

Final Draft

This is an interview of Dr. Norman Anderson, who worked on centrifuge development at Oak Ridge National Laboratory, taken on February 25, 1995. The interviewer is Dr. Carl G. Baker, former Director of the National Cancer Institute.

Baker: Norman, could you give us just a brief statement of your background? You've had an excellent career of variety starting with your training and your Ph.D., which was in physiology, as I remember.

Anderson: My original training was at the University of Minnesota in abnormal psychology and in sociology and in motion picture production. And I then spent 5 years as a combat photographic officer in the Navy. I was in the Navy on active duty before the war started. And that included work on antisubmarine warfare and blimps. I set up the experimental systems for studying eye movements during instrument flight for a joint British-U.S. study in that area, and flew all the experimental stuff myself.

Then I was assigned to the Submarine Service for the rest of the war doing combat photographic work with them. And then, after the war, I went to Duke University, changed careers

Ridge National Laboratory under Alex Hollander, worked there for 21 years in various capacities, and set up the joint NIH-AEC Zonal Centrifuge Development Program, and had the use of the Separation Systems Division of the Oak Ridge Gaseous Diffusion Plant to develop new instrumentation. And, out of that program came a number of things which included:

The K2 vaccine centrifuge, of which there are about 150 around the world making vaccines, including previously the Heptavax vaccine made by Merck, a number of influenza vaccines, and now large-scale AIDS or HIV production;

Then the centrifugal fast analyzer, of which there are about 8,000 machines in the world, which is the guts of many clinical analyzers; and going on to,

The development of high-resolution 2-dimensional electrophoresis and a number of other systems first at Oak Ridge and then 9 years at the Argonne National Laboratory.

Then, in 1985, we moved to Bethesda, initially associated with the ATCC, and now in a private company working on contract work, Government grants, and we also have a program in sales. But our objective is still to do the kind of research that we were doing at the National

Laboratories with a little bit more freedom.

Baker: Well, that's certainly a fascinating background and a good succinct summary. And, as you know, we want to try to get a little history down of the development of the Cancer Viruses area from the NCI. Originally it was called the Special Leukemia Viruses Program and, as we got additional evidence of possible viral connections of other tumors besides leukemia, it was changed to the Special Cancer Viruses Program. And I know you were watching the developments in this program, so we're appreciative of your being willing to respond to some of the questions I'm going to ask you.

So, let's move to the first question, which, as you know--I sent copies of this to you beforehand for you to think about them--so the first question deals with your views as to the five, or more, most important scientific results highly significant to the viruses cancer field during the period 1950 to 1980, and perhaps key scientists who were involved?

Anderson: Well, I think the key, both scientific and administrative, development was the concept that you needed and could do planning, systems planning, for a program. That was a relatively new idea in biology. It was resisted by a lot of

people. But it had been successful in other areas, including nuclear weapons, nuclear power, space, et cetera, but there had been no demonstration of how you would plan a program, a large program, how you would integrate people into it, and how you would provide resources for it. So, even, no matter how it turned out, that, I think, was a key idea which gradually has seeped into other areas of biology and especially biotechnology, and I think you were a key person in that particular area.

And the other scientific achievements, of course, have to do with a variety of different viruses that could cause cancer; with the fact that you could, under certain conditions, immunize animals against-- You could immunize them in a way that would prevent formation of the cancer later.

And then, from my own point of view, I was always interested in the idea that cancer involved the re-expression of proteins and other gene products that were important to early development. And our way of pushing that idea was to stress fetal antigens as recurring in cancer. In a way, that was a tactical mistake, because the way this should have gone was to say, "These are cancer antigens that happen to be

important in early development." And the oncogenes are that. If they had been stressed as being oncogene products, I think the whole field would have gone a little bit faster and a little bit quicker.

Baker: Of course, we didn't know about that in those days.

Anderson: No. We knew that tumors did involve the re-expression of antigens that occurred early in development. But I'm saying that in selling that idea it should have been stated somewhat differently.

And the other developments that I think are of first rank have to do with integration of industry and the scientific community so that reagents, virus preparations, assays, et cetera, were developed that could be used generally, could be distributed, et cetera, and could therefore be relied upon. Up until this program there was a tremendous amount of resistance to any real collaboration with anything but the chemical industry. You trusted the chemicals; you didn't trust biological reagents. After this program, I think you did. So, I think the major contributions I see, besides a host of individual ones having to do with specific viruses, specific attempts at therapy, most of which didn't work

but had to be tried to show they didn't, it was the organizational part of it that was most important and still has a big residue.

Baker: You recall that virology was not considered very important in cancer research prior to about 1950. People thought it didn't have anything to do with cancer induction. Ray Bryan was sort of a pioneer of keeping that work going, and it was Ludwig Gross's finding of the transmittal of leukemia by cell-free extracts in 1951 which, I think, was the first really key break in the pattern here, but nobody believed him for a couple of years until his work was finally confirmed, and then things took off at that point.

