This is an interview of Dr. Robert Miller, who was Head of the Clinical Epidemiology Branch in the NCI, taken on April 19, 1995. The interviewer is Dr. Carl G. Baker, former Director of the National Cancer Institute.

Baker: Bob, we appreciate your willingness to give us your views on some of the areas and, before we get started on the questions, which you had a little bit ahead of time, would you tell us about your background and how you got to where you are, where you went to school and so forth?

Miller: I'm a pediatrician by birth, and when I finished in pediatrics I didn't feel finished and so I looked around for something that wasn't too narrowing and found a fellowship in radiation biology. Then that led me to Japan to study delayed effects of the bomb in Hiroshima and Nagasaki on the children. That was epidemiology. I knew I liked epidemiology but I'd never heard of it, and that introduced me to it, and when I came back I got some formal training in epidemiology. I got more or less of an honorary degree because I didn't really work for it, a Doctorate in Public Health in Epidemiology.

Baker: Where was that?

Miller: That was at the University of Michigan. I went to the University of Pennsylvania Medical School. So I have two doctorates. In

Germany you're supposed to say, "Doktor, Doktor," however many times a person has a doctoral degree.

Baker: So your mentor at Michigan was?

Miller: Was Tommy Francis. Except he was away most of the time. But Jim Neel, a geneticist, was there.

Baker: What year was this?

Miller: I graduated from Michigan twice, once with an M.P.H. in '58, and with a doctorate in '61. And I graduated from medical school in 1946.

So, I looked around for a job, and the natural place was the Neurological Institute because they had the Collaborative Perinatal Study, which was pediatrics, but a full-time hypothesis writer was wanted, and there was no hope in that. At NCI I was interviewed--this will be interesting to you--I was interviewed by--Mike Shimkin wasn't here. He was the head of that unit, the field studies unit. But I was interviewed by Bill Haenszel, who probably never told Mike about me. So I was reviewed by Margaret Sloan, who knew me from when we were both at the National Academy of Sciences. Mike invited me down and I came again.

At the interview--it's important, I think--he said that he didn't

want a nose-counter. He thought of routine epidemiologists as nose-counters, that is demographers. And I told him that didn't interest me; I promised him that I would be doing what nobody else was doing because, if they were doing it, there was no need for me to. So, in spite of that, he accepted me, and then left after two years so there was nobody to defend me. I did what I thought was best, but others perhaps didn't think was best. And it's interesting that when I came I was a GS-14. I should have been higher, because I had left medical school 15 years earlier, and instead of counting from then, people in personnel counted from my doctorate in public health which was two months; they counted me as being a doctor for two months instead of 15 years. Also, I said to Mike, "This personnel action form doesn't say I'm the Chief of Epidemiology." And he said, "Well, to me you're the Chief," but really I wasn't the Chief.

Baker: Who told you that?

Miller: Mike Shimkin.

I asked, "Can I see the annual report from the unit?" And he said, "They all burned. There was a terrible fire and we don't have any." He didn't want to show it to me because there were only some holdovers from the previous century, and they were doing some really funny--strange--studies. I don't know if you

remember Ben Carroll and Pope Lawrence, but they were having a plane fly over Washington County, Maryland, and measure little tiny variations in background radiation and relating those little peaks and valleys to--they weren't peaks and valleys, they were little bumps and depressions--relating that to, I don't know, something in the potatoes, or what the people were eating, and seeing whether radiation of the potatoes--

Baker: It was called "microepidemiology" I believe.

Miller: No. This was "ultramicro."

Baker: Well, you might be interested to know that that's one of the things I killed when I became Scientific Director for Etiology, but I had a hard time killing it.

Miller: Well, I thought Mike was helpful because he called me in one day when I was still new and said, "What are you going to do about Hagerstown?" And I said, "What's wrong with it where it is?"

Baker: Did he appreciate that?

Miller: He said, "You have 15 people there." And that was the first I knew that there was anybody there.

Baker: That were supposed to be reporting to you?

Miller: Yes. But he forgot to tell me that. He didn't show me the annual report, so I didn't know. But I thought he was helpful in RIFing [reduction in force RIF] them. There were 15, and 14 of them got

other jobs.

Baker: But, you know, that "microepidemiology" project kept rearing its head again through the grants area.

Miller: Yes, because Comstock took it over. He's at Hopkins. And he uses it for--

Baker: And Frost. Didn't Robert Frost--isn't that his name--at Hopkins?

Miller: No. Not Robert Frost.

Baker: I think he was involved in it somewhere along the line.

Miller: Maybe a long time ago. His name isn't Robert. That's the poet. But, it's Jack Frost. And he was much revered as, as I said, a statistician at Hopkins. But anyhow, Comstock made a go of it and he continued up until the present. It's still going. But he's using it as a population laboratory, not flying a radiation-measuring airplane over it any more. Anyway, when I came, my interest was in--as far as cancer was concerned--in children or in birth defects too, and we hit upon the idea of looking at birth abnormalities in type-specific childhood cancers. We knew that leukemia and Down syndrome occurred in the same patients. What else does? Very quickly we found Wilms' tumor (a kidney tumor) and aniridia (absence of the irises).

Baker: Yes. I remember that.

