**Dr. Janet Hartley, who worked in virology in the National Institute of Allergy and Infectious Diseases (NIAID), during the period from 1953 to present. Interview date: June 20, 1995. Interviewer: Dr. Carl G. Baker, former Director of the National Cancer Institute.**

Baker: Dr. Hartley, before we get into looking at the Viruses Cancer Program itself, could you give us a little bit about your background, where you went to school, and what experiences you've had? You've been here at NIH so long you probably haven't been very many other places.

Hartley: No, I really haven't. In fact, I got my Ph.D. while working here at NIH. I was a student at George Washington University and, because their Virology/Microbiology Department was very small and I really wanted to do my research in virology, I was very fortunate in getting a job as a technician in Bob Huebner's lab in 1953, and I've been in this building ever since.

Baker: And your degree was what year?

Hartley: 1957.

Baker: And who was your mentor?

Hartley: Mary Louise Robbins.

Baker: Yes. I remember her.

Hartley: Remember her?

Baker: Yes.

Hartley: She's been in Japan for a year since she retired. She helps Japanese with writing English scientific papers.

Baker: Well, we're pleased to have you tell us about some of this history, particularly since we can't talk with Dr. Rowe or Dr. Huebner, and they both made so many contributions, and maybe you can give us a little flavor of how it looked from your perspective?

Hartley: Well, I'll try. I know it's a lot of years to try to compress. But, when I first came here, it was just at the height of the excitement of the discovery of what later became known as the *Adenovirus* group. The first isolations had been made from cultivated tonsils and adenoids, and the work was just beginning to try to understand what a broad spectrum of viruses was involved and what they had to do with human disease, with respiratory disease in the military, and with *Trachoma* and with pink eye and all the things that are now known to be associated with *Adenovirus* infection. So, that was the major focus of attention when I first came.And then we went on to studies with the *Cytomegaloviruses*, and actually I did my Ph.D. research with *Cytomegaloviruses*.

And then we progressed, or moved, from there to studying indigenous viruses of mice, because we were beginning to use mice a lot for experimental purposes, and it became very clear that there were a lot of viruses already in the mice that weren't recognized, hadn't been classified, or tests worked out for their characterization. So, we got rather deeply into mouse viruses. I guess it was a very natural transition from that into the *Polyoma* virus which was the first real tumor virus that was worked with in this lab. Of course, Bob Huebner and Wally Rowe were leaders of all of this work at that time. And when Sarah Stewart and Bernice Eddy isolated *Polyoma* virus, we got involved in seeing how it could be handled in the laboratory and began a whole series of experiments that had to do with studying the natural history of *Polyoma* virus infection in lab mice, and Bob Huebner's particular interest in mice in the wild.

Baker: Exciting times.

Hartley: They were very exciting. There was so much we didn't know. It seemed

as though every day we learned something we had no concept of before. But I've always felt that one of the key things to sort of opening up tumor virology was the isolation of a virus that you could work with in the lab that produced changes in tissue culture. You could do a hemagglutination test with it--you could do serology, as well as the animal pathogenesis studies. And I really think it was the beginning of the very broad field of DNA tumor virology, just knowing that you could work with these things. They weren't mysterious. They were like other viruses and you could do things with them and ask good biological questions and get some answers. And Wally Rowe--

Baker: It became quite a change because, as you know, before 1955 nobody thought viruses had anything to do with cancer.

Hartley: That's right.

Baker: And Payton Rous's findings, that couldn't be a virus because it--

Hartley: Because it was a tumor. That's exactly right. That's right. And Ludwig Gross's induction of leukemia in mice with AKR thymic lymphomas met the same sort of reaction. "It can't possibly be true."

Baker: Yes. It took about 2-3 years before that got confirmed, and then it opened up a whole new perspective.

Hartley: Exactly, exactly. Just being able to work with these things in some reasonable latent period, and then being able to work with them in cell culture, I think, just made a tremendous difference.

Of course, in the mouse field we were always kind of tagging along behind the avian field, because they discovered everything before we did.

Baker: That changed though.

Hartley: But it was an extremely rewarding and exciting time. But the *Polyoma* work, of course, led Bob Huebner and Wally Rowe then into work with

SV-40 when that was shown to be a transforming virus with tumorigenic potential, and studies with *Polyoma* and SV-40 and then, a little bit later, with *Adenovirus*, really began the understanding of T-antigens and the gene products of tumor viruses that were associated with--that were necessary--for tumor induction. And all of these things, of course, led to tremendous input in other areas over the years, things that have developed greatly.