Would you agree that Ludwig Gross was a key figure in this?

Anderson: Right. And I remember Art Upton attempting to repeat his results. I helped him try to do that. And eventually it was possible. But that work, and the Bittner virus, the Rauscher virus, all the other cancer viruses that came after that, made the field explode. I wouldn't call it a tragedy, but the unfortunate thing was that there weren't discovered really important counterparts in man.

Baker: Yes. That's still a bit puzzling I guess, when

you have so many experimental animals.

Anderson: Right. That's right.

Baker: And I think this illustrates what manipulation in the laboratory can do to distort some of the pictures in the natural setting.

Anderson: And the last time I heard Albert Sabin speak that's what he stressed was the fact that one had this tremendous wealth of experimental data in animals, and he ended up his presentation by saying that he didn't believe that any major human cancer involved a virus.

Now, Albert was prone to a little overstatement at times, but nobody challenged what he said. And I think those are important way-stations on a very long and difficult road which ends up with our present view that cancer is due to a series of mutations in a set of important genes, genes that are mostly important in early development.

Baker: But, of course, a second key step in that process was the oncogene finding of Baltimore and Temin which now, in a sense, shifted attention from viruses *per se*, to stretches of coding in the viral DNA as well as the animal chromosomes, and that made a shift, I think, from viral cancer work to oncogene and other genetic aspects.

Anderson: That's right. And now these are exploding.

Baker: But this led to biomedicine and biotechnology breakthroughs, I believe you would agree?

Anderson: Yes. I would agree.

Baker: And therefore, the program might also be considered as foundations for molecular biology.

Anderson: Well, it was. And what you have to say was that, given the technologies that were available at that time, and the idea that we have to explore all alternatives, one has to explore the ones that one can, and we did not have the technology then to do the fine genetic analyses that we can do now.

Baker: The second question you've already touched on. What do you think were the key administrative or management decisions? I think you've answered that.

Anderson: Well, there was one I would--

Baker: And who made them?

Anderson: Well, the one I would add to the second question is this; the idea of making the program a national one, of involving the President, and of attempting to leapfrog a whole series of layers of command and decision-making. I think that was terribly important. Nobody before had made it a national program and had tried to encompass industry, academia and Government laboratories all together.

Baker: Well, at first, of course, was the special request for an extra \$10 million dollars.

Anderson: Almost exactly the amount of money that was initially asked for, for atomic weapons. Remember it? I think \$20,000 dollars was the initial request to buy a stockpile of uranium ore, and they didn't think it would take much more than that.

Baker: \$20 million?

Anderson: No, \$20,000. Yes. A small amount.

Baker: Well, we're talking about \$10 million on ours.

Anderson: I know. But it was a small amount of money. And you asked, in this field, for a small amount of money and then grew it up from there.

Baker: Well, Endicott, I think, played a key role in actually making the decision to go and ask Congress for this money, but Shannon made sure that there was justification for this. So, there was a memo prepared from Endicott to Shannon outlining the reasons for asking for this, and Shannon bought that.

Anderson: Shannon was a very forward looking individual. He could be a little prickly at times, because I know he got very mad at me one time. But--

Baker: What was that about?

Anderson: It was about the fact that we spent a lot of money all at once in a project, instead of

evening it out over the year by months, you see.

And anyhow--

Baker: Well, one time I proposed to him that, "What's the sense of making the really outstanding scientists write all these applications for grant support when you know that they're continuing to work well and are going to get approved? Why not lengthen the average length of grants for these people to 10 years instead of 7, as was the average in those days?" And he wouldn't buy that idea. And, of course, now the average is only about 3 years.

Anderson: That's right. That's right. And that's a mistake.

Baker: And so the amount of effort going for writing applications and reviewing them now is getting worse and worse.

Anderson: That's a whole additional topic that ought to be looked into because my calculations are that somewhere between 50-70 percent of what I would call the emotional and intellectual juices of the scientific community go into fundraising.

Baker: Yes. It's a waste.

Anderson: It's a waste, an extraordinary waste.

As to who really made this go, I think Shannon, yourself-- Bob Huebner sitting poaching on the sidelines saying that he would cure cancer

in the wrong institute and providing you with all of the galling sorts of things that make you function, played an important part. I don't know how much part he played in the actual organization of administrative machinery. I imagine rather little.

Baker: Rather little, but he was a stimulating fellow.

Anderson: He was. He was a burr under the saddle.

Baker: And I might tell you that we raised a question of his moving to the Cancer Institute and Endicott obviously would like to see this happen, but he didn't have any money. So I was Head of Etiology then, and he said, "Why don't you see about bringing Bob Huebner over?" And I had to cut out from my budget and space the resources for him to do this, but I thought he was worth it, and I don't think that was a mistake.