Miller: And that was a big finding because, along with retinoblastoma, it

led to recognition of tumor suppressor genes. And the interesting thing is that, if you study children's cancer with malformations, you learn about breast cancer, because a substantial proportion of it is caused by tumor suppressor genes. But you can't recognize the existence of a tumor suppressor gene, unless you have a clear view. In children, because there are no other environmental factors, you can focus on the connection between the tumor and the birth defect. And then Knudson, of course, put it together and figured out that there were tumor suppressor genes. So, you learn about breast cancer by studying children's cancer with malformation. It has nothing to do with breast cancer, but it has everything to do with it because you learn something fundamental. Anyhow, that's the kind of thing we pursued. And then, we collected the death certificates for children throughout the country who had cancer, and we collected case histories in hospitals, which you could do then. Instead of getting an honorarium when I gave a lecture, I'd ask if I could look at the records, and then I'd abstract them for each tumor, one type after another. I knew there was a big interest in virology and a big interest in the possible transmission of leukemia from one person to another--horizontal transmission--and so I set about writing a review paper and it was published in 1964 in *The New England*

Journal of Medicine; it was directly relevant to the SVLP. Is that right?

Baker: Yes.

Miller: And what it does-- I have a copy of the paper here, the title is "Radiation, Chromosomes and Viruses in the Etiology of Leukemia." To get something into the Medical Progress section is not easy. The problem is, these reviews have a half-life of only about 2 years, not even a half-life--a full life--of 2 years, because people don't go back to review papers; they go back to original papers when they're looking up the literature. You would think that a review paper as old as one from 1964 wouldn't have anything you'd be interested in anymore 30 years later. But, it shows that radiation is clearly linked to leukemia in the atomic bomb survivors and others. In Down's syndrome and now we know in other syndromes, the chromosomes are affected by inheritance. And the question is what about viruses? We looked at all the possible ways that could reveal a virus, and it did not show anything that looked like evidence for radiation or chromosomal effects. So the point is, comparing virus etiology with what we knew about radiation of chromosomes, there was nothing there. The last line says, "Despite these impressive laboratory observations about leukemia, epidemiologic research,

so effective in defining other factors in leukemogenesis, has been unable to reveal convincing evidence of virus-like spread in leukemia." But for that paper (it was before photocopying), we got 1,200 requests for reprints. There were four key words, and I figure we got 300 for each key word. I think it had an important influence on Huebner (that nobody knows for sure, and maybe this would be one of the better things to find out on your interviews of other people as well as me). He read the paper very carefully apparently and I believe he was convinced that leukemia isn't transmitted horizontally from one person to another, as in a classroom or a bedroom. He and Todaro got together and published, as you know, in 1969, the concept of oncogenes, where it's vertical transmission instead of horizontal, and that worked out. So, I do believe that this paper had some influence. I don't know if Todaro would know that, and unfortunately we can't ask Huebner any more.

Baker: Unfortunately.

Miller: But I think that did lead, in part, to the hypothesis about oncogenes, which was really a very major development.

Baker: Yes. I remember having a problem reconciling the conclusion of your paper with the extensive activities and concepts in the Viruses Cancer Programs. I should have given more weight at

that time to this important paper of yours. Were you involved in the studies on clustering?

Miller: Yes. Very much, very much. I can tell you one anecdote about that. Clark Heath, you may remember, was at CDC, and in about 1963 they were called to investigate a cluster in Niles, Illinois, a suburb that's near Chicago, where they had--I forget how many--five cases of leukemia in one parish, and all the families went to the same church. Heath was impressed with that, as he should have been, and his group started studying clusters in that year. We were in on it right at the beginning because of a fellow who was here when I got here, named Leo Zelkowitz. He was a 2-year Clinical Associate, had worked on a cluster in Orange, Texas, where there were 3 kids with leukemia and 3 with congenital heart disease, or something like that, as if in some children an environmental agent caused the leukemia and in other children the same agent caused heart defects. That was published in *The Lancet*. It's interesting that CDC then studied over 100 clusters in the next 20 years and never found the cause of any of them. The biggest one was in Woburn, Massachusetts, in about 1979, and there they had 12 kids with leukemia in this one town. And usually when CDC studies a cluster there are no more cases after they leave but, in this instance, there were 8 more. It went up to

20. And it's the biggest cluster of leukemias known with no explanation. Some people at Harvard, Zellen and Lagakos, published a paper, but I'm sure it's not correct, that TCE was responsible; there is no evidence for that really, and MacMahon was very critical of that paper, and justifiably so. But anyhow, clusters became very important and then what happened was we published some papers, as other people did, stating that you can't look at the cluster and then draw the boundary around it because it's gerrymandering. It works the same as gerrymandering in politics: you get an excess. You have an excess to begin with and you just do a test of statistical significance, and it has no meaning because you already knew it was too high. We published a paper on clusters in Los Angeles County, leukemia deaths, in a 5 year period and we had 9 clusters as big as Niles when we drew the boundaries tightly around the cases.

Baker: That's an interesting comment on the effects of gerrymandering. It reminds me of the problem of whether psychological factors affect the incidence of cancer. But all the studies I've seen have not been prospective, controlled studies; you had the conclusions when you started.

Miller: Yes. That's right. That's right. And so it has to be. But what it did though was it motivated several people in the U.S. and

several in England to think about how to analyze clusters. Nathan Mantel was very active in that with some of our people in figuring out how you could divide, say, Connecticut, into squares of space and time, actually it must be a three-dimensional thing, but anyhow you have units, and then you distribute the cases and you see how many of the squares have excesses or too many cases. First you divide the time and the space and then you insert the cases. And they didn't find any excess. When you use the same procedure for poliomyelitis, we got the biggest X^2 in the history of statistics, indicating that it was transmitted from one person to another. Now, you wouldn't expect that much in leukemia, even if it was transmitted by a virus, but there was nothing. We kept getting inquiries about it, and we still get calls about it. It's very interesting that newspaper people, in particular, think that you can list all of the clusters of cancers in the U.S. because they think there are not that many. Actually there are tens of thousands of clusters because there are at least 30 different cancers that you can group individually by type. Then in enough periods of time in 10,000 towns and villages and other groupings, such as occupation, and you're bound to get clusters by chance. So, we came to know a lot about clusters and I've continued to be interested in it. We make a point always of saying about clusters

that almost everything that is known about causes of human cancer, or birth defects, is from clusters. Clusters have a good side. That's how we found out that asbestos causes mesothelioma, or that almost every human carcinogen was first recognized by a cluster, usually by an alert clinician.