Baker: By the time I left NIH there were over 200 viruses known to induce tumors in animals, and yet we had very little in humans. Why do you think there is such a difference between the animal picture and the human picture?

Hartley: Well, of course, in mice, the inbreeding of mice specifically for development of particular kinds of tumors, or reaction to induction technique. I mean, you have an inbred mouse like AKR that was bred for high incidence of thymic lymphoma, and you didn't have that in humans. And I think that the genetic uniformity of many of the animal test systems has a lot to do with that.

Baker: Well, in a less friendly way, I suggested that we manipulated the laboratory animals in such a way that it led to that, but we didn't do that in humans. We couldn't.

Hartley: Well, that's true. That's true. Yes. The animal systems were designed to pick up something if it were there.

Baker: Of course, that gave us motivation that surely we must have something in humans, which some people look back now and say, "Well, you went the wrong direction there." I don't think it was, from what we knew at that time.

Hartley: That's right. You had to take the approaches that your model systems

and your background indicated. And, I mean, it's easy to say in retrospect that we shouldn't have looked so hard for human viruses, but until you looked you didn't know.

Baker: Could you give us a little bit of insight into the personalities of, first, Dr. Huebner and then Dr. Rowe? They're interesting people.

Hartley: Indeed they are. My first experience with Bob Huebner was when I came for an interview. I don't know if you know it, but in those days in Building 7, all the investigators wore blue jumpsuits. Everybody, and I met with Bob Huebner, who was a big man, and his jumpsuit was a little too small for him, so you had the feeling he was about to burst out of his suit and out of his office and everything else. But he was so full of enthusiasm for what they were doing with these *Adenovirus* isolations--the use of a new tissue culture technique, and finding something that had never been seen before--that, you know, I could think there is no place that I've been that I want to work more than this place.

And then he took me back in the lab and introduced me to Wally Rowe, who was in a blue jumpsuit and was sitting up on a lab bench--very young, very handsome--and I met him and the two of them decided that I could come and work here. And that was one of the most exciting and happiest days of my professional life.But Bob Huebner was, of course, full of tremendous enthusiasm and full of great energy, and he was a motivator. He could get other people interested and enthusiastic in what he conceived of as being important. And he had a broad knowledge of biological matters. I mean, he had, of course, worked with *Rickettsia* and done some fabulous epidemiology that--

Baker: Q fever.

Hartley: Q fever and rickettsial pox, and epidemic floridinia, and just had really

opened up the virus rickettsial epidemiology field in many ways. He just went out and did things that nobody else had the nerve to do. But, in the lab he was very insightful, but he sometimes got a little carried away with his enthusiasms. Wally Rowe, on the other hand, was tremendously knowledgeable, a very, very brilliant mind. He understood genetics and mathematics and statistics and all aspects of medicine and virology. And he was really sort of a self-taught virologist. And he was a kind of an analyzer. And I was sort of the facilitator.

Baker: Between the two of them?

Hartley: Well, no. I just sort of saw that things got done. You know, they were busy thinking and talking, and somebody had to get things done.

Baker: Well, Wally Rowe was very critical, in the high-quality sense, and he was a very good one to have him assess something.

Hartley: Extremely. They made a very good pair because Bob had the unusual ideas and the enthusiasm, and Wally had the ability to sort out what was doable and really what should be followed up and then went ahead and did it.

Baker: They worked together on some things, but they also had other work that was separate from each other.

Hartley: Yes. They worked fairly closely together for the first number of years I was here. They interacted all the time. Wally always had a little project of his own, but generally they were looking at slightly different aspects of similar questions. When Bob, of course, became Laboratory Chief and then, after he left to go to the Cancer Institute, by that time Wally had pretty much established his own programs and his own staff--

Baker: That's what I understood. Yes.

Hartley: --and we decided to stay in NIAID, and Bob went off to NCI. And we

still had a lot of collaborations and interactions, and we got some extremely valuable support from Bob in terms of positions and help on a contract that made possible the development of the murine leukemia virus ecotropic congenic mouse strains that Wally used.