Anderson: I don't think it was a mistake either but, of course, you soon found out that you never knew what his resources were because he was always setting up new little field shops and then sending you the bill.

Baker: Well, we kept on top of that pretty well.

Anderson: Right. But the full story of all those details would be fascinating. They can't be reconstructed--

Baker: I considered him General Patton. You wanted to

support him, but you couldn't let him have all of the resources.

Anderson: That's right.

Baker: And he buttonholed me one day in O'Donnell's Restaurant in Bethesda complaining because I didn't approve something he'd requested. And he was pounding me on my chest with his finger, "I could be a better Director than you." And I smiled at him and said, "Well, that may be, Bob, but I got the job and I'm going to make the decisions." And so we got along fine.

Anderson: I think I can just hear him saying that.

Baker: Everybody heard him.

Anderson: But, one thing I would like to know is who set up the meeting at Airlie House to do all the planning?

Baker: Well, I did. And Carrese was my key lieutenant on that.

Anderson: Well, that was a real adventure because, to sit 8 hours a day with a pencil and a pencil sharpener and try to write all that stuff out was interesting and exhausting.

Baker: Now, it got out of hand after I left because the administrative trivia swamped the science. If I had stayed there I don't think I'd have let that happen. And part of the reason was we had an excellent man who was almost too efficient on the

managerial aspects, Jack McShulkis; so he wrote too much detail into the managerial and administrative aspects, and I would have kept more focused on the scientific side. But I might have gotten into trouble with the accountants later too, but that seemed to have gotten out of hand. It got too voluminous. It didn't have to be that way.

Anderson: In spite of all the resistance and the reports later on, which raised questions about the whole program, the idea still remains that there can be organized programs, although they cannot be predicted in detail.

Baker: Well, we weren't trying to predict in detail, of course. And also we kept emphasizing that plans need changing at least about every year or year and a half. And also there was great confusion between program planning and planning of experiments. We weren't trying to tell anybody how to do their experiments, and yet a lot of people thought that's what planning meant. And program planning is a very different hierarchical level than what they were afraid of.

As John Moloney said the other day, "You think we could have directed Sol Spiegelman to do his research?" Nobody was going to direct Sol Spiegelman to do his work, and we weren't trying

to. But how do you allocate resources and request resources in a total framework? With priorities.

Anderson: Unfortunately, maybe a majority of scientists are unaware of what is on the other side of the grant application and grant system, what decisions have to be made in order to set that up, make it work, get funding for it, et cetera.

Baker: That's true. And I'm not sure they need to because they've got their own problems. But in developing the budget request, yes, a lot of work goes into it. And the way I got into the systems networking was that I needed a framework for consideration of competing priorities in the budget request.

Anderson: Yes. How do you cut the pie?

Baker: And this was a useful tool, because you could reiterate mixes with different emphases in a total picture.

Anderson: Well, network planning, I think, also has another tremendous advantage, and that is it's a good method for communication. You can say, "Here, in summary, is what we're trying to do."

Baker: And so we got along fine with the Bureau of the Budget for that reason, while the old pitch, you know, a lot of it was, "Well, these scientists, individual scientists, best know what he should

be doing and he puts in his request and it's reviewed by the peers and you don't need any other decision-making." Henry Kaplan was a strong advocate of that philosophy, as many academic scientists, of course, are. And I had that same view when I was in the lab. It's not wrong; it's just incomplete.

Anderson: Right. It's narrow.

So, now, the main leaders, I think we've gone over that. But the membership of the advisory committees, I knew some of them, but I didn't have much chance to-- You know, I never sat in on those or knew what they said. I had to do with a relatively small number of people, among them Huebner, and I owe a great debt to him because he was the first one who saw-- Well, the discussion was this:

"Suppose there is going to be a cancer vaccine?" I said, "Do you think that's what you're trying to do?"

And he said, "Yes, we want to make a vaccine that's available to everybody."

And I said, "Well, do you understand that that can't be done?" I said, "There is no way to purify that amount of virus. You're thinking about a killed virus vaccine to begin with." I said, "You may be able to grow that much stuff,

but you're not about to purify it." And I said, "Talk to Rod Murray, who was then in charge of the Division of Biologics Standards, about his view of giving anything to man that's been raised in cancer cells." I said, "He's totally against that unless he's sure it's pure." So I said, "How are you going to do this?"

And he said, "Well, you know, we've never thought of that before."