Baker: Well, in a sense, it's a key element in the definition of disease and, of course, the definition of disease changes with the eras. That makes an interesting history, to follow how the concept of disease has changed from early Roman times or Greek times to the present. It really changes drastically how we look at disease.

Miller: Yes. I think that right now less attention is being paid to clusters than previously, because the Laboratory of Molecular Biology is foremost. But syndrome delineation is the other thing we were especially interested in, and that really paid off big.

Baker: That's a form of clustering.

Miller: Exactly. It's family clustering instead of geographic. And you can study 108, as CDC did, environmental clusters, or geographic clusters and find nothing, and you can study family clusters and find everything.

Baker: Well, provided it's genetically related.

Miller: Correct. But the Li-Fraumeni syndrome, I mean, it comes from our style of research and from this Branch. It's really been a key

to understanding how cell cycle regulation can cause a diversity of cancers. So you're not just studying all bone cancer in a family, but you're studying bone, soft tissue, leukemia, breast, brain, and adrenocortical types, all occurring excessively in these families, often as double-primaries, multiple primaries. That was the kind of thing we were doing, and it really was paying off. It took a long time for the payoff at times. For example, the Li-Fraumeni syndrome, the first clinical case, was in 1969. This was in the midst of the SVLP really. Fred Li went to a dinner party and someone said, "We have an interesting family history of a child who just came in with a rhabdomyosarcoma," and so Fred went and found this case and three more. I had mentioned earlier that we got these case histories from hospitals instead of getting an honorarium, and so in our files we had three more of what later became known as the Li-Fraumeni syndrome. Fred tried everything to figure out what caused these cancers to cluster in families.

Baker: And what kind of cancer was this?

Miller: Well, it's those six that I just mentioned: soft tissue, osteo, breast, leukemia, adrenal cortex, and brain. Well, osteo and soft tissue go together. It's really the same thing. He tried everything for 20 years to see who had a lab test that could reveal what was the

mechanism. Well, he had to wait for the lab technique for molecular biology to develop before one could find the mechanism. He went to Stephen Friend, a pediatrician-virologist, with Robert Weinberg, at the Whitehead Institute. Friend said that p53 was a possibility. In other words, they didn't have to search for it; he guessed that it might be p53. And luckily, in two of the cases they tested, the p53 gene showed a mutation, a germ cell mutation present from conception, so that all the cells of the body have it and that presumably is why more than one organ can be affected, but not all organs. So, then it was quickly confirmed, because someone else got wind of it at the Navy and immediately tried to beat them to publication, but missed by two weeks. That report in *Nature* confirmed the NCI study. But what I wanted to say is that I had to present what we were doing to the NCAB, I guess it was, and I said that Fred had struggled for 20 years and finally, in Boston, he found someone that could help him. And Dick Adamson got very upset by that, because he thought I was saying that he didn't even try to find someone who could help him at NCI. But he had tried all over the place. So, we had to calm Adamson down because he thought that we were disparaging NCI. One of your questions, if I can go to your questions out of order, is what would you change. And the big thing to have

changed now, as well as then, is for a better interaction between epidemiology as we were doing it and the laboratories. You see, the laboratory people were wonderful, but they were doing their own studies. They had their own protocols that they were following, their own research plans.

Baker: Well, when I was in Etiology, I tried to bring about that kind of interaction, even collaboration, because I recognized the need. I thought it got a little better. Fraumeni seems to have crossed over somewhat.

Miller: Somewhat.

Baker: Yes. One time at breakfast with Ernst Wynder in Zurich I think I first used the term "biochemical epidemiology", which he picked up on and now is in widespread use, but has recently been transformed, of course, into "molecular epidemiology." You tend to get at the heart of the matter better when you approach a subject with epidemiology and laboratory inquiries, such as molecular biology, jointly, as you were saying.

Miller: Well, molecular biologists have no idea where the concept of the syndrome came from; they just pick it up as a syndrome. What they don't realize is someone had to define the syndrome and show that it occurred with an excess of cancer. And that has been done in one instance after another. There is Fanconi's syndrome,

with non-lymphocytic leukemia, there is Bloom syndrome with a whole variety of cancers, pediatric cancers, young and adult cancers. There is a whole slew of them. We're studying Werner's syndrome now. These are people who get very old when they're 30. And they have, in Japan, 124 of them with cancer, multiple primary strange cancers, different from Li-Fraumeni, but similar in the diversity, and we're just about to send the report off for publication. But it's one more syndrome where there is a tremendous predisposition to strange cancers, and when they find the explanation for that I think they'll have one more ingredient in the understanding of diversity of target tissue carcinogenesis. So, it all began at the time of SVLP. Sometimes it was directly related to viruses, but eventually it came back to molecular biology, the work we were doing, for an explanation. But in instance after instance we had to wait for the lab to catch up, for the lab to develop. First it was chromosomes and cytogenetics and banding, and each time they develop something new you could apply it and see where the break in the chromosome was and how it connected with another chromosome.

Baker: I'll ask you a hard question. Do you think the activities of the Virus Cancer Program accelerated any of the development of laboratory techniques that are important here, or not?

Miller: Oh, yes. I think that's the main thing they did is to accelerate the laboratory development. It's interesting that once it gets rolling, as in molecular biology now, it really goes so fast you can't keep up with it.

Baker: It's amazing the pace of new findings now.

Miller: And the patterns are so diverse. For example, retinoblastoma, there are only two events, and you need the mutation on both members of the pair of chromosomes. But in colon cancer you need about 6 events. You know, you have one chromosome change, one genetic change, and then another, and another, and another.