Baker: I don't know how much you know about the Cancer Institute's background on the move of Bob Huebner to NCI. Endicott very much wanted this to happen. I was Head of Etiology then, and so I was all in favor of it too. But Endicott wasn't in a position to give me any additional resources and, as you know, Bob Huebner could use resources.

Hartley: Indeed.

Baker: So, I had to carve these resources out of my hide, so to speak, but I thought it was worth it. I was always glad we did that from the Cancer Institute's standpoint, because it added so much to the program. We were already putting a fair amount of money in behind some of the work while he was still in NIAID.

Hartley: Yes, I know that.

Baker: And he was always, of course, after us for more reagents.

Hartley: Well, he used to say, "The cheapest thing that we have is money." I don't know if you remember hearing him say that. But in many ways it was. If you've got it, that's good.

Baker: It's like it's only important if you don't have any.

Hartley: But, I mean, he was instrumental in, or instigated, the development of relatively simple ways of detecting presence of the avian and then, in our studies, the murine leukemia viruses in cell culture, or in the mouse; I mean, things that weren't able to be done. You know, the assay system, for many years, was to infect mice and see if they got sick, with absolutely no way of telling whether the virus was replicating, except

maybe electron microscopy, no way of quantitating the level of virus in field specimens or in cell culture, and so, I mean, his enthusiasm for lots of reagents had to do with the techniques that were developed for doing that. You know, antibody was essential to the first tissue culture assays that were developed.

Baker: Do you recall ever hearing him talk about Ray Bryan's quantitative estimates of the Rous virus?

Hartley: Oh, golly, I can't remember specifically.

Baker: It was some of the earliest quantitation, where Bryan showed that the dose made a difference. You got a lot more tumors if you gave a lot more virus.

Hartley: Yes. Of course. Sure.

Baker: And, of course, that didn't quite fit in with how, if the virus is infectious and grows, why do you need bigger doses to get more tumors. And I'm not sure we understand that phenomenon even yet.

Hartley: Well, I suppose it's basically the defectiveness of the virus too, that you've got to have several hits with a defective virus to get anything going. And that was one of the areas that I think Wally Rowe made a tremendous contribution in was the real quantitative analysis of the processes of infection with these viruses, first with developing a plaque assay for the murine leukemia virus, the XE assay, which is still widely used, and, you know, a perfectly useful quantitative plaque assay, with a virus where you can infect tissue culture cells with it, but you can't see any morphologic changes or anything that tells you it's there. This was a way of actually doing a quantitative titration.

Baker: I guess we owe something to Renato Dulbecco for plaque assay development. The assays for murine leukemia viruses developed in your

lab proved to be so much more significant than the electron microscopy which, in the early days when we didn't have anything else--

Hartley: Of course. It was the only thing. That's right.

Baker: But it sort of misled us sometimes. I found the electron microscopists weren't having controls very well.

Hartley: Well, that's true. And you couldn't always tell a live particle from a dead one.

Baker: But it helped stimulate the field anyway.

Hartley: Sure it did. But then Wally used that titration technique to show that murine sarcoma viruses were defective, that they required helper virus to produce their cell transformation. He used it to show that it was a multi-hit dose-response, and also the same technique for showing that-- Our lab showed that there were, among the ecotropic murine leukemia viruses, that there were N-tropic and B-tropic variants and that inbred mouse strains were either FE1-B or FE1-N, and their ability to be infected, or the ability of their cells to be infected, depended on matching the tropism of the virus and the FE1 allele of the mouse strain. And we showed that the restriction, in a restrictive FE1 situation, could be overcome by high multiplicity infection and you could show it with data. And that was something that hadn't really been done, at least for the murine viruses.

Baker: Were you faced with a decision on whether you would move to the Cancer Institute or not?

Hartley: Well, we were invited, but we decided that we didn't want to leave.

Baker: You probably had good resources with the space being vacated by Huebner, and you got some of that space, I presume?

Hartley: Sure. And we had good people.

Baker: And we could work together almost as well anyway, I think.

Hartley: That's right. And he was so generous in his support of our work. And, you know, I think it paid off.

Baker: Well, that's why the Cancer Institute continued to put money in, even when Huebner moved, I mean, because Rowe and you and the others were doing a good job.

Hartley: We were very aware of that help and very appreciative.

Baker: Anything else? Can you think of any anecdotes that--

Hartley: Oh, goodness, there are so many years, it's hard to single things out.