And so I said, "Well, you come up to the end of that line and then tell me all about it." And so he wanted to know what could be done and I said, "Why don't you get a group that is interested in large-scale separations to worry about that?" So he was my main contact. And then I had a lot of discussion with Rauscher and then with people like Joe Melnick. And Melnick was a very interesting and supportive person and one that I enjoyed working with a lot. But I didn't know who were the people who were really calling the shots. I knew you at sort of a distance, but I didn't know who the objectors, or the advocates, for the overall program were and who really made the triumvirate go with the President and who set that up.

Baker: Well, Endicott was the focal point. This was, of course, discussed--after Shannon's approval--with

the National Advisory Cancer Council and subsequently we had a couple of committees growing out of that. Chuck Evans, at the University of Washington, was chairman of one of the very helpful committees in pushing this along. Then there were a lot of internal committees with group chairmen who were responsible for different areas and they had advisory groups at the technical level and so we hope, in this history, to spell that out a little more clearly. And it's amazing how your memory makes it difficult to recall exactly how this was done, so we're trying--

Anderson: Who walked into the White House and said to Nixon, "Here's something you ought to do?" I'd like to know how that was pulled off.

Baker: Well, I don't know that I know the answer to that. Once Shannon approved it, then we were allowed to testify in favor of it.

Anderson: Uh-huh. But that wouldn't get to him, you see.

Baker: And somehow that probably was okayed through the Bureau of the Budget channels. But I don't know of any scientist who went to the White House.

Now, Wendell Stanley was a very key witness before the Appropriations Committee and spoke very eloquently of the need for expanding this area of viruses cancer work. So, Stanley was

probably the most influential one, but that was directly on Congressional Appropriations Committees. I'm not aware that anybody--any scientist--went to talk to the President, per se.

Anderson: The reason I raise that question is I worked on a project that was set up through Mrs. Roosevelt with Roosevelt directly and, at one time--I still do--I have a pass that allows me to go anywhere in the world that our armed forces are and do any photographic work that I think I should do.

Baker: That's quite a pass.

Anderson: I had never talked to the President, but I worked with a fellow who did, who set it all up, and I found out what real power and clout can be like. And that's a totally different story of how it was all done, but it was done by personal contact, and you don't usually get away with setting up something like this, the project we're talking about--Nixon's Cancer War--unless somebody--

Baker: Well now, Nixon's Cancer War is a different story than the \$10 million dollars. This exercise of power can be exhilarating sometimes, but you've got to watch it; it can be dangerous.

Anderson: Oh, yes. You have to watch it.

Baker: You remember Nixon dedicated the Frederick facility from a germ warfare to a cancer center?

Anderson: Right. Right. But he had been talked into that too.

Baker: And I had the pleasure of briefing him, along with Zubrod and Rauscher, on the NCI program. But he said he wanted this done *post haste*, so the Army, of course, controlled the Frederick operation, so I got a report from my staff that things weren't moving very fast on renovations up there, so I called up the three-star general in charge and explained to him that I understood that things were sort of dragging up there and could he do something about it? "Oh, yes, sir. I'll get right on it." And it was interesting. Here I was-- He was outranking me, but he jumped to it when I mentioned that the President had said he wanted this done real fast.

Anderson: How did the Virus Program, which had many names, gradually evolve into Nixon's War on Cancer?

Baker: I don't think I would put it that way. The viruses area was just one part of the total cancer effort. The therapy side was Sidney Farber and Mary Lasker pushing that. But they were pushing the whole program. And so I wouldn't describe the Nixon War on Cancer as evolving from the Viruses Cancer Program.

The planning of the Viruses Cancer Program and the Chemotherapy Program laid groundwork for

the kind of planning that went on behind the scenes for the Nixon expanded program. We had the Airlie House meetings on that program.

Anderson: Right. I remember those. Yes.

Baker: We had had smaller programs from the Cancer Viruses Area and so, in a sense, you got experience. But I would say the Nixon program grew out of the Lasker-Farber--

Anderson: It absorbed the virology?

Baker: Yes. It was just another program.

Anderson: In public discussions, columnists writing about this, they usually don't make that distinction. There is a tendency to equate Nixon's War on Cancer with the Virus Cancer Program.

Baker: I don't see it that way.

Anderson: You don't see it that way? Well, you were there.

Baker: I think it was influential in showing, perhaps, the way to go, particularly on planning. But the Lasker-Farber forces, of course, with the committees of Congress, particularly the Senate, developed a sudden increase in proposed cancer activity. That was the first time a billion dollars a year Cancer Program was brought up. When I testified before the Senate Panel co-chaired by Benno Schmidt and Sydney Farber, I said I thought the public would be willing to pay that kind of money. Of course, now it's \$1.2

billion. So, I would say we had a lot of experience from the Viruses Cancer Program that helped in planning for the other, but I don't see it as a direct outgrowth of it.

Okay. Shall we move to number three? You've already touched on some of this, but maybe a sentence or two. As you say, you weren't really right in the middle of this, but you participated on the protein separations and the centrifuge development.