Baker: Well, it's always been difficult to explain why we don't have more cancers.

Miller: Yes, it is. Yes, because we have all those mutations occurring all of the time.

Baker: And one part of the answer is that it takes more than one event for it to come off and then the other is that you've got multiple feedback loops in metabolic pathways which provide stability to the complex system we call the living organism.

Miller: Well, age is a big factor. It must have to do with the cell getting weary.

Baker: Is that *cumulative* insults, or is it something else?

Miller: Well, I think that they just get plumb wore out, like Joe Montana; they have to retire.

Baker: I don't know whether you remember when I came over to head Etiology, you and I had a nice chat, and I said that you did a great job in fishing out of the literature genetic connections in family cancers and what not. But what about areas where we don't have any data and, had you thought about generating data? And you did. You came back and you presented it before the Council, your Childhood Cancer Registry, which you set up. And I remember you looked over at me to say so much as, "There, now I did it." Remember that?

Miller: I don't remember that. I mean, I remember that we set it up, but I don't remember looking at you. I tried never to look at you! The other big interest we had was demography, which is what Mike Shimkin didn't want. But for childhood cancer, Court-Brown and Doll had begun to look at leukemia, but the other cancers nobody had looked at. We didn't know how frequently neuroblastoma occurred, because neuroblastoma can occur in the head, or the chest, or the adrenal, and it gets coded to each place that it occurs, not to neuroblastoma. There was no code for that. Well, maybe there was, but it only got a small percentage of cases. And so you couldn't tell what the frequency, the age distribution, or the sex

distribution, or the international comparisons were. So, we got the U.S childhood death certificates, 50,000 of them, and recoded them as to histology. Then we could see what the distribution was and how strange it was for some cancers. Some cancers have a peak very close to birth, like kidney, Wilms' tumor, leukemia, neuroblastoma. But bone doesn't. Bone doesn't come along until adolescence. It seems to go with the growth spurt. It's bigger in boys than girls. It lasts longer in boys than girls.

Baker: Big dogs.

Miller: Big dogs, that was part of it. Right. We also thought that Texans might have more bone cancer because they were taller, and basketball players, members of the Watusi tribe.

Baker: Are they really taller?

Miller: It didn't pan out. But the dogs, that was another part. Mike Shimkin had established the Veterinary Unit a few months before I came, and they were the ones that, let's say, documented the dogs better than they had ever been before and then established this Surveillance Program of Veterinary Medicine, which is another kind of demography.In human studies we generated data in two ways. One was by abstracting records and the other was by death certificates, especially. And, in fact, Joe Fraumeni's development of the maps came from the death certificate

distribution. We had one wild man here as a Clinical Associate named Fred Burbank. He loved the computer, and he collapsed 17 volumes of mortality data into one volume. He published a book on this, a very good book of graphs. It's a book of graphs. He said, in leaving, "Now you should do it by county." We didn't know how to get it done by county, but a man stopped by who said he wasn't happy with what he was doing. He was working in the building. We told him what we were doing--he was a computer specialist--and he said, "That sounds interesting." He stayed with us until about 5 years ago.

Baker: Who was that?

Miller: Bill McKay. F. William McKay. It was interesting, because he couldn't express himself in words, but he was crazy about the computer and he made these wonderful maps. He was a main figure, really, in the County Mortality Maps, which came from this Branch. So, the County Mortality Maps was a big development and it still is today because you can find clusters so easily through them and they mean something. Let me give you an example. Just playing with the computer, I found that in Lancaster County, Pennsylvania, there were seven women who died of mesothelioma in a short interval of time, and we fooled around with it and found they were all in their 50s. Now, what in

the world is going on in Lancaster, Pennsylvania, that would cause mesothelioma? Well, later we found that the Armstrong Cork and Linoleum Company was there, and they used asbestos. That may be the connection. You can find clusters by this, but you can also target research. You can look to see where cancers are and which are the most frequent. We can look at, say, the State of Florida for cervical cancer in white women and black women and see how they compare. There the black women really need prevention or early detection. You can focus the early detection on certain counties. That report was published in *The American Journal of Public Health* about six months ago. There has been a tremendous demand for the tapes, for the diskettes, so the locales can look to see what they have that they should be paying attention to.

Baker: There are great developments here with computer developments.

Miller: So there is an example of prevention, a method of prevention, that comes from demography. Demography and genetic cancer were two of our main interests. One interesting thing: it's very hard to develop people in this field, although we had great luck because we had Joe Fraumeni, Fred Li, and John Mulvihill, and that's a pretty good record. But it should be much better. We had many people, but they just didn't have the aptitude for it. I can

give you one wonderful example. We had one person that was with me for 5 years and I really thought that she could take over because she was trained in pediatrics and chemotherapy and then with us we overlaid her knowledge with epidemiology. But she just couldn't get it. And she went to Children's once a week and I said, "See if you can see anything interesting." And the last time she went, the fifth year, she said, "I saw a kid with bilateral retinoblastoma and a pineal tumor." Well, I thought that might be trilateral retinoblastoma because in the pineal there are retinal cells. You know embryologically they are connected. And, sure enough, that's what it was. And we quickly found 10 more cases and now there are many cases, several dozen at least, that quickly came to light. The gene can act on the aberrant cell, the cell that's wandered off course, or stopped in its migration embryologically and make a cancer there, so you get the cancers in the pineal and along the optic nerve and in the eye. And then we found two in the cheek, and cells had somehow wandered down the cheek. I don't know how they do that. When the gene acts on them it makes a cancer in that spot where the one--I presume--one cell lies. And I gave that information in a lecture at Minnesota and a fellow called up 6 months later who heard the lecture and said, "We just had a third one in the cheek with both eyes and the

pineal." So, from these unusual observations we can learn things, but we can't find the people to make the unusual observations. They just let them go. You know, they say, "Well, it's another unusual occurrence," and it slips away.