Baker: I can tell you one you might not have heard about. When I was Director of the NCI, one day Bob Huebner saw me in O'Donnell's Restaurant, and he had asked for a tremendous increase for some more resources, and I had to tell him no on that, and so he wasn't used, I guess, to having somebody tell him no from above. And he got kind of hot there and he was punching me on the chest with his finger and he says, "And moreover, I could be a better Director than you." And I smiled at him and said, "Well, that may be, Bob, but I'm in the job and I've got to make the decisions, and I'm going to make them." And we got along fine.

Hartley: Well, you could talk to him. You know, he would sometimes kind of fly off the handle, but then he'd come around. But he was an extremely stimulating and exciting person to work with. I think his illness is--

Baker: Such a shame.

Hartley: --such a tragedy. It's just the last thing that you--You know, your worst enemy wouldn't wish Alzheimer's on a man like Bob Huebner. And, of course, Wally, losing him, really when he was being so productive and so important in the development of cloning and all of this.

Baker: Any comment on Wally Rowe's illness?

Hartley: Well, it was devastating for all of us. We felt that it was such a loss, not only personal or--

Baker: How did that happen, do you think?

Hartley: I don't know how this cancer happened. You know, it was just one of those terribly sad things, but there is no evidence at all, that I'm aware of, of any connection with his disease and anything that he'd worked with. It's just one of those tragedies. And everything was done, I think, that could have been done. He had the best surgeons. He was very reluctant to have any therapy that would interfere with his ability to work, and maybe, I think it was just too far gone.

Baker: Okay. Let's turn to the questions. You've already touched on several aspects of the first question about the advances.

Hartley: Yes. I found it very hard to think of five--

Baker: And not every question here necessarily fits your situation exactly, but it's a good outline for sort of guiding discussion.

Hartley: Well, as I mentioned, I think that in the 1950s the isolation of viruses like *Polyoma* and SV-40 and then the demonstration of transmission of thymic lymphoma in mice just sort of gave us a way of working with tumor viruses and a way of learning that they weren't strange and mysterious and that they really were involved in tumors. And the things that were learned led to the tremendous advances in the years afterwards. Just the recognition of the importance of early gene products of the DNA tumor viruses, that followed pretty much, I think, Bob Huebner's desire to work out serological methods for detecting these viruses.

Baker: On the SV-40, do you remember the scare from the polio vaccine?

Hartley: Of course. Yes.

Baker: Were you involved in any of that?

Hartley: Not directly. No. I didn't get pulled out of the lab to do that.

Baker: I hope to talk to Ruth Kirschstein about this. She was directly involved in it.

Hartley: Yes.

Baker: And, of course, I was with Dr. Smadel, and there was a little concern about whether he did the right thing, or not, on preventing some of the information from coming out. But I think he was really asking a number of people like Wally Rowe to check the validity of this. Before you let that information out, you'd better be sure of what it was. So, Smadel got blamed for being too hard-nosed, I think, but I think he probably was right in showing that--

Hartley: Well, in the long run, nobody has ever--as far as I know--ever made any connection with that virus and human disease.

Baker: Well, we didn't know at the time.

Hartley: Of course not.

Baker: And we followed those patients for several years, and, as you say, nothing seems to have shown up.

Hartley: We were very concerned too because of the *Adenovirus* vaccines that we had been instrumental in preparing in African green monkey kidney, because this was a good medium for replicating the virus. And we worked hard to adapt some of these *Adenoviruses* to monkey kidney culture.

Baker: Did you have much to do with John Moloney?

Hartley: Not directly. I worked with his virus a lot. But I never had any really close contacts with him, except occasionally at meetings.

Baker: He was Ray Bryan's technician before he got his degree after working here a while too.

Hartley: That's right. That's right. Well, there was that whole Rutgers group Wasn't it Rutgers that Ray Bryan was from?

Baker: Well, he lectured there and worked with Groupé. Earlier he was with Goodpasture at Vanderbilt and worked with Joe Beard at Duke.

Hartley: And Bob Mannaker.

Baker: So Bryan wasn't exactly from Rutgers, but he was a friend of Groupé, and Groupé's students. Rauscher was one of them, and Lou Sibal, and Mannaker.

Hartley: Yes. I'm sure of that.

Baker: And, of course, Sarah Stewart and Bernice Eddy, they were an interesting couple of ladies.