Anderson: Right. One of the things I was interested in is how you could work completely across disciplines and technologies. And I was struck by the fact that most of the technologies, with the exception of the electron microscope, which were in use then, came from Europe, a large number of them from Sweden, and it just didn't seem to me that in this country we developed many of the tools that we needed and that there ought to be the possibility of doing that in the National Laboratories, if no other place.

I was extremely impressed by one study done at Oak Ridge where they took the Calutrons that had been used in Y-12 for uranium enrichment, and set up a program to produce all of the stable isotopes of all of the natural elements for characterization. And they did that in a

systematic way. They decided how many grams of each they wanted, went through, did their neutron absorption cross-sections, all their physical properties, and developed big books of basic data. That kind of work had been done as pure research, labors of love, in academic laboratories, and here it was done, just organized and done, and that was, to me, an eye-opener that you could do this in science.

Baker: Well, I think it demonstrates the difference between a lot of academic scientists' outlook and the engineers.

Anderson: But these were physicists. The physicists wanted the data.

Baker: But the engineers sounded like they were in there too because those handbooks that were developed in engineering, I wish we had that kind of thing in biology, but it's not that simple.

Anderson: But the physicists, the best physicists, that I talked to would not ever bother to discuss with you basic versus applied research. If they did, they said, "It's a continuum and we don't see any break. We need one hell of a lot of engineering, and we're going to get it, because we know what to do with it." It was so different from my biological background that I found it very appealing and very interesting that that could be

done, that people would cooperate with you. And so, when this chance came to develop centrifuges with a classified group at Oak Ridge, then I had a chance to put into effect some of the ideas that had been generated in me and others by watching what happened in nuclear physics.

Baker: Good. You mentioned the special preparative ultracentrifuge separation in relation to vaccine development. Would you consider that your main linkage with the Viruses Cancer Program?

Anderson: Yes. That, and the work on fetal antigens which, as I say, would have gone a lot better if we'd used different words.

Baker: I understand what you mean.

Anderson: Hindsight. Hindsight.

Baker: Okay. The fourth question. I guess we've already discussed that pretty well.

Anderson: I think we've been through that. Yes.

Baker: So we'll move on to number five, and you touched on that, and I told you that we're going to try to cover that better than it has been covered.

Anderson: And, on six, I would just say that there are some of the major contributions of the whole effort, to open it up, to somehow make people in industry--in a variety of industries, in a variety of disciplines--talk to each other and to show that work done in industry was as good, and

many times better, than what was done in academia, certainly insofar as the preparation of materials was concerned.

Baker: Take tissue culture. The thread of development of tissue culture from the early work of Ross Harrison, George Guy, and Wilton Earle carried right on through to the present time, or at least to 1980, is probably a story worth telling that hasn't been told very well either.

Anderson: Right. And one interesting aspect of it, as I recall, is that Wilton Earle was frustrated with materials that he got, getting mostly fetal calf serum, and so he said, "We've got to have some way to get this besides a purchase order." And so what could that be? Well, that could be a contract, which was a stunning and new idea. And so it's my recollection that the first contract in which your contracting officer had some say as to what was being done and could have a finger in the actual works was his attempt to get good fetal calf serum, and then the Contract Program grew from it. That's what I remember, but I don't know whether it's correct.

Baker: Well, that's worth looking into further. I think I remember that he did get involved in some contractual arrangements.

Anderson: But that was all new. Nobody did that before.

It was the germ of the whole thing.

Baker: Of course, I think we have to also mention that Harry Eagle made tissue culture much simpler. Earle was so concerned with bacterial contamination and what not that he had such an elaborate system, and then Eagle was able to show you didn't really need all that.

Anderson: Well, it was a religion up until Eagle.

Baker: Right. And after that things really took off. But then the problem with contamination is another important issue here on quality control again, and at the American Type Culture Collection, of course, those developments were crucial in much of this, and Stevenson's concern with *Mycoplasma* contaminations and what not, and mis-identification of cell lines, and chromosome counts to make sure you at least had the right chromosome numbers corresponding to the names. So, all of that.

And then, while we didn't really end up needing as many of the monkeys and similar animals as we one time thought, when we were testing human samples we thought that the other primates, were necessary and at the start of the program it was very difficult, not only to get enough animals, but also to get them so they were reasonably healthy.

Anderson: And well taken care of.

Baker: And so the program put a good bit of developmental research money into animal husbandry, which, of course, wasn't of much interest to the academic scientists, but it proved that we could produce clean animals in captivity if we need to. So, we still may need to someday, but we know how to do it now anyway.

Anderson: Right. Apropos of academics and technology, when we were trying to set up a group at Oak Ridge to worry about biohazards we had to set up a committee, and Joe Melnick was chairman of it, the first Biohazards Committee there ever was. And so he said, "We don't really need this."

