, "Ruth, we have a new project. It is the study of the system of peer review for grants." I said, "Good." He said, "We would like you to be a member of the committee." I said, "Oh, that would be interesting." He said, "In fact, we would like you to chair the committee." I said, "Well, I am the newest kid on the block. I have spent my career up to now either in the intramural program or for this one year at the FDA, so why are you picking me?" He said, "It is precisely for that reason. You can bring a fresh approach." So he said, "We would like to talk about who should be on it." I sat down the next day and the next week and talked to him about it, and we more or less picked the people. Then I said, "But it would be helpful to me if I could have somebody who has had a fair amount of experience in this, even if you want me to chair the committee." He said, "We have just the person for you. She has retired for the second time from a long career in the federal government. The first time was from the Neurological Diseases Institute, and the second time

was from a stint at the Heart Institute. She would like to come back and work on this as well. Her name is Matilda Soloway.” I had heard of Matilda. I cannot remember whether I had actually met her or not, but we hit it off instantaneously. Do you know Matilda?

Hannaway: I have never met her.

Kirschstein: Matilda Soloway is a dwarf. She comes up to about here on me. She had gotten her Ph.D. degree in microbiology at Columbia P&S. She had really wanted to go to medical school. When she was born—I cannot remember the exact medical title for her condition, but she has a very large head and is somewhat peculiarly shaped and is very, very tiny. Her parents obviously had some money, and they felt that she was not going to live [long]. They gave her everything. By the time she finished college, which was, I guess, in New York somewhere, she wanted to go to medical school—in 1919 or whatever it was. She is 91 now—and they did not think she could make it, so she went and got a Ph.D. in microbiology instead and worked for a while in New York. Then, at the beginning of World War II, she came down to work at Fort Detrick on biological warfare things.

At the end of the war, a whole group of the people who had been working on the war effort *per se* and who were biological scientists found themselves without much to do. Although the Army was going to continue the effort, they did not need all of the people. At that time, the NIH was growing and its extramural program was growing, and so the NIH was beginning to hire a number of people. Many of them came, Matilda being one of them. First, she was hired by what was either NIGMS or its predecessor, DGMS, and she helped set up some of its programs. She did some things in peer review. Then she moved to the

Neurology Institute—I think it was still called Neurological Diseases and Blindness—and set up their research centers program. She worked there for a long time, and finally retired from that. Then the Heart Institute brought her back to do a number of things. She was particularly interested in neurological diseases. She never married. And when she retired, the neurological diseases community wanted to honor her. They had a big party. She said that she did not want a gift, but if they wanted to give her money, she would give it to the foundation [FAES, Foundation for Advanced Education in the Sciences]. They established a Soloway lecture every year. For a long time, she has put more money into this fund for a young outstanding neuroscientist [‘s lecture]. The lecture has been given every year in the spring. It must be 30 or 40 years, 30 years, I guess.

So Matilda came and worked with me on the Peer Review committee. I was the chair and she was the executive secretary. The plan was to have a group of meetings here on the system and learn and think about it, and [then] hear from everybody else. We were going to solicit outside comment, and put a notice in the *Federal Register* asking for letters. We went around to all the study sections, talked to the members, and asked them to send us their opinions. We talked to all the scientists out in the community. We had three public hearings, one in Chicago, one in San Francisco, and one here in downtown Washington. We then broke up into small subcommittees that looked at various aspects of things, and, at the end, wrote a very complete report. Now, in the middle of the period, Bob Stone, who was the director of the NIH, resigned. That was after the turmoil over Dr. Marston. We talked previously about the position of NIH director becoming politicized. After Marston and Bob Stone left, [Dr. Donald] Don

Fredrickson became the director. Don, in the middle of an ICD directors' meeting—in those days it was known as BID, Bureau, Institute, and Division—turned to me and said, "I understand you are doing something about peer review. Why are we wasting our time [on this]?" I may have the terms wrong, but [he said] something to that effect. I said, "I had better come and brief you." His first instinct was to say, "This is nonsense, forget it." A couple of people talked to him about it, and finally he said, "Okay, go ahead and finish." When the report was finished and we made this enormous number of very important recommendations, he took great credit for it. But he really was not interested in it originally. You have to also remember that, although Don Fredrickson had been director of the Heart Institute for a short while, he came at being NIH director from having been in the intramural program. He probably had very little if any experience with either the peer-review system or with getting grants. I had none either, but I began to see the reasonableness of the system. So that was the genesis of the report. It took us about a year and a half to do it.

Harden: I want to establish one thing. The decision to do the report came from within the NIH because of things coming...

Kirschstein: Because there was feedback, and because I think the people here at the NIH—Lamont-Havers, John Sherman, and some of the others—realized that we had stood up and said that many of the things we did were based on scientific merit as established by peers and that it would be important to look at the system again. I am absolutely convinced that that is true and that we ought to look at it many times. We have had several reports since. I think our entire structure is based on

how strong our peer-review system is, and, without the system, it would go down the tubes.

I actually testified in front of a science committee. The NIH is not part of the groupings of agencies which each has, as its authorizing committee, a science committee in the Congress. We are at the Health Committee. Yet we are a scientific agency as well. I was asked to testify about this once, and I used the phrase that, just like liberty, the price of good peer review is eternal vigilance, and I really do believe that.

Hannaway: Had there been questions from scientists saying that they did not feel that peer-review panels were appropriate?