Hartley: Extremely interesting. And again it was their drive and their persistence, conviction that they had something, that led to success

Baker: Sarah got accused of doing it by intuition without the necessary controls, but her intuition was pretty good.

Hartley: Well, it worked. It worked.

Baker: I'll tell you another little story. When Dr. Mider went over to Building 1 to be Deputy Director for Intramural Research, I was Acting Scientific Director of NCI for a while, and the only advice Dr. Mider gave me was that Sarah Stewart would come in once a week and cry.

Hartley: I didn't know that.

Baker: Well, she didn't. She came in sometimes, but I don't think she ever cried with me. But, you know, Dr. Mider was known as "Dr. No." He would tell everybody no when they asked for something. But it was his method of testing them. He thought if they hadn't really thought it through then they didn't deserve it. But he got that name because there was a movie about that time. You know? So these are interesting little side-lights.

Hartley: Moloney virus and Friend virus and Rauscher leukemia virus, these that we call "lab-adapted" strains, where they maybe weren't the way the viruses are occurring in nature, provided us with tools to allow the beginning of to development of tissue culture systems and assay systems to look more broadly at what these viruses were doing in nature. And we began to do tissue culture assays in normal mice of all different strains, and were able to show that the viruses were relatively widely distributed. And because we were able to develop tissue culture methods, we could begin to characterize them. And from this came the N- and B-tropic realization of an *in vitro*--and, I mean, eventually realization of other classes of murine leukemia viruses that were different.

Baker: This work also laid the important groundwork which led to the oncogenes, really, because of clarifying the way the information got transmitted.

Hartley: That's true.

Baker: And so trapping feral mice was part of that story, which Bob Huebner was very much involved in.

Hartley: That's right. This was a little bit later, but he was very interested in what these viruses were doing in real nature. I mean not lab inbred strains, but in mice in the wild. And we learned some extremely important things from those studies of the California wild mice. We isolated B viruses and learned a lot about transmission of the viruses, because it was different from laboratory mice and provided, again, new reagents just for broadening our understanding of what murine leukemia viruses were all about. I mean, I don't want to ignore the tremendous impetus to all these studies that the avian sarcoma viruses and leukosis virus field made, because that, again, opened up the idea of defective viruses, of viral

interference, of replication competent helper viruses and different host range classifications of viruses. And we saw very similar things, although not necessarily mechanistically the same, in the mouse field.

Baker: Early on I like to think that Bryan and Joe Beard kept the flame of cancer virology alive while everybody else was in the dark. That was earlier.

Hartley: That's right. They did. But people like--

Baker: Burmester should be there.

Hartley: --Burmester and Rubin and Peter Vogt, of course, who goes on forever making valuable contributions. Howard Temin, his provirus hypothesis led to--

Baker: A revolutionary change of outlook. Yes.

Hartley: That's right. And to prove it, all of these things came together and, of course, are--

Baker: We should add Baltimore, of course.

Hartley: I was going to say, and--

Baker: It was at the same time.

Hartley: But Howard Temin was the one who really formulated the provirus idea. But then Temin and Baltimore got the reverse transcriptase business which, of course, has made--you know, you can't begin to measure the impact of that discovery on the field.

Baker: No. It shifted our thinking from viral causation to information with key sequences which happened to be pretty much present in both the animal-causing viruses and elsewhere.

Hartley: Well, that's right. I mean, it led to--

Baker: And so that changed from the viruses to the informational genetic aspects. So I consider the first transition was Ludwig Gross' opening up so that people began to think about viruses in cancer, and then the next

revolutionary transition was the reverse transcriptase and the oncogene. And the Todaro-Huebner paper on oncogenes was important for stimulating ideas, even though they weren't quite on the right track.

Hartley: That's right. It was tremendously important. I mean, nobody pretends that they had it exactly right, but the amount of work it stimulated, the amount of thought, it's just not measurable, and the tools were just then coming along to be able to really look at things and to realize that there were cellular homologs of viral oncogenes and all of these things that were so exciting.

Baker: And then Bishop and Varmus sort of pulled that together.

Hartley: Bishop and Varmus and Hanafusa and all of them. It's just--

Baker: A wonderful set of rapidly developing, not only data, but ideas.

Hartley: That's right.

Baker: Anything else you can think of on the first question?