And I said, "Have you ever had anybody in your laboratory come down with a laboratory virus infection?"

He said, "Yes, one. And just one fatality."

I said, "How many people have you had working total?"

"Well, you know, 40 or 50."

So I said, "Two percent in your lab died of a virus infection."

Baker: You got his attention then.

Anderson: I got his attention.

Baker: And Question Number seven. You may not have much

grasp of that.

Anderson: The grasp I have is that this needed to be looked into because, sitting on the edge, I could see a tension between grants and grantees and contractors and all the administrators involved in that. And the fallout of that has been an attempt of each to inhibit the other a little bit, and that results in more paperwork and more kinds of reviews and concept reviews and all these steps are put in to slow things down--were put in--and that still exists. I think it ought to be gone through and cleaned up.

Baker: Well, that was another attempt, and part of the planning was really designed to cross over those lines and not worry quite so much about whether it was grant funded or contract funded, because you're right, we had different philosophies, and they are conflicting. But it seems to me multidisciplinary research, which is clearly required for cancer, you ought not to be arguing over the mechanism of funding to the extent we've argued.

Anderson: Right. Right. Now, so far as what all this really paid off doing, I think it was absolutely essential to the development of molecular biology, because that has evolved from virology in very significant ways. The only way you could

move DNA around, the only little pieces of it you had to study that you were sure were homogeneous, they were all viral.

Baker: Well, again, the supply of characterized virus preparations played a very key role here. Moloney said the viruses that Baltimore worked with were supplied by the program.

Anderson: Sure. Sure.

Baker: But most people don't know that.

Anderson: That doesn't show. If you said, "Why can we do that here in place of Uganda?" the answer is, we've got the back-up and the materials here, and other people can't and don't compete with us many times purely for that reason, except now they can get them, thanks to the program.

Baker: Question Number eight, you've already indicated one thing you might have changed if you had a chance to do it over, and that was the label you had on the embryonic antigens.

Anderson: Right. Right.

Baker: Anything else you would like to have seen changed in the program?

Anderson: Yes. What I would like to have seen done was something much more basic than was done, and that's what I was trying to preach at Oak Ridge. Dr. Alvin Weinberg, in 1959-1960, decided that nuclear energy was here and the laboratory should

be redirected into something else, began to think of what their future would be now that nuclear energy was going to become commercial. So he asked different people to give position papers as to what should happen, and I gave the one in biology. Nobody else would do it.

So I said-- I went through what had happened with the stable isotopes. I pointed out there were 300 analytical chemists on the lot there; that we had lots of mass spectrometry going on. We were in separations. Oak Ridge is separations. Why don't we take the complete analysis of human cells as a problem? The whole thing.

Baker: I remember your proposing this idea.

Anderson: Now, I wish that idea had been taken up a little more widely as a National Cancer Institute-NIH objective. And I think a good share of our present funding difficulty is due to not coming up with ideas like that, because if you look at NASA, they want to find out about the origin of the universe--basic questions. You talk to people in nuclear physics, it's the fundamental structure in matter. We've got to understand that. I haven't heard anybody say lately they've got to understand what is really unique about life, and that is a little naive for the

scientist but not for the man on the street who is paying the bill. He wants to know that you're really trying to get at the fundamental problems.

And so the two things I tried to do after this is first with Senator Cranston in 1980 there was a move to set up a complete human protein index, and hearings were held. Everybody who was supposed to be attending those hearings was out with the Reagan election. Otherwise, I think it would have happened. And then, in 1983, I wrote a proposal for DOE that caused a big ruckus at Argonne to do the human genome. The first proposal ever written on this subject. It got us relieved of our jobs at Argonne. And we got it published subsequently, but that was the first proposal for the human genome.

Now, we were mistaken in how this ought to go. The genome had to come first because it was technically doable. The rest of it isn't so obvious as to how you would really go at a complete index, but the people who are in genomics now, that's the next push; how do we now characterize all the gene products. And we, unfortunately, are stuck with a whole series of categorical institutes, which is the way to get money, but not the way to get really large sums

of money in one overriding attempt to go the whole distance.

Baker: It just occurred to me that the grants system, with its relatively circumscribed projects, generate a total effort that's really quite different than what you're proposing. You'd never get enough magnitude and mix if you're going to approach it in bits and pieces. But, on the other hand, few people are courageous enough to be willing to look at the whole broader program at one time.

Anderson: And that was one of the big arguments why people in the funding agencies didn't think it was a good idea. But I think the counter-argument is this. And that is, suppose that we did set up a project of some reasonable size, suppose the human protein index had been done and we systematically separated out every gene product we could find out, what then? Every one is a career. Now, the grantee is essential. Here is Protein 1,478, and it's found only in glial cells. What does it do? That's the project. The thing that makes R01 research important would be having the complete set of all gene products and all genes available, and you pick yours and now tell us about it; how it changes in development, how it changes in disease; how it

changes between different ethnic groups. That can't be organized and run. It makes what everybody at the bench level wants to do, namely have an important little project of his own.