Baker: Well, you've done a good job in drawing conclusions from some of those unusual things.

Miller: Yes. That's what we try to do the most.

Baker: You've done that very well.

Miller: So, that's where we are. We can look at some of the questions now.

Baker: Some of these questions don't apply directly to you, so don't worry about it if you don't know the answers to some of them.

Miller: Well, I don't know the people. For the first one, the five most important scientific results, to me, I don't know if reverse transcriptase came out of this or not.

Baker: No. It came right after--well--right after I left, for example.

Miller: Oh, really? But didn't it develop because of this?

Baker: Well, that's debatable. I believe it's quite clear that Baltimore obtained a lot of materials from the Program, and I think he had some funding from it too. But Temin I'm not sure did. I think he had a grant, but I don't know that he had much to do with the Special Program.

Miller: I would have put in, from my own limited knowledge, which is not typical--everyone else has a broad knowledge--I would say Huebner and Todaro made the biggest contribution that I know of.

Baker: Well, that certainly created a shift in the outlook, but so did the earlier findings. The reason I picked 1950 here is because nobody thought viruses were interesting at all in cancer and nobody was working on it except Bryan and Joe Beard, and maybe Bittner at Minnesota. But with Ludwig Gross' demonstration that cell-free extracts could produce leukemia, once people confirmed that, and it took about 2 years before anybody believed him, and then Sarah Stewart's polyoma, I think they made a shift in outlook so that we began to see a lot more virologists getting into the cancer field. And part of this, too, was that some of these fellows who had finished their job in polio were looking for something to do. I was with Dr. Smadel in Building 1, and we actually talked with a lot of them as to whether they would be interested in coming into the cancer field, and a lot of them did.

Miller: Well, at the time when you were thinking about horizontal transmission of a virus from one person to another it occurred to me, at least, that it could happen, but it wasn't the main cause of

leukemia; that there might be some pockets of leukemia of some unusual type. And, in fact, it came out to be that with regard to AIDS there was a virus that transmitted a tumor in 1980 or '81. It was so pronounced that you could see in the first few cases that there was a cluster that was really significant, and it was related to a virus. There have been some other clusters like that, one in Turkey, where it looked suspicious. So there was always a possibility that there would be a specific virus that could do that, but that we weren't able to identify it at the time.

Baker: Well, the other thing, of course, that affected the thinking was that by 1970 or so, there were about 250 viruses that produced animal tumors and it was hard to see why man would be so different. What I think has happened was that the viruses were manipulated in such a way in the laboratory that these tumors were produced. And, again, Huebner was important for looking at field mice, as well as those in the laboratory.

Miller: Well, we were very much influenced by those findings and eventually, I think it was Beard, who concluded that the Avian virus was not transmissible to man. I think it was he who said that, eventually, after he reviewed all the data, which was a very important thing. And then there was cat leukemia, and that was a big thing, and people were thinking that if you got scratched or

bitten by a cat that you would get leukemia. It was funny that my friend was moving into a house in Scarsdale and the previous owner had 3 cats with lymphoma, or leukemia, and he called to ask if there was any danger for his children to live in that house. So I called Huebner, and Harriet Striker answered. I said, "Can you get cat leukemia from a toilet seat?" She said, "Only if they are very sophisticated cats." So a couple of years later I reminded her of that and she said, "Did they get leukemia?" And I said, "No, the parents got divorced." And she said, "You see, cat leukemia causes divorce." We had papers on cat leukemia. It's interesting that these different species have very different susceptibilities. Some of them don't get leukemia at all. I think the hamster doesn't get leukemia. Isn't that right?

Baker: I thought Eli Nadel had a strain that did.

Miller: Mostly they get aplastic anemia, or something like that, instead of leukemia. And dogs don't get much leukemia. But cats get a lot of it.

Baker: Well, biological diversity is a most fascinating subject.

Miller: Right.

Baker: Does anybody else come to mind on making major advances?

Miller: Well, you mentioned a lot of them, and I agree that those were important

Baker: Well, how about administrative people and management people?

Miller: Well, administrative, it's nice to have creative administrators as well as creative scientists, and I think the administration was creative. The thing that you asked later, what would you do differently, and it would be to leave room for serendipity, more room for serendipity, because if everybody is targeted then nobody can wander off and find something that nobody was looking for but really wanted to know. I think it's pretty important to have people that are able to do that sort of thing available without requiring, or pressing, them to target their research.

Baker: Do you think the Special Virus Leukemia Program prevented that?

Miller: They encouraged it.

Baker: Encouraged which?

Miller: They encouraged targeting.

Baker: Yes. But did they rule out the serendipity or freedom of activity?

Miller: They didn't rule it out, but they made it plain that you weren't a member of the team. Let me mention one strange event, and I don't know if you want to put this in or not--probably not. But after one of those meetings--I forget what it was called, an SVLP meeting, if that's what it was called--where we were voting on funding this, or not funding that, and I went into the parking lot

afterwards. Lou Carrese came down and we happened to be near each other and he grabbed me by the shirt and picked me up and said, "Cut it out." I thought he was kidding, but other people who saw it said they didn't think he was kidding.

Baker: Really?

Miller: Yes. So, I don't know if you consider that coercion or not.

Baker: I'm surprised at it, actually. From where I sat, of course, I was trying to do both, and I don't think there is a stronger supporter of the grant system and the philosophy of it for exploratory research. But it seemed odd to me that you should try to do everything that way and my main concern was how to integrate the various research projects of different disciplines when, to get at the problem, you really needed multidiscipline approaches. And the grants philosophy doesn't do that very well, and so that's what led us, I think, to using contracts.