Kirschstein: There were questions from some scientists. One of the major issues was the fact that many people thought that the peer reviewers constituted an old-boys' network. In point of fact, the way the members of the study section were appointed was that the current study section members recommended their successors. It perhaps had a bit of an incestuous flavor to it. It was an era when women were beginning to apply for grants and they were not happy with what was happening. There were very few women on the study sections. There were even fewer minorities. There still are, but we try harder. There was a feeling that the average age of reviewers was getting older. It turns out that it is not much different now than it was then. But we really did open up the procedure. One of our recommendations was that people be allowed to self-nominate. Others were that there should be a serious attempt to have women and minorities represented and that there should be an opening up of the nomination processes.

Harden: Who actually makes the selection, then? Does the former study section actually choose whoever has been nominated, or is it the executive secretary, or someone else?

Kirschstein: The director of the NIH has always had the final selection. Now, it was impossible for him or, in the case of Bernadine Healy, her to do this in great detail, so it went through channels. In reality, the executive secretary, who is now called the scientific review administrator, SRA, as opposed to exec sec-- which is still hard for some of us to remember--was in charge. He or she would usually consult the chairman, and then it was, "Oh, I know Joe Blow," this one and that one. So that has been opened up considerably.

Harden: So today.

Kirschstein: The same people make the decisions, but it goes through a better process. I review every slate to be sure that it has some balance to it. It goes with the openness of government and the freedom of information that you were talking about, because not only did they want to know the representation, as these evolved, of women and minorities, but also the geographic distribution of committee members as well. It went in the Federal Advisory Committee Act activities [?]. So we have improved. We have not always done as well as we should. There were other things we did. The most important recommendation made was that whereas the summary statement, which is the description and then the critique of the grant application, is needed for the second level of review, which is the council level, nevertheless, they should be routinely provided to the applicant, the investigator. That was a revolution. And after some discussion,

Dr. Fredrickson did accept that. I think he accepted almost all the recommendations. That was probably the most important one.

Harden: I have a list here of a number of things relating to peer review. I am not sure you received this list. But I just wanted to go through each one of them. You have talked about them all, except perhaps you could tell us a little more about the system that you recommended to establish a formal appeals process.

Kirschstein: Yes. That was the one that was not accepted, although some variant of it was. We were only funding maybe a fifth of the grant applications, sometimes even less. There was a feeling that the study sections, being composed of humans, made mistakes, and if, for one reason or another, the advisory council did not find those mistakes of fact or whatever, that there should be, as in any peer system, a method of appeal. We actually recommended that there be an appeals mechanism and that an ombudsman should be appointed. That was not accepted. That was in the 1970s. We are now in 1999. Well, when [Dr.] Harold Varmus came, in 1993, he appointed [Dr.] Howard Shachman as the NIH ombudsman to the research grants community. Usually, the things I want get done eventually.

Hannaway: If I could just add a comment, that I think I was a beneficiary of your reforms, because very early in the 1980s, I became chair of the study section on the history of medicine, and I was a lot younger then.

Kirschstein: They were looking for women.

Hannaway: Yes, right.

Harden: I was thinking back about a scientist with whom I have chatted. I remember him telling me that he had to request that a certain person not be on the study section

because he felt that the person did not like him personally and did not support his work, and so would never recommend him for a grant. I presume this was one of the things about which people complained.

Kirschstein: This was one of the things we heard when we went around the country to have gotten written material [?]. The NIH is a pretty conservative organization, and while we were able to open things up considerably, we were never able completely to break the back of that. We could get agreement, but if there was a strong feeling on the part of a scientist that so-and-so should not be on a study section, we would probably honor it. But it was always said by the administration that the final decision was ours. We will listen to you, but the final decision is ours. Now, most of the time we probably did listen as things evolved, but we were never willing to say [to a scientist], “You have a veto over it.”

Harden: It is interesting when you hear what people say, because leading scientists especially are generally not afflicted with too much modesty. The most recent experience I had along these lines came up in conversation with a gentleman who was receiving an award at a meeting of the American Society of Microbiology. He was complaining about not getting some grant. I said something about the decision being a peer-review procedure. He said, “I have no peers,” and there was not a trace of irony in his voice. So I am sure what you are detailing here was a real problem, and this is something that continues to go on and has to be governed.

Kirschstein: That is right. Now, you see, one of the things we found—I do not think it is any different today than it was then—was that none of the scientists really understood

the peer-review system. It is a beautiful established system if all the parts work properly. The grant application comes in. There are appropriate science administrators who look at it and decide to which study section it should go. If they are unbiased, it will go to the appropriate one. You can build safeguards into that by saying—and that was something that we did suggest—that the scientists be allowed to say, “I would like my grant application to go to study section A, B, or C,” something like that. It then gets reviewed by this body of people who all 12, or 18, or whatever number it is, are supposed to be more or less reviewing each of the grant applications. In point of fact, over the last number of years, only two were assigned to review each grant application, and report to the others who would depend on that completely. There then should be open discussion. There should be a consensus or a vote. There should also be separation between what you think of the merit [of the proposal] and what you think of the size of the budget. That does not happen. You have been on the study section, so you know: “Well, I could get more enthusiastic about this grant if it was only asking for \$50,000 rather than \$100,000.” Or if he did not want three technicians, or if he wasn’t spending, blah-blah, and I do not like the pH of the solution. It should be something else. The members get into things that they really should not. Then if you had a duly constituted second-level review, the council, which not only has distinguished scientists, but also some lay people on it, and you get to where—we did this at NIGMS where we asked them anything they wanted to discuss, we would discuss. The staff had attended the study section meetings. I had a terrific scientific staff. And they picked up mistakes or errors or controversial points. They pointed them out to the council. Sometimes they wrote what was called a staff summary statement explaining which way it