Hartley: I guess this maybe applies more to your fourth question about--which is the one about molecular biology? This is the period when things like the restriction enzymes were developed and DNA transfection was shown to work. I mean, all of these things came together to round out the story--Wally's virus congenic mice, and all of the things that proved the proviral hypothesis and set the stage for understanding endogenous viruses in so many species--that it's just very hard to say what-- You know, you're going to leave out something critical because so much was going on.

Baker: Oh, well, we appreciate your telling us what you have already told us. The second question, you may not have been involved in that enough to know the story of that.

Hartley: I don't really think I can help at all on that. I mean, there were a few names that we knew of people who were involved, but probably not at

the top administrative level. I don't know them. Other people might.

Baker: That's understandable. Yes. Well, I think you've pretty much answered 3, but is there anything else that comes to mind there?

Hartley: No. I think I've pretty well mentioned the things that were involved in isolation and characterization.

Baker: Doing good lab work with high quality.

Hartley: Just learning how to work with these things in the laboratory.

Baker: I'm sure you worked more than 40 hours a week.

Hartley: A bit, a bit. I still do, as a matter of fact.

Baker: Okay, we're moving right along now, aren't we? Number 4, again, I guess you touched on a lot of that, but any other people you think of that we haven't mentioned? For example, Joe Melnick, I think, is an interesting fellow who had a different slant on some of this, but was very helpful to us in the Cancer Institute.

Hartley: Of course, and people like Maurice Hilleman, who was involved in the adeno/SV-40 hybrid business and in other studies. The Henle's. The whole EBV story with Burkitt and Epstein and then the Henle's working out the infectious mono connection. George Klein, I think, has been tremendously influential over the years in a lot of areas of tumor virology.

Baker: Klein is a synthesizer. He puts information together from a lot of sources.

Hartley: Yes. That's right.

Baker: And comes up with some interesting ideas that people chew on for a while until he does another synthesis.

Hartley: But, you know, he's been involved in many areas of this field for a long time. Oh, Robin Weiss, again very active in working out assay

techniques, working out clean ways of studying the avian viruses and the murine viruses. I'm not sure that he gets the credit he deserves. Harold zur Hausen, you know, all the people, Doug Lloyd, Peter Howley, the people who have been involved in *Papillomavirus*.

Baker: Zur Hausen's results have become quite important, I think, in cervical cancer.

Hartley: Absolutely.

Baker: Very good. Again, I don't know. You may not be aware of too much about membership on key committees.

Hartley: No. I mean, I was on some of them but--

Baker: You were busy in the lab.

Hartley: Well, I was on some of those committees.

Baker: Do you remember which ones you were on?

Hartley: No.

Baker: Isn't it hard to remember that stuff?

Hartley: I can remember the first one, and I don't remember what exactly the content was. This was long before Bob Huebner was in NCI. It must have been just after the sizeable influx of money. And Bob Manaker had a committee to decide how to spend the money. And I just can remember him standing there and saying, "We have all this money and we don't really know the best places to put it, and we're getting committees together--"

Baker: He didn't? I thought I did.

Hartley: Well, he hadn't asked you, or he hadn't listened to you. But I remember he was sort of plaintive.

Baker: Do you recall who the Chairman was?

Hartley: No.

Baker: Yes. Isn't it hard to remember some of this stuff?

Hartley: I don't remember that at all.

Baker: Okay, we'll move right along again then. The next one deals with this question of resources and is sort of a comparison between how things were earlier in this period compared to later. I remember when the polio story was drawing to a close and you had a lot of good scientists, like Melnick and others, who had worked in the polio area, and they were really sort of looking for where they go next. And so NCI first had a million dollars earmarked for viruse cancer work, and that was in grants. That was before the Special Program was developed. And I was with Smadel then. So one afternoon we called up all these virologists from the polio area and asked them if they would be interested in maybe working on the cancer problem. And most of them did, and the V&R Study Section agreed to review their proposals especially-- around this million dollars, and so several of them came in. That's the way they moved from the polio game to cancer. And then, of course, a lot of those also were in the program when we had the Special Program developed. But I had fun with them on this question of resources. I said, "You guys are very good about exchanging samples to check the quality, but by the time you've exchanged samples you've used it all up and you don't have any to work with. We need to make much larger batches. And the way to go on this is industry with a contract." Well, at first, you know, it was, "Well, they can't make it good enough," you know, forgetting about guys like Hilleman. And I said, "Well, I'll tell you what. Let's go this way and you don't have to use it if it doesn't meet your criteria." And I knew that we were over the hump when Moloney came in one day and he said, "We just a new batch of virus from Pfizer and it's as good as anything we ever

made, and we've got buckets of it." And so that sort of got us over the hump of the academic people thinking industry couldn't do it well enough.