Miller: Yes. Well, I don't have anything against contracts.

Baker: Or that same philosophy of planned program. Now, we weren't planning anybody's individual research. That seems to be misunderstood by a lot of people. They thought we were trying to tell them how to do their research. Not at all. Program planning is a different thing than research project planning, and we weren't in that latter game at all. But, sure, it influences things. But, to

me, it was that you needed both. Now, whether you wanted to play in that game or not, yes, you ought to have some choice on that. You shouldn't be too coerced. But as Endicott said one time, when you need to get a job done, try money.

Miller: But there was a feeling, though, that if you weren't with them, you were against them. If you were not with the viral targeting, you were not a team member.

Baker: I never really felt that way personally, although it was clear that a lot of people were fundamentally opposed to it. Fine. That's their prerogative.

Miller: Well, I wasn't opposed to it. I was willing to have it if I could find a way to do it.

Baker: We didn't have too much resistance on the resource side. Where the resistance came was when we were funding research contracts. That was stepping on the toes of those in the grants arena, and there wasn't enough money in grants, so they wanted the contract money to be in grants, and that's understandable.

Miller: Well, one of the greatest things about NIH is that a young person can get money to explore new ideas without having to go through the usual--or at that time--without having to go through a baptism of fire.

Baker: Yes. I hope we don't ruin that system with the current committee

activities that are going on.

Miller: Yes. I know. I know. You know, now we couldn't do what we did then. What we did then, as I told you, we abstracted medical records in different hospitals. Now you can't do that. You have to get permission from the IRB and you have to get permission from the parents and from the doctors. You need so many permissions you can't do it.

Baker: You remember how we were stuck, even then, with the requirement that we had to get approval from the Bureau of the Budget to question more than, what, six people, or some silly thing like that?

Miller: Ten. More than 9, I think, so we always limited everything to 9, or we just didn't mention it.

Baker: Yes. That was a pain.

Miller: Yes.

Baker: Okay. Let's move along. Well, who do you think made some of the major decisions in this area from the management standpoint, or administrative, if you don't like management?

Miller: I don't know. I just thought it was the people at the top who were doing it, and that was--

Baker: How far up do you mean by "the top?"

Miller: I mean at the--I'm trying to think. It depends on who was the

Director, but I forgot the sequence. Who came after Endicott?

Baker: I did.

Miller: So beginning with you, and Rauscher.

Baker: Actually, it started with Endicott. He made the key decision to go to ask Congress for the additional $10 million. But Rauscher, and I, and Ray Bryan had a lot of inputs into justifying that.

Miller: Well, I wasn't so aware. Bryan was actually working near us, in the same building, on the same floor. I knew he was a virologist, but I didn't really know what he was doing.

Baker: Well, you should have gone down.

Miller: Well, I did talk to him a lot.

Baker: You know, he didn't take to the managerial side very well and that is why we switched to Rauscher to run the thing, but they were all very helpful.

Miller: But I was a little distant from knowing who was doing that. I knew about that famous circular target, and for some reason I thought Carrese had developed that, you know, the bullseye?

Baker: Yes. Well, he and I together did. I defined the hierarchical informational content, and he came up with the idea that if the hierarchy was folded, it would form a target with the program goals at the bull’s-eye. I recruited him about 1962 to help with some planning ideas I had, and we wrote a paper called "The

Convergence Technique," which is a modification of systems planning to fit research.

Miller: What I was saying is that if you're in a university you have to be testing hypotheses and you can do the other exploratory research as a side activity but not as a main activity. Here at NIH you have been able to do it as a main activity and someone like Gajdusek could do what he did and win the Nobel Prize. He couldn't do that at a university because he couldn't spell it all out in advance of making the findings. So I think that's a big advantage.

Baker: Well, the third question deals with your participation. And I realize that you were not actually in the Program *per se*, but--

Miller: Well, as I said, I was trying to determine through epidemiology if viruses caused any kind of cancer, and we have a number of papers on that.

Baker: So certainly your contribution was to give additional evidence that there was no horizontal transmission?

Miller: Well, that was one. But you remember the SV-40 story and the polio vaccine, where we figured out a way to look for evidence of increased cancer incidence in those who received polio vaccine with SV-40, and we couldn't find evidence of any increase.

Baker: Oh, yes. That was very important work too.

Miller: It's interesting that *JAMA* asked us to write our own editorial on

our own paper, so we had two papers, one with the data and one commenting on our own data.

Baker: That is unusual.

Miller: They felt we knew the most about it.

Baker: Well, I guess we've already talked about number four, unless you have any additional thoughts on that. Number five, do any of the outstanding people on committees, or individual advisors or consultants come to mind that you're aware of?

Miller: Well, one person who was a big help to me was Bob McAllister, and he was a consultant on everything virologic that we were doing, and for that paper I just showed you he was very helpful.

Baker: How did you make that contact?

Miller: Oh, that's really interesting. Aside from Hagerstown, we had three people at L.A. County General Hospital. I inherited them. They were doing vaginal cytology. And being a pediatrician I couldn't understand the words. I kept thinking they were saying "vaginal psychology," and it sounded interesting, "vaginal psychology." But I went out there to visit and it was really strange. The building was abandoned. It was empty. And you'd go up in a creaky elevator with a sliding ancient metal door and go out into the hall and the mattresses are folded up on the beds with cobwebs to the light bulbs. Then you go in a room and there

were three people sitting there belonging to our Branch and they were counting up cases of vaginal Pap smears that they were finding in a half a dozen hospitals. One of them was a physician and one was a wonderful, wonderful clerk whose services we made great use of in the future after that. The third was a secretary. I had at about that time wanted to have some activity in Los Angeles, so we moved them from what they were doing there to L.A. Children's Hospital and set up a hospital pediatric cancer registry for them. And we found a number of good cases there. Our people did a wonderful job. But the hospital staff there is very territorial and they got nervous. So they kicked us out because they were afraid we would find something that was theirs. We found things, but we always gave them credit. We always got permission to publish. But it was a great development to have that unit there. And then Fred Li went to Boston. Actually, Fred was in Boston because Sidney Farber had asked Mike to send him someone there and he sent Miriam Manning--I don't know if you remember her--but she was in the PHS assigned to Boston, in our Branch, and then Fred went there because she was there and he wanted to get some further training. He got married and never left Boston. He worked there very effectively ever since. So, what we did was a lot of *ad hoc* things, you know,

just wandered into something and then let it grow. And those are two examples. But anyhow, that's a little bit different from what you're asking.