should go, and then the council could make a recommendation. The final decision as to which grant should be paid and which one should not is that of the director and his or her advisors. If I was convinced that there was something unique in a grant proposal, we would reach—that was the word we used—beyond the pay line. Now, a director can do that. You can do that in a hundred percent [of the cases] if you want to. That does not make much sense. You could do it in less. We would probably do it in the order of 10 to 15 percent a year, and we did pretty well with it. I have had institute directors, some of whom are no longer here, who would tell me that the peer-review system is so sacrosanct that if the priority score was 152 and the cutoff was 151, they would not dare to fund a grant. Now, come on. When we went to the percentile system, it was 27.3 versus 27.4, something like that. I believe firmly that the precision is about 25 points, maybe even more. But it has to work perfectly, and it cannot. It is a human system like all others. But we did try to explain it. We described some safeguards. There actually was put together, several years after we suggested it, a very formal appeals system with a person over here in Building 1 who got scientists together to review [rejected grants], and what was the outcome of that? It took about a year and a half for a review, and then it was suggested that, okay, you won, put in a new grant application, we will look at it again.

Hannaway: That is not so helpful.

Kirschstein: But, on the whole, the system works remarkably well. If one has the ability to pick out the instances where something goes wrong, that is important, and then you can handle those. Part of the reason that I think that it is important to keep the system in as pristine a shape as you can is that it keeps you safe from the

politics. We used to get a lot more requests from congressmen and senators about particular applicants and applications, and we could always talk about how we depended on the peer-review system.

Harden: You suggested in the report from this study that you thought better scientific merit might be obtained if the reviews were conducted without reference to the budget. I just want to clarify that this recommendation was not adopted.

Kirschstein: That was not adopted. Just recently, in the spirit more of reinvention of government than anything else, about a year and a half or two years ago, Dr. Wendy Baldwin and her staff—I had not come up against this and so I had not thought a lot about it—suggested that we go to a system of something called modular grants where a scientist could put in his or her grant application in modules of \$25,000 or \$50,000. If you give me \$50,000, I can do this much; if you give me \$75,000, etc. The study section would not then consider the budget, just simply say this is worthwhile, this piece, this module work. I think this one is too, and this one and that. Beyond that, I do not think so. That is somewhat of a similar thing, but it is not quite the same. Dr. Varmus likes that, and somewhere along the line it is being adopted. These things were all in response to the fact that our budgets were really tight. If the budget is not tight, then there is not a problem. In 1998 and 1999, the budget is not going to be that tight. Who knows what will happen in 2000? We just rolled out the NIH budget yesterday, and the President's proposed increase is 2.1 percent over fiscal year 1999. The Administration wants to say that it is, therefore, 17 percent over two years.

Harden: Right.

Kirschstein: But, nevertheless, the amount of wonderful, exciting, groundbreaking—I do not like that word—cutting edge—I do not like that one either—progress that we have been able to make in science is so astounding and so far above what most other developed countries in the world have been able to do that you cannot help but say that we are doing it right.

Harden: Periodically, there are debates over how much the system should support basic research and how much should be devoted to applied research. Having been at NIGMS, you were right in the heart of that debate. Would you expound on that a little?

Kirschstein: If you say, as some people do, that the NIH is not the National Science Foundation and that it is the National Institutes of Health, then you ought to say that a good deal of what we support ought to be applied to improving the health of the people in our country. But we know from experience that the basic fundamentals are going to move you along that continuum very considerably. So I would argue that the need is to be sure that the scientific opportunity is there, to assure that peer review is working in both segments of this, and then for experienced scientific leaders—that is what the councils are supposed to be, that is what Dr. Varmus's advisory committee should be, that is what the directors of the institutes, including me when I was one, should do—should look at this balance in NIGMS. NIGMS was set up differently than what it is now. It was actually set up, there were people who would argue that NIGMS ought to be called the National Institute of Basic Medical Sciences. That probably would not be a wise idea. First of all, everybody knows that it is called NIGMS, and to change it now would be difficult. Second, I still think it needs to be anchored a

little in some health-related activities. However, for the mix of basic and applied research, there is a formula that the Office of Management and Budget uses. They call it the BAD system, Basic, Applied and Development. We have to report every year to them on the percentage of dollars that go for research in each of the institutes and in the NIH as a whole that are B, A, and D. It is perfectly natural, and should be, that NIGMS is 60, 70, maybe even 80 percent basic research, and small amounts in the other. It is equally natural that, for the Heart Institute, the Cancer Institute, or something like that, that that might be somewhat reversed. I think the problem has been that the opportunities in basic research, with the recombinant DNA revolution and some of the other wonderful discoveries, protein structure and chemistry, etc., are so vast that you could ignore that proportion if you did not work at it. Clinical researchers have a hard time. Some of them cannot devote full time to doing research because even in clinical research at hospitals and medical schools, the academic health centers and medical schools are pointing out to them very much the need to earn their way by seeing patients and earning an income. So we are trying to revitalize, and we have been doing it for a long time. Clinical research takes off and then it dribbles, and then it takes off and then it dribbles again. I think overall in the NIH's terms, there should be an appropriate balance between them. I do not know if it should be 50/50 or whatever, but I think it should be there.

Harden: What I want to ask you next came from a curious phone call I received one day from a man who had worked in research with the Agriculture Department. He was writing a paper on the different approaches to research. The Agriculture Department takes the approach of spreading the money around geographically according to the state and the size and amount of the state under agriculture. This

is very different from the biomedical research emphasis on excellence, wherever that happens to be. The man just requested some information about how this difference happened, but I have given a great deal of thought to this. He was arguing that there have been tremendous advances in agriculture under their system of funding, and he asked didn't we think that biomedical research would advance just as well if it were funded on a geographic system. I thought I would put that question to you and let you comment on it.