Hartley: Sure. Sure. Oh, I don't think there is any question that the availability of resources--reagents--and the increasing desire for quality control--I mean to really know what these reagents were detecting--because, you know, an awful lot was done pretty blindly. I mean there were multiple viruses present in some of those stocks that nobody knew about because they hadn't been identified.

Baker: And the tissue culture cell lines, a lot of those were not what they thought they were.

Hartley: That's right. Or they were *Mycoplasma* contaminated. And people were doing great studies on how to detect *Mycoplasma* when they thought they were detecting something else.

Baker: We had to put a few dollars into that area because at the time we had to work it out.

Hartley: Well, nobody knew how to get rid of it. Nobody knew how to characterize--I mean, we didn't have DNA techniques. We didn't have anything that's available now to really--

Baker: And primates, that didn't really pay off, but at the time we started we didn't know how to really produce clean primates. Most of these that were imported were full of diseases.

Hartley: Sure.

Baker: But we ended up finally by putting R&D money in there--I think is a better way of labeling it--to develop animal husbandry. So now, if we need to produce clean non-human primates, we know how to do it. So, we had a problem of eventually cutting back on that, and that led to some

people worrying about the monkeys, you know, which is sort of the extreme.

Hartley: Of course. It led into a whole other area of problems. But the same was true of mice in the development of specific pathogen-free mice.

Baker: Well, the Chemotherapy Program had already upped the production of mice tremendously.

Hartley: Yes. But I mean understanding the cleanliness of them and how many things were influencing immunologic tests and everything else and, I think we have a tremendous improvement in that area.

Baker: So, I get the impression that a lot of people, a lot of scientists, particularly academic ones, don't seem to appreciate the effort it took to get some of these resources. Now they're commercially available, but the developmental research efforts, I think, were largely in this Program that allowed it. Now we can buy stuff that, of course, you couldn't at all in those days.

Hartley: Yes. People are still using reagents that were made under the Special Virus Cancer Program antibody production systems. You know? They're still in a catalog that people use. And some of them, nobody has ever found a way of doing it better. I mean, there are a lot of new things now--monoclonals and very specific epitope spectra--but back in those days just to have something that was specific and highly active was a marvelous gift to the community, and I don't think--

Baker: I guess you're not really knowledgeable of who made the key decisions on these things?

Hartley: No.

Baker: Earlier Harvey Scudder and Bob Stevenson were very much involved.

Hartley: Right. And we were involved in a lot of the evaluation of some of these

reagents but, you know, we were dealing with the people making them, not with the people who decided whether they should be made or not.

Baker: Well, I, of course, listened to Bob Huebner on where the needs were. I compared him to General Patton. You couldn't let him have all of the gasoline, but you wanted to back him. And so when he talked about needing some new reagents I usually listened to him, and most of the time I could go along with it. But that, of course, led to problems with the Zinder Committee later. Were you involved in any of that?

Hartley: Not really.

Baker: You're probably glad you didn't have to get involved in that one, did you?

Hartley: No. I remember hearing about it, but I wasn't involved.

Baker: You see, some people worried that, as they saw it, Huebner had all these contracts just for his own personal work. And I didn't look at it that simply, but a lot of people did.

Hartley: And I don't think it ever occurred to him that these were personal supports for him. His idea was to answer questions and, if it took 2 or 3 people working on the same question--And this was sometimes a problem. You know? He'd assign the same question to 2 or 3 people and then, all of a sudden, they find out, "Well, why am I doing this if so-and-so is doing it?" But his idea was to get a correct answer and to put whatever resources into it that were required.

Baker: Yes. I found he wasn't at all bashful about throwing an idea out that he'd had if the evidence didn't support it.

Hartley: That's right. And he was not a selfish man. He was not self-aggrandizing. His whole idea was to ask good questions and to answer them.You know, this is a little bit beyond the 1980 cut-off, but it was still becoming clear that there were other viruses than the ecotropic murine

leukemia virus that could be present in mice and that were contained in some of these virus stocks. But experiments were still planned using these stocks that could never come up with a clean answer because the input virus wasn't clean. That's the kind of thing that bothered me as a virologist.