Baker: McAllister? How did you get in contact with McAllister?

Miller: Oh, McAllister. I met him when he was at L.A. Children's. He had gone to Penn and was a year ahead of me in medical school. So I sort of knew him from the dining room. I used to visit him when he was at Los Angeles Children's, and he would show me all the virology he was doing, which I couldn't understand.

Baker: I never got to know him, although he was a friend of Smadels, I know.

Miller: Yes. He's a wonderful guy. Political figures. I didn't have any connection with a political figure.

Baker: Well, Sidney Farber I would call a science-politician.

Miller: Oh, yes. He was good. Yes. He was really great.

Baker: Helpful.

Miller: But he made you feel so wonderful. He made you feel like he really knew you when he didn't. He could carry it off beautifully.

Baker: Well, he certainly was the ideal person to testify before Congress because he could combine so many desirable images. He was a Harvard professor, he was a professor of pathology. He was lucky enough to discover one of the earliest chemotherapeutic

agents in childhood leukemia. He was a kindly professor and practitioner, plus being very articulate.

Miller: But he had a kind of a bedside manner which you don't expect in a pathologist.

Baker: Yes. As I say, he had all these things combined. I used to go up, before he testified, to brief him on the latest stuff so he could use his good presentation to further the cause, and I always had the same meal. I went up one day and back the same day, and we always had lunch in his office, and it was always peas and lamb chops. It was good.

Miller: The next one doesn't apply to us.

Baker: The sixth one is, I think, one of the important contributions made by the program was that you got standardized, quality-controlled reagents, and animals, and tissue culture in large supply.

Miller: Well, let me tell you what I inherited. A committee of famous epidemiologists got together in 1957--before I got here; I got to NCI in '61.

Baker: I think I've got a copy of that picture you're holding. Isn't there a picture of that in one of the journals?

Miller: There might be. But they decided they should do a case-control historical study, and they picked out 12 pediatric centers, and Miriam Manning was in charge of that. They were supposed to be

collecting data on how often subjects were x-rayed, received vaccinations during pregnancy, given drugs during pregnancy, how much smoking occurred, and all that. Each place did it differently; so, you couldn't combine the data. They were not combinable. And you had to try to rescue something from that, which we did do. It wasn't worth the cost, but there were some good observations, some really good ones, individual cases, among these 500 leukemics and some non-leukemics. And we did make contracts for people to analyze the data. One of these contractors was Saxon Graham. So we had data that we made available for analysis, particularly since we couldn't analyze it ourselves, and he thought he could. He couldn't. I mean, it was not usable because it was so heterogeneous. But we've always tried to make the data that we have available, whether it's on the maps. Map-making especially is an example. That doesn't come from the Special Virus Leukemia Program but, to the extent that virus is a part of the occurrence of leukemia, say in households or things like that, we had information on that and it was available but it wasn't a big feature of what we were doing.

Baker: No. You probably have no knowledge of the relative amounts of funding in grants compared to contracts. We'll look that up.

Miller: I had a clear impression that some people were very well funded,

Murray Gardner for example, and I remember one experience with Horsfall at Sloan Kettering-Memorial. The time came for their epidemiologist to get a contract, and they presented the information and it just didn't add up. It wasn't a good investment, no matter how much or how little it was. And he ended up not getting the contract, and that may have alienated him a bit. I think one of the problems is when you have consultants on committees like that they expect to get a contract approved when they have a contract before the committee. That wasn't a problem for me, but it could be a problem.

Baker: Well, it's a general problem. How do you get the best people to review something and not expect them to get funded? It's a dilemma.

Miller: Yes. Right now they don't get the best people and they fund the wrong things. If you could change anything? Well, I've already mentioned that if epidemiology could have been directly linked with the labs so that-- But they can't be performing just a service and they kind of said that what they would do for us was service, rather than as their own research. After you, when Greg O'Conor was running the Division, he had pretty good meetings of the Branch Chiefs, and I remember Skolnick and Aaronson presenting to them the Wilms' tumor aniridia, and they would say,

"Well, you know, that's not on our research agenda, and you can get any commercial lab to walk around the chromosomes and find the gene. We don't have to do that." And it turned out to be a monumental finding. That was the tumor suppressor gene. And they didn't see how it fit their research, which was understandable, but it's too bad, because that finding could have been here instead of in Boston or Philadelphia. So that was a missed opportunity. And it's not to blame anyone, it's just that people don't think of epidemiology as contributing to their own research, and it does, but they didn't realize it.

Baker: Well, we're all so specialized these days.

Miller: Stephen Friend, in Boston, with Robert Weinberg, the retinoblastoma gene, Weinberg didn't want to study that, and Stephen Friend, being a pediatrician, did. And he more or less got a reluctant Weinberg to agree to let him do it, and that was the big finding with the tumor suppressor gene, and Weinberg gets much of the credit for it.

Baker: Question Number Nine?

Miller: Yes. I think we already talked about that.