Kirschstein: Twice in my career, I have been asked by various groups to study parts of the Agriculture Department. Once was an Academy study and the second, I think, was a Department of Agriculture study of its own operations. The problem with what they do is that, yes, quite appropriately, the money is geographically distributed, but it is also right politically. They have members in Congress, primarily [Representative] Jamie Whitten, [Democrat] from Mississippi, and some others, and I know that not only from my studies of the Agriculture Department, but because of the history of the Food and Drug Administration growing out of the Department of Agriculture. So the authorizing and appropriating committee—appropriating, maybe not authorizing, committee—in the Congress for the FDA is part of the agriculture group, and I have had the pleasure of being in front of Jamie Whitten. There are a number of different parts of the Agriculture Department setup. One of them is the ARS, Agricultural Research Service, which has a certain number of intramural activities, the biggest one of which is Beltsville, and which is not terribly dissimilar in how it thinks about going about its business than our own intramural program. Nevertheless, it has not been nearly as successful, and part of that is related to underfunding. Then they have the land grants, and that is what the basis of geographic

distribution is, and there have been a number of advances made. There are many more to be made. There is a group now that wants to sequence the corn genome and one wants to sequence the rice genome, and so forth. I think each organization needs to put its own house in order, if you will. My friends over the years at the Agriculture Department recently are coming much more toward our type of peer review.

Harden: Thank you very much.

Hannaway: I think we have discussed most of our concerns about the peer-review system at that time. We had a more general question. You have alluded to it already in discussing about when funds were tight and how this affected the grants system. We wanted to ask if you would evaluate the effects on the NIH of inflation in the wider economy. You have said a little about it, but there was also a significant increase in the number of scientists applying for grants. Would you be willing to comment on that aspect of it?

Kirschstein: First of all, as we began to move to an economy that had serious inflation, and also into a biomedical research activity that became more technologically based—recombinant DNA technology, instrumentations, spectrometers, microscopes, etc.—biomedical inflation in the 1970s and early 1980s was far greater than the general inflation in the marketplace, if you will. Our money never kept up with that. Also, as we began to think about these new scientists that we had trained, it was clear that we should and would have to do something in order to make the progress we had hoped we would make and that we were making, and be able perhaps “to spread the money” a little more. Don Fredrickson, in conjunction with the Secretary of Health, Education, and

Welfare, [Joseph] Califano, began talking about the need for stability in the system. Fredrickson had a series of meetings here--Califano came out and talked--and Fredrickson came up with the idea that we should be trying to fund 5,000 new and competing grants each year. As you know, the grants are awarded for a period of anywhere from three to five years in one unit, and then there can be renewals. Some people thought that what they meant was at most 5,000 grants a year. In fact, the original statement was at least 5,000 a year. It became a sacrosanct number that translated itself during the appropriations hearings, particularly in front of some of the senators, maybe Congress, the House as well, that no matter what, you had to have 5,000 grants. If in order to get the 5,000 you needed to reduce the size dollar-wise of each grant, you could do it. So we moved from [having] a study section that had already been quite chary about the money and had imposed what it considered peer-reviewed budget cuts to an arbitrary downward negotiation that was set across the NIH. We could not break it unless there were very specific ways to do it in order to get 5,000. That became the mantra, literally. At the same time, in the late 1980s, young people were finding that they were getting out of graduate school, some of them out of medical school--but, at that point, we already had Jim Wyngaarden's famous clinical researchers as endangered species--and they noticed that some people were getting grants for three years and had to apply again, and some people were getting grants that went for five years. And that the intramural program was staying about constant. When things get really tight, the grantee community out there says, "Well, there's a billion dollars," or whatever it was [for the intramural program], "that could come into our system. Just get rid of those intramural folks. They are not peer-reviewed like we are." Furthermore, although we said

the intramural scientists were peer-reviewed, and indeed they are, it is a retrospective peer review. “We have to do prospective peer review.” So out of the 1993 hearings—I guess that was for the FY94 budget; I think I am right—came this report language from Congress that demanded that we have the average length of the grant be 4.0, as the precision people do—not 4.1, not 3.9--no more than 4.0 years, and that we study the intramural program. That was where things stood when I moved into Building 1 in July of that year. There did not seem to be, on the part of the Congress, much realization that we were going to be changing directors, and so I began to set up the Marks-Casell Group, which consulted with Harold. He actually picked _____ [?] as the chair, and then we picked _____ Gail Cassell, who was at that time chair of microbiology at the University of Alabama _____ the director of _____, and also began looking at the inflation and the 5,000, and the cost of living for grants. We had a whole series of groups which studied the cost of living for grants. I think some of the things we said and did were right. I think we would have come to it anyway. The Marks-Cassell report was extremely important because it did point out that while the intramural program had considerable group strength, it had some weak areas. That is true in the university community as well. It led to Harold Varmus really beginning to strengthen the intramural program back up to its heights. Of course, the intramural program’s great height was when all those young doctors came here to avoid going to either Korea or Vietnam. Then, when they left, they were the ones who made the medical schools of our country so great because they peopled them. Until fairly recently, most of the chairs of medicine, pediatric surgery, etc., were the young men—and women—who had spent their two years of service at the NIH.

Harden: Would you talk a little about the increase in indirect costs as a factor in the grants?

Kirschstein: There has not been a remarkable increase in the indirect costs. The indirect costs as a percentage of the total, from the time I started looking at them in 1974, was 37, on the average, or 37 ½ percent. It is now closer to 40. Over 20-something years, that is not an enormous increase. There has been great discussion about indirect costs, and we have had study after study. I think most people are beginning to talk about not calling them indirect costs anymore. They are now calling them F&A, facilities and administration. The real question is whether or not it is an appropriate cost. I think most of us think it is. It turns out it is much lower here within the federal government, but we still have, in one way or another, to account for these costs. So if you can get rid of some aspects of it, like the bouquets of flowers that you usually find when you go as a guest at a university, and that Donald Kennedy got caught doing at Stanford and had to resign as president. One of my favorite people, a sad story. I do not think the costs are outrageous at all.