Baker: Well, the way I sound here, I may sound like I'm not in favor of the grant system. I am, for a large proportion of the funds ought to always be in the grant system because you don't want centralized control for everything. You want exploratory research to be open-ended, and therefore I would defend the grant system just as much as anything else. But I don't think that's the only way to do things.

Anderson: No. I don't either. I don't either. Well, I think if you say, "What are the problems that we face now," these are the ones: the integration of different disciplines, somehow stating problems at a higher level that will get the funding that then allows all the ROIs and other projects to be done, but also being sure that they're important because they can attack important problems. One of the big frustrations of the whole grant system now is that the ordinary grantee can't have access to all the facilities that he feels he needs. He doesn't have the latest ultracentrifuge, he doesn't have this; his competitor has that, et cetera. That means

shared facilities, that means reagents analyses done by other organizations for you. Somehow you've got to do what the physicists have done with their big accelerators. Get all the nuclear physicists interested in one area together. Give them time on the accelerator. Make them part of the show.

Baker: Do you know how difficult it's been to get that these days?

Anderson: You know Trimblepiece, who is head of the Oak Ridge National Laboratory? We were discussing this exact problem. He said, "I'll tell you what the problem is. When physicists are in trouble they circle the wagons, they load up their guns, and they shoot out." He said, "When biologists are in trouble, they circle the wagons, then they shoot in."

Baker: At each other. Well, it certainly occurs to me that what you're proposing here would be perhaps an ideal course of events for the National Labs. But how do you get this idea sold?

Anderson: It's too late for the National Labs.

Baker: In other words, the National Labs did that in the nuclear energy Manhattan Project idea.

Anderson: That's right. That's right.

Baker: So they ought to be used to that, although they probably are not--

Anderson: But, you see, they don't have the biological leadership.

Baker: Well, that's part of what I was coming to. You need to change the kind of effort. But the things you're proposing, if you could get that sold, would seem to fit the National Lab idea very well.

Anderson: Oh, yes. It would bail them out. It would bail them out.

Baker: Well, not only for that, but the output would be something that's hard to come by. So, it's probably a selling job, but this time doesn't seem to be too likely to pay off.

Anderson: Except for two things. We are not curing AIDS. We are not curing cancer to any astonishing extent. And that suggests that we have to do something different and probably bigger.

Baker: While we're on that, why do you think we haven't been more successful, considering all of the manpower, hours, and money that's been put into cancer research?

Anderson: You want my rock-bottom answer?

Baker: Well, sure.

Anderson: Okay. Because it was not possible. I wouldn't blame anybody. But I don't think it was possible for a variety of reasons to come down to the basics and say, "We are now going--come hell or

high water--to find out the difference between some normal and cancer cells, and we're going to go the whole distance no matter what. We're going to sequence all the DNA. We're going to separate out all the proteins. We are going to get to the bottom of this problem." And there will be lots of little careers in here for people. There are some that will be found to be obsolete. But we have to really know the difference. And I think that bring us now the problem that the Genome Project faces. Once through the genome, what do we do, disband? No. What we want is--I'm working on a little write-up of this right now--we want a curve that shows how fast we are generating sequences and, if you do that curve on the basis of present data, somewhere like in 2020 we will be doing somewhere between one genome a year and one a month, depending on how you interpret this curve.

Baker: I think you'll be doing better than that myself.

Anderson: Okay. The people who are talking about it, this is managing all the data, et cetera. What is it that you want to know about cancer first? If there is a genetic component, and there certainly is, a somatic genetic component, you want to know the sequence of the whole genome for the untransformed cell, and then at every stage in

the progression to malignancy. How many changes are there, how many mutations? Many things are being developed now, but they're for individual genes. I'm saying for the whole genome. That means you've got to do one a month.

Baker: Have you seen the article in *Scientific American* that just came out by Webster Kavanee (who incidentally is Director of the San Diego Branch of the Ludwig Institute for Cancer Research)?

Anderson: Yes. There is a good one on the mutations in one gene.

Baker: And the repressor genes as well as the stimulating genes?

Anderson: Right. But you see, again, we're always here on one little discovery of, here is a suppressor gene. How many of them are there? We don't know. How many other changes are occurring at the same time? We're always looking through a keyhole. We've got to open the whole door or take the roof off. And so my problem is I don't see the definition and the setting of an overall project that says, "Here are two cells that differ and we intend to find all the differences."