Baker: Number ten is a much broader question and deals with science, not necessarily even biomedicine. It's a question of whether you think the public is more knowledgeable of science now than, say,

in 1960, or less so, or about the same?

Miller: I don't know because it's hard to speak about the public in general because there are people in little towns throughout the country.

Baker: I'm not asking for evidence. I'm asking for an impression.

Miller: My impression is that there is much more published that's really good material on cancer and other research. *The New York Times* is really excellent at it. You know, Natalie Angier, she won a *Pulitzer Prize* for writing about molecular biology, translating it with metaphors into things that everybody could understand. She wrote a wonderful book.

Baker: Who is this?

Miller: Her name is Natalie Angier. And she wrote a marvelous book called *A Natural Obsession: The Search for the Oncogene*. It's a funny title, and actually it's the story I just mentioned to you about Stephen Friend. She actually was living with the lab at that time, going there every day and making rounds, as they discovered the retinoblastoma gene. Then she went to work for *The Times*, and she writes this wonderful material on molecular biology that makes it really understandable. But they have other very good writers at *The Times*, and *The Times*, I think, more than any other popular publication, has the best reporting and they win prizes for it, as they should.

Baker: Well, I agree there is better information available. That doesn't mean that the public necessarily reads it.

Miller: That's why I said I can't speak for the public, in general, but I think those who read her column in *The Times* are very well informed, and that read the others too. Gina Kolata is another one. And *Science* does a good job within the scientific community, and I don't know if that's new. I just don't remember it from before. But, you know, in the front of *Science* are reviews written by scientific writers, but not laboratory scientists.

Baker: Barbara Culliton?

Miller: Well, she used to do it. But they have -- Jean Marx is a big one now, and Eliot Marshall is another. A lot of them went to work for *The Times* after they left *Science*. Gina Kolata worked there as well.

Baker: Do you think the funding for scientific research is going to be the same, more or less, or reduced?

Miller: Oh, I think it's going to be reduced.

Baker: Why is that?

Miller: Because they're doing it by formula now. You know, they just say, "Get rid of 10 people."

Baker: But, if they had enough support for science, it would be an exception and, in a sense, NIH's budget was an exception this

year.

Miller: Well, the thing is that in budget cutting--you must know this, I mean this is so obvious that it's not worth saying--but when you have to get rid of people, you have to get rid of the young people because they don't have tenure--they're here as fellows--and you keep the people that are doing the ordinary jobs and office work and things like that because they have tenure. They are career employees, and you can't have them terminated. They're not contributing to science.

Baker: Should we get rid of tenure?

Miller: What?

Baker: Should we get rid of tenure?

Miller: Possibly. Although that's one area…

Baker: I think there is a movement at NIH to reduce the percentage of people who get tenure.

Miller: When they changed the rating system called the EPMS, Employee something-or-other Management System, you know, you had to fill in the form and say whether the person is outstanding, excellent, all the way down to unsatisfactory. The first year it came out we had a person that was really unsatisfactory and we thought, "If this is what they want to know, we'll mark him as unsatisfactory." And we did. And it was a

mess.

Baker: I know. I know the problem.

Miller: I mean, it looked like you could be rid of them then, but you couldn't.

Baker: Well, you could, but you had to invest half your life's effort to make it stick. We had that problem when I was here, and that's not even tenure, that's just Civil Service rules.

Miller: Another terrible thing that's happening is that the best people used to come to NIH, but now the universities have developed so well, like Johns Hopkins and Harvard and places like that, that they go there instead, and they don't come to NIH. And if you go to the Clinical Center now..maybe you do. Are you treated here or somewhere else?

Baker: No. I usually go to Navy.

Miller: Well, I'm treated here. And can see the difference. I mean, the people really are not very good doctors, the Clinical Associates, or the people on rotation from the Army, or wherever they come from. Some do the worst physical exams I could ever imagine. Even for something like follow-up with cancer, it's too superficial.

Baker: Well, when the animal rights groups get through you're going to do all of your anatomy on a computer. How would you like your

surgeon trained on a computer?

Miller: Yes. I saw where they're doing surgery by computer now in some far-off place.

Baker: Well, for some things that might be all right.

Miller: But I think that the staffing of NIH with scientists is very difficult. When we ran out of people, we advertised and heard from people who are unemployed, Third-world people who are unemployed and stuck in this country, or wanting to stay here, and they don't have any of the background, or foreground, to look promising. So, we ran out of people. One of the reasons I retired a year ago is that we ran out of people. We're like the canary in the mine, because it's hardest to find people who are interested in what we're doing as compared with laboratory people. So, the laboratory scientists can staff their labs easier than we can. We've always had a problem, and now it's almost impossible to find people.

Baker: Your schools of public health are not tending to this?

Miller: I went to a school of public health. It was probably the low point in my career. They teach people as pupils, not as scholars. And now physicians, I think, seldom go to schools of public health, and what they have is..

Baker: Sociologists.

Miller: Yes. And people that want another few years of training after they leave college and go into epidemiology, but they go for a Master's degree.

Baker: Let me ask you another question, off the track. What's your opinion of the Office of Alternative Medicine?

Miller: Well, I only read a little bit about it. It doesn't seem like a good investment to me.

Baker: Well, that's a good under-statement, I think. Yes. I'm very concerned about that sort of development, and it seems to me that more and more political decision-making is being applied to scientific problems, and I don't think that's good.

Miller: Well, especially for breast cancer, for example. They added $210 million dollars to the Army budget for breast cancer research.

Baker: Well, it seems an odd place to put the money.

Miller: Yes, it is and eventually they had to do it the same way NIH does, namely through the National Institute of Medicine.

Baker: Anything else you'd like to say?

Miller: No. I've probably talked too much already.

Baker: Oh, I don't know. I appreciate it very much.