Harden: Let us shift here for a moment, then. I was struck by the fact that at the same time as you were working on this grants peer-review study, there was this outside initiative, the President's Biomedical Research Panel. This was constituted under the Ford Administration in 1975. It issued a report with multiple appendices and supplements in April 1976. Can you tell us much about the impetus for establishing this committee and elaborate on what it did?

Kirschstein: I can tell you what it did. I do not remember the impetus for it. I would not be shocked—maybe Don Fredrickson is the one who needs to be asked about that--

if he did not engender it himself in an attempt to show the importance of biomedical research and how we might be able to get more money. One of the important people on that panel was Benno Schmidt. Benno Schmidt, if you remember, had been Richard Nixon's friend—this is the Benno Schmidt of J. H. Whitney and Company—and had persuaded Nixon relative to the war on cancer. Schmidt became a great advocate for basic research, originally for cancer and then for research in general. I would not be a bit surprised if that is not how it happened, but I do not really know. I do remember the committee. It was chaired, as I recall, by Dean [Robert H.] Ebert of Harvard, and the president of the *L.A. Times*, whose name I cannot remember, but there were lots of sub-panels, one on basic research that [Dr.] George Carlotti [?] ran, one on clinical research, and one on everything else. It came out with this very long report, and many of us went to many of its meetings. Some of them were held on Saturdays, and it was kind of interesting stuff. What it essentially did was reinforce what everybody thought to begin with that the NIH was really a very important place. There had been other reports on the same thing. There was a study of the NIH by the man who was head of the Rand Corporation. There was a study on the NIH called the Steelman Report.

Harden: A report every year or two?

Kirschstein: Yes, probably every 10 years or so. That is what the panel did. It was probably very useful in an era when Congress was beginning to think about whether it should provide more money or not [for the NIH]. So I think it served its purpose, but I cannot remember what its origin was.

Harden: One of the things that people often quote from that report is the well-known article by [Dr. Julius H.] Comroe, and [Dr. Robert D.] Dripps on the gap between basic and applied research.

Kirschstein: Yes. I have it somewhere.

Harden: This must all have fed into this whole idea that there was a question about basic research and the long-term applications

Kirschstein: Yes. The Comroe-Dripps article is quite remarkable because it shows how many things really did get applied to clinical activities that everybody thought were going to go by the wayside. It is still a very important document.

Hannaway: In question 17, we had, in the version that you have, two achievements listed, but there is also a third that we would like to discuss. Let us first of all talk about the two that we had listed. Those are, first, the human genetic mutant cell repository, and, second, the genetic sequence starter bank, or Genbank. Would you tell us about these, how they came into being, and what their significance was?

Kirschstein: I would say number one that one can be very proud of the human genetic mutant cell repository, but it was Hans Stetten who started that. He felt very keenly that we were going to need cells from people with various genetic diseases. It was in the same period that we talked about [previously]. Hans was the one who started the genetics program at NIGMS, and he started that repository as well. Hans's daughter, Gail, was very interested in genetics. She had gotten her Ph.D. at Brown, I believe, with one of the well-known geneticists up there. Hans got turned on to genetics as a biochemist, and so he started the repository. We

expanded it considerably. We put more money into it. It is at the Coriell
Institute for Medical Research in---

Hannaway: Philadelphia?

Kirschstein: Just outside Philadelphia, in Camden, New Jersey. [Dr. Lewis] Lew Coriell was a very fine virologist, who learned how to do tissue culture and grow cells and grow viruses in cells. I knew him quite well. He went out on his own after he left whatever university affiliation he had. It may have well been the University of Pennsylvania where he was. So the repository was there. We began expanding it. We began to realize that you should not put all your faith in growing skin cells or muscle cells or whatever, and that it was probably important to begin to study, to be able to freeze away lymphocytes so you could extract DNA and do some things. It has been going ever since. [Dr. Judith] Judy Greenberg runs it for NIGMS and it has been a great success. In terms of GenBank and the genetic sequencing activities, that is an interesting story. We have, of course, here at the NIH, above and beyond all of the institutes that either support basic research or clinical research, either organ based or disease based, two other organizations. One was NIGMS, which started as the Division of General Medical Sciences, and the other one was the Division of Research Resources, which is now the National Center for Research Resources. There has been considerable argument about whether the two should be put together. Did we discuss this?

Hannaway: No.

Kirschstein: They had actually both grown out of the Division of Research Grants, which until the 1950s awarded grants [extramurally.] And somebody set up these two

organizations. One would be called Basic Research and Training, the other one would be providing facilities and resources, but the same person [Dr. Frederick L. Stone] ran them both. They gradually got separated, and Fred took the Division of Research Resources. There must have been considerable discussion, because when Bob Stone appointed me as director of NIGMS, he said, "What I would like you to do is to have you and some members of your staff study the Division of Research Resources with the idea of combining the two." And we did. We put together a study, and Dr. Thomas Bowery, the director of DRR, came to see me and said, "What are you doing?" In the end, they backed off and did not do it. Something like three more times in my tenure at NIGMS, similar studies were made and similar suggestions were made. Part of the then Division of Research Resources was moved to NIGMS, namely the minority programs. By that time they had been through three directors at DRR. Somewhere in the middle of that, Dr. William Raub [?], [or Dr. Thomas Malone?] who was, I guess, at that time, what was called the associate director for extramural research, not the deputy, and who was always interested in technology and new things in computers, had heard that some geneticists at Rockefeller, which was still an institute at the time, not a university, were interested in making sure that we began collecting DNA sequences of various animals, bacteria, etc., because they thought there might be similarities between them. In fact, they knew there would be similarities. He picked two people from the Division of Research Resources, and they went up to visit the Rockefeller people. There was a meeting there. They came back never having told anybody what they did, and if they wrote a report, I never saw it. That was in the late 1970s. About a year or so later, I began to get messages from some people at Cold Spring Harbor about, whatever