Baker: Well, at the time the decision was made to produce, say, some of this plasma and all, did we know that then?

Hartley: Well, eventually. I mean it was one of those things that kind of--

Baker: I'm trying to separate hindsight from-- Put these things in perspective.

Hartley: Sure. But it was one of those things that kind of got started and just kept on going. And even at the time when we were understanding some of these things they were still making the product and planning to use it for this or that. There was a lag period.

Baker :Now what year are we talking about?

Hartley: I'm terrible about spotting years, but I would say probably mid-'70s.

Baker: Yes, because I'm trying to pinpoint, you know, when should that have been cut off, since you said earlier that it should have.

Hartley: Yes. Well, I don't know exactly, but I just know that there were stockpiles that never were used.

Baker: Yes.

Hartley: And I think there must have been a crossover point when, you know, if someone had really taken the time to look at it hard, they would have said, "This isn't what's going to be needed next year, or five years from now; we're going to need a different quality of material." And it's tough.

Baker: A lot of people have trouble turning things off, but you've got to do it.

Hartley: I know. That's right. It's hard. You learn how to do something so that you're getting a--

Baker: It's a different mindset to turn something off, and a lot of people don't have it. And I learned from Endicott that you've got to identify these decisions and make them.

Hartley: Well, I think that you know it got hard to do because there were so many people who had been supported for so long, and it was hard to re-evaluate and begin to cut off certain areas of support.

Baker: Especially when some of them were advisors.

Hartley: Exactly. I didn't want to say that, but--

Baker: Well, why not? It's real life.

Hartley: That's right. So that I think that must have been very hard for the administration to control, and I have no idea how it was done or not done, but I think that's the kind of thing that disturbed some people; that there was an element of waste and money that could have been making materials that would be more useful. But, as you say, it's awful easy to say what was wrong.

Baker: No, but part of putting this together is where did it perhaps get off the track, and that's a good example of it, I would think. And it probably led to some of the Zinder Committee's conclusions too.

Hartley: I would imagine.

Baker: Well, on the ninth question you've already alluded to the idea that it did lay foundations important for molecular biology. That's a loaded question, but I don't apologize for that.

Hartley: I don't think there can be any question of it. I mean, absolutely, if it hadn't been for what was learned in the sort of hard biologic assay-- I mean, it wasn't just learning about the viruses, but it was learning what the questions were that could be answered. And, as molecular biology began to develop, obviously questions that you never thought could be

answered became approachable. And all of that background of biologic questioning and characterization was important in leading to reverse transcriptase and transfection and Southern blotting, and all of the things that make it possible to do what you do now.

Baker: And part of that is the resources, I believe.

Hartley: Yes.

Baker: You probably didn't have any direct knowledge of the Cancer Act of 1971 that Nixon signed and all that?

Hartley: I don't remember any details. I just know there was one.

Baker: One of the interesting things is people describe history as though a lot of things started with that program but, as I see it, it was a direct continuation and there is no sudden difference. The only difference was the money jumped. But conceptually, and the kind of work going on, I see it as just a continuation.

Hartley: I agree. I never felt that there were basic new ideas except just as they naturally developed from continuing work. I mean, a lot of things had already been started, as you say, and it made it easier to make faster progress with money and contracts and things that turned out good reagents that could be used.

Baker: You probably didn't have any knowledge of the planning activities that went behind this?

Hartley: Well, I remember the presentations and the sort of flow chart of, you know, how you're going to get from here to there, and I always thought it was an extremely difficult sequence to hope to complete; that it was pretty optimistic.

Baker: Well, I was very careful never to put a date on it exactly.

Hartley: That's true.

Baker: I think DeVita got trapped into making predictions by the year 2000 or something, but I never fell into that trap because I don't know the answer to that and there is no way to tell.

Hartley: That's right. But I think the feeling was given that there was some sort of finite time span that was envisioned as giving us a--

Baker: Well, see, you should read the paper on the planning process itself, because that was one of the key points that in research you cannot do that, even though the networking techniques came out where you did have definite endpoints on time, but you can't do that in research.

Hartley:Right. Right. No. I think it was just the way it was presented sometimes, but not by you, but by--

*Interview concludes*