happened to this plan to do DNA sequencing and have the federal government pay for it? We know that so-and-so went to a meeting.” I asked around, and it was clear that somebody from DRR was expected to do something that never happened. So we held a meeting. We joined forces with the National Science Foundation and a couple of other people and set this thing up. Now, along with this was the fact that for a very long time there was a woman, whose name I am not going to remember, at Georgetown University who was doing this all on her own with a little bit of support, I think, from the Department of Energy. But most people did not think she was doing it very well. And the question was how anybody could do it on their own? So we put it out on bid, and she and several other people bid, and she lost. Then there was a furor. And we started it small. The National Science Foundation put in some money, NIGMS put in most of it, DRR put in some, and we ran it through NIGMS, under [Dr.] Elke Jordan, for a while. It began to grow. And budgets were tight here, there, and everywhere. Everybody else began to back out, and we found ourselves with more and more of the budget, and knowing how important it was. We had an advisory committee which consisted of some of the real mavens in the field, Rich Robertson[?], _____ who won the Nobel Prize[?]; David Fonstein [?]; David Baltimore, etc. It was quickly eating NIGMS out of house and home, and our grantees were delighted to have it. We were providing them the information for free. But nobody else was keeping up with it. Meanwhile, some work was going on intramurally with some of the brightest scientists in the intramural program. [Dr.] David Lipman was one of them. David and I used to have long talks and he wanted to do more. He could not get much support from the institute he was in. The next thing I knew, David and [Dr. Donald] Don Lindberg came to see me to

say that they thought that this was rightfully a library activity. It was a bank like a library. And David would go work for Don Lindberg and the NLM. I said, “You are going to have to pay for it.” Actually, again, science took over because some of the things that made sequencing easier, some of the computer programs that David developed, made it a much more vital thing than it had been even in the earlier stages. NIGMS always had the tendency to start something and other people took it over. So we did that. David Lipman got set up in the National Center for Biotechnology Information, which began to explode, with the achievement you did not mention here, which is the Genome Project. Was that going to be your third?

Hannaway: That was in my mind too.

Kirschstein: Okay. And so we transferred it. It was growing like topsy, and Lindberg could not keep up with it either.

Hannaway: But he was funding it?

Kirschstein: He was funding it, but David needs more and more, and he is right. Harold is trying to figure out a way to give him more, so that is where we are with that.

Harden: Very interesting.

Hannaway: The other thing I was going to ask you about immediately was this mechanism for obtaining scientific instruments.

Harden: The shared instrumentation program.

Hannaway: Yes.

Kirschstein: Again, the Division of Research Resources. Where are you getting this information? What are you reading to know all this? It is wonderful.

Hannaway: It is things that you have written and speeches you have given.

Kirschstein: The Division of Research Resources did have the responsibility for providing big instruments in centers for the scientific community. But Marvin Cassman from my staff, who is now the director of NIGMS, and some of the people who worked with him in our biophysics and biochemistry support program realized that there was a whole series of somewhat smaller instruments [needed]—spectrometers, small electron microscopes, small DNA sequencers, etc.—that were being cut by study sections that were thinking all the time about how budgets could be cut. “He doesn’t need that; he can go use somebody else’s down the hall,” or “Why don’t they share?” or something like that. So Marvin came up with, and very quickly sold me on, something called a Shared Instrumentation Program, where in one university or one academic setting--occasionally, if the instruments were going to the same city, it could even be across two universities--scientists who needed 10 percent or 20 percent of a particular instrument and whose research was already funded, could put in a shared-instrumentation research grant application and explain how they would collectively use the instrument, how they would use one technical person for all of them, how they would maintain it, and where the money would come from. The dollars [for the instruments] were set at \$100,000 to maybe \$200,000, and it has changed over the years. It became a very worthwhile program. Marvin still does some of it. The program has now been transferred to the National Center for Research Resources, and they have the responsibility, but that is just fine.

Harden: Thank you.

Kirschstein: But are you going to get to the Genome Project?

Harden: Would you like to talk about it now?

Kirschstein: Or do you have it somewhere else?

Harden: We were going to come back to it when we get to the 1980s, but if you are ready, go right ahead. We will come back with additional questions.

Kirschstein: All right.

Harden: Let us pick up then. You are going to tell us about the beginnings of the Genome Project.

Kirschstein: The reason for bringing it up here, although it started later, is that it was a direct outgrowth of the genetic sequencing. Because of the ability to sequence the genetic material and because of the importance of realizing the very close relationship between all DNAs, from bacteria all the way on up, it became clear that the scientific community, sparked primarily by [Dr. James] Jim Watson, would like to have the entire human genome sequenced. Watson talked to a number of his colleagues and found that some of them were very interested; while others felt it would be much too expensive and that there was more junk DNA than maybe important genes, and asked why should we, in this time of tight money, waste our money. Watson came to Jim Wyngaarden, who was not the least bit interested. But the people at the Department of Energy were very interested. Now, the Department of Energy seems a strange place for all this, but you have to remember that the Department of Energy took over the national

laboratories, and that at least one national laboratory, Oak Ridge, was where all the mouse genetics was done. Actually, [it was] between Bar Harbor, which was a private laboratory, and the national laboratory at Oak Ridge, where [Dr.] Arthur Upton, who subsequently became the director of the Cancer Institute, had done [research]. And mouse genetics was based on radiobiology. You irradiated the mice and then you looked for the mutants. It all came out of the atomic bomb, the Atomic Energy Commission. So the DOE had that responsibility, and they had people who were interested in that. They also had people who used big computers out at Los Alamos who were interested. They then hired somebody from the NIH, Charles Louisey [?], to go out there and run their science programs. He was going to make a mark for himself and them in being the first people to think about the human genome. There began to be meetings at Woods Hole and various other places, and this is where politics plays a very interesting role. Los Alamos is in the state of New Mexico, and the most powerful senator from the state of New Mexico is Pete Domenici [Republican]. He was going to see to it that they got their fair shake. He had a hearing out in Santa Fe, which is not very far from Los Alamos. Well, Jim Wyngaarden was resisting all over the place, but finally he said, "We had better have representation." He looked around and he thought about all those institutes that were interested in diseases and decided, "I had better keep this out of the disease arena, so, Ruth, you go."

Harden: Why was he not interested, by the way?

Kirschstein: And he was a geneticist! He was not interested because he saw it as many people did, as a technique, a mundane thing where you just mindlessly sequence, then you have to go back and do all the studies, and maybe you could just as well do it

from the disease point of view. To some extent, first, when it was very expensive to do, and, second, when you could not do very much of it at a time, he was right. He, therefore, did not think it should be done. But when Jim realized that this was biology, and this Department of Energy man Valisi [?] would take it over from him, he began to say, "I guess we had better be represented."

Harden: He was sending you to this meeting when I interrupted you.

Kirschstein: Yes.

Hannaway: The meeting in Santa Fe.

Kirschstein: Yes, the meeting in Santa Fe, to which Senator Domenici came. We had this hearing, and the Department of Energy people were there. I was sort of backpedaling and forward-pedaling because I could not commit very much as Jim had not quite gotten there [yet]. But Domenici wanted to know something about the science, and the physicists at Los Alamos could not tell him about biological science, so I did. I came back to Washington, and about four months later there was something else, a different kind of hearing. I cannot remember what it was, it was down on the Hill. Domenici was on the committee, and he spotted me in the audience. Jim Wyngaarden was testifying. Domenici said something, and then he said, "That little lady back there who taught me everything I know about genomes, she's here," or something like that. I cannot remember exactly. That has happened to me more than once. The senator from North Dakota on our Appropriations Committee, [Mark] Andrews [Republican], way back once called me the Mother Superior of research training in a hearing.

Hannaway: That was quite a comment.

Kirschstein: Jim Watson, meanwhile, was whomping everybody up. He has, subsequently, in his own inimitable way, said in public that the reason he was interested in it was because he wanted to know about his own DNA. Watson came out and he talked to Jim Wyngaarden, and Jim said, "Okay. We will start it as a small little unit of that genetics program here at NIGMS. Ruth will go around and see if she can get the other institute directors interested in it," which I could not. They were interested, but they did not want to spend any money. So Wyngaarden gave us some money to do it. It was not a lot. There were then meetings down at the Office of Technology Assessment, and we began doing some things. Jim Watson came down to sort of consult with us. He stood up one day at the Office of Technology Assessment and said, "The NIH needs to do this." People were all around, publicly. "But I would feel better about this if [Dr. Vincent] Vince DeVita were going to run it in the Cancer Institute than that institute run by..."

Harden: A woman.

Kirschstein: Exactly. It is very funny because of what happened subsequently. You know, I could care less. And so Watson came down. He had a meeting of the whole group of people up in Boston. They came to the conclusion, because they called me up and told me, that "this project is too important to be left to the feds to do. We are going to manage this ourselves. The way we are going to do it is we are going to get Jim Wyngaarden to appoint Jim Watson." So they moved it out of NIGMS at Jim Watson's request and made it an Office of Genome Research, Office of the Human Genome, in Building 1, and Jim Watson was the director. He took the best staff I had in NIGMS with him, Elke Jordan and [Dr.] Mark Guyer. Elke had been a graduate student in his department. She knew what

Watson was like, but she went anyway. And it started slow. I was not particularly worried about it. It was hard to get money for it. It costs a lot to sequence genes. They are talking now about 10 cents a base; it was well over a dollar at the time. It may have even been two or three, and it was really expensive. Jim Watson came down a couple of days a week and then went back to Cold Spring Harbor, and Elke ran the shop. Then Dr. [Bernadine] Healy came. She knew about Watson's antipathy to women, number one. She also knew about his antipathy for bureaucracy, and she knew that he was not going to be very respectful. She found that he was in serious conflict because he had continued all his private industrial consultations while he was doing this. But she found a way to move him on. By that time, the organization had become a center--the National Center for Human Genome Research-- and she asked me and [Dr.] George Vande Woude to chair the search committee for the director. We went out and worked very hard and got a lot of good people to apply. Meanwhile, she was sitting over there and talking to [Dr.] Francis Collins, and we finally figured that one out. We invited Francis in for an interview, and the rest is history.

Harden: But the change in leadership from Dr. Watson, then, was more than just a disagreement over this patenting of cDNAs, which was the disagreement that became very public.

Kirschstein: Oh, yes. There was much more to it than that. That had something to do with it, but it was really more the other. We can talk about that some other time.

Harden: In the few minutes that we have left today, I want to wrap up some of the main things you did at NIGMS by asking you about the two personnel programs that

you championed, the Minority Access to Research Careers Program, the MARC program, and the Medical Scientist Training Program, the M.D./Ph.D. program. Could you talk about those and how you view them now?

Kirschstein: Both of them again were actually established, before I came to NIGMS, by Dr. Stetten. The MARC program came about because he had an individual on his advisory council who, as the administrations became more and more interested in making sure there were women and minorities, was an African American female with a Ph.D. in biological sciences. Her name was [Dr.] Geraldine Woods. She was the first African American woman to get a Ph.D. in biology from Radcliffe. She never did anything with it after that. She married and did good work thereafter by helping minorities, but she never did any science, which was too bad. She came to see the director of the NIH--I think it was probably Bob Stone, but I am not sure. It could have been Marston—to tell him that the time had come to do something about getting more minorities into research, and that she wanted to travel around the country with some of his staff and show them why this was necessary. He turned it over to Dr. Stetten. They did some traveling and began to set things up. Some of my own staff who were there at the time were non-African Americans who later moved into the ghettos in Atlanta to live for a while to see what things were like. It was a very small program when Geraldine Woods started it. Hans set it up, and then he left. She became a consultant, and she was off the council. It was a four-year term. And I came. I realized that this small program, which was set up to be fellowships for minority students to go and get some advanced training, and for visiting-scientist type activities where, hopefully, a non-minority professor at a major university would go and spend a year or so at HBCUs—historically black colleges and universities--

was not going to work. The only way we might be able to do anything was if we became quite radical and if we moved into the undergraduate level and turned young men and women at HBCUs, or any other school that had significant numbers of minorities, into being interested in science so they would go on for graduate-level training. We devised something called the Honors Undergraduate Research Training component of the MARC program. We had to sell it to the department because the health part of HEW was not supposed to be in the education business. It was supposed to be in the graduate training business, graduate biological or chemical, or whatever training for research, but not in education. As far as the education, part of the concern was four years of college, even the last two, were education and were not training. So we devised something to address that issue. These young men and women have to get the background [in science], at least in their junior and senior years, and then learn how to do research through honors courses so that they could in a seamless way move on to graduate school afterwards. It must have been a year or so, but we finally got the department's permission. So, my contribution was not the establishment of the MARC program itself, but particularly the [establishment of the] honors undergraduate minority access to research program, which is now the predominant part of it. Probably 80 percent of the program is that. We started quite small. The first awards were something like 13 in number. We went out, site-visited every school that submitted applications, had these wonderful peer-review study sections that wrote the summary statements, a part of which was the history of the schools, how Bennett College in South Carolina started, for instance. Almost every one of them had started as a small, one-room school to teach the freed slaves to read and to do numbers, and they were very much

intertwined with the black churches. It is really a wonderful story how the colleges evolved. Now, Howard University is a little different because it was not like that. It was actually started as black hospital, which also was post-Civil War. But almost all of the others began as schools. And, then the land-grant colleges. You talked about the Agriculture Department. Most of the great universities in the Midwest—Illinois, Idaho, Iowa, Nebraska, maybe Texas—were all started as land-grant colleges, and their counterparts in some of those states—Texas A&M, Florida A&M—were the historically HBCUs, as well as some of those on the East Coast. I presume, though I do not know for sure, that the original separate-but-equal decision of the Supreme Court was handed down in the 1890s [1896]. Then there was an amendment to the land-grant college legislation to include the HBCU land-grant schools so they were then eligible for agriculture money and other monies. We started out with 13 schools in the Honors Undergraduate program. I had on my council at the time probably the most prominent African American biological scientist in the area of molecular biology, Luther _____ [?]. I used him for advice and talked to him about the fact that this was going to be an honors program, that so few students could do it, and that so few schools could really undertake it. How were we ever going to increase the numbers? He said, “You want to increase the numbers of those who are really good, you do not want just to increase the numbers.” We began to include schools that traditionally had never had minorities, such as City College, Hunter College, others all up and down the East Coast. Some colleges are probably 98 percent black and Hispanic now. I had an uncle who went to City College in the 1900s and it was then 100 percent Jewish, approximately. So they were eligible. Of the 110 to 115 historically black colleges, maybe 30 were good

enough to handle our honors program. We started with 13. We had two great champions of the program besides Joe E. Woods [?], who knew everybody. One was Senator Ed [Edward] Brooke, Republican, from Massachusetts, the only black senator ever. The other one was Congressman Gerry Studds, Democrat [?]. We worked with Senator Brooke and he worked with us, and I became a very close friend of his. There are large numbers of schools now, and although one can argue that maybe we did not succeed with the honors program completely, we changed the face of those schools. The curricula and the faculty improved. The students who wanted to do science increased massively in numbers. Most of them went to medical school--and why not if it assures you of earning a living, which you might not be able to do if you became a biology professor--and some people have questioned whether that was worthwhile because the program was to foster research. I would argue that many of those people became science literate, think about science, and many of them will be doing some sort of science.

Harden: Not to mention, they will have children who may do things as well.

Harden: This might be a place to stop.

Kirschstein: Do not let me forget next time, then, to talk about the Minority Biomedical Research Scientist, MBRS, program and the Medical Scientist Training Program.

Hannaway: One follow-up here. In your first interview—you may not recall this—you mentioned your experiences on your way to Tulane, and you made a comment at that time that you thought these early experiences of yours with segregation in the South influenced your attitudes about these programs later. You said, “I would like to come back to that.”

Kirschstein: Yes, absolutely, because, while there were people who felt that there was so much exciting science to do that even this measly amount of money that we were giving these programs could be better used elsewhere, I had a deep commitment then, and I still have a deep commitment. A lot of it came out of those early experiences. There is no question.

Harden: Thank you, Dr. Kirschstein.