Baker: Well, one reason I was not in favor of bringing Cancer Control back into the NCI was that this is another example of diverting efforts away from

this fundamental question that you are posing, made worse now by other diversions so a lot of staff aren't really working on cancer research, of course, but that's a social problem. And it's interesting. You know, my answer to my question of why aren't we further along is a very different one from yours. Basically, my answer is because of the complexity of biological systems.

Anderson: I was saying the same thing.

Baker: Maybe.

Anderson: I was saying the same thing. If you take me up on it, you say, "Okay, Norm, you're saying we've got to find out all those differences, so what are you going to do? Tomorrow, give me the list." No. Then we say we have an idea what the data would look like, all the mutations, base substitutions, transpositions, everything that would happen, but we don't know exactly how to get at that, but now we're going to ask if sequencing is the way we have to go, let's get a good systems analysis group together and say, "What happens if we scale this procedure up by a factor of 10 and 100 and 1,000? What are the limiting factors?" It turns out storage is a limiting factor. It turns out numbers are a limiting factor. You're going to have more

little bottles than you can put on any reasonable bar code.

Baker: I suppose it isn't any worse than the astronomical data we're getting from satellites. We're generating such numbers we're buried under numbers.

Anderson: Right. Well, optical disks are just--

Baker: So I assume that's going to be solved.

Anderson: Right. But what we have to do is what is done in the military. And this is very interesting. The military will say, "Here is strengths of materials versus time and they're getting better. Here is lumens per watt output of bulbs. That's getting better. The size of storage systems for data storage, they're getting smaller. So we will say we can build an aircraft that will go 2,000 miles an hour that will weigh such and such and amount, and that's what we're going to target for 2040 on the basis of these curves."

Baker: It's a goal-specified--

Anderson: And we have no idea how those are going to occur. None in this world. We just assume that, look, metals got better, then composites came in, and so we've got to get up here. That's what we have to say in biology, that we don't have a clue as to how some of these problems are going to be solved, but they are not important, and so now we

have to put together whatever kinds of staffs, or whatever it is, and if we're going to do 3 billion bases per month, what does that look like? What is it going to require? And we give Dupont a prime contract, if we have to. We just say we want to get there and, if we can't, we want to know why.

Baker: Do you think we've got enough people who think this way in biology to move it?

Anderson: No, I don't.

Baker: It's not just a matter of leadership at Oak Ridge Laboratory, but the whole field.

Anderson: I would redefine your question. There aren't enough people in biology, but there may be enough people who are, or will shortly, be unemployed in biology to do it. Those are the flexible kind of people who may want to do it. You see, there is tremendous opposition, but you also have to point out that the real aim with all these big enterprises is to make the work of the individual investigator more important.

Baker: Well, there is a great fear on the part of most individual investigators that they don't want to have somebody else tell them what to do, and that's what they see planning and this big programming you're talking about doing.

Anderson: You've read, I'm sure, Kuhn's work on paradigms

in science?

Baker: Yes.

Anderson: Okay. That is, in some respects, an extraordinarily cynical work. He says the average scientist works within these paradigms and it's perfectly obvious what he will do. It's within that circle.

Baker: Well, you need some cleaning up of details like that and so you've got to have that.

Anderson: He's cleaning it up. And that's what most science is all about. So, it's directed. His environment has directed him as to what should be done, what's important. The review committees are the enforcers of paradigms. "Outside this paradigm? No, you can't go." So, he's limited and he thinks he is free and open with the whole universe in front of him, but he's on a little desert island and it's completely circumscribed. You see? So, the answer is, if there is no other way to go, he will cooperate. And physicists do what they do because of their experience. This is the only way they could get things done they wanted to get done, the only way the money was available. It wasn't the physicists having any kind of a lottery or a vote. Nobody asked the astronomers to vote on the Space Program. That was just set up. And the Nuclear Energy Program,

what it did was to beat a lot of people into a different shape in a short period of time. And when they went in they were one way; when they came out they were another way. And I think the biotechnology community is beating a lot of these people into a different shape.

Baker: Somewhat. Somewhat. But that's not as much at the research end, I think, as more down at the other end.

Anderson: But, you see, how do you define research, if what you are doing--

Baker: Well, I should have said the more fundamental end of the things then. I agree it's a continuum really.

Anderson: But look, what is fundamental? The people upstairs from us in Human Genome Sciences say they're doing absolutely the most fundamental work that's being done in biology today. They're discovering all the genes.

Baker: I'm thinking of a conceptual thing that encompasses that and is broader than that, particularly in reference to cancer, of what keeps the control so stabilized for so long a time, and then what happens when that shifts. And this takes the conceptualization of the organism that I think is rather different than most people are thinking about.

Do you know a guy named Stuart Kauffman?

Anderson: No.

Baker: He's a physiologist who is interested in some complex-- Did you ever hear of the Santa Fe Institute?

Anderson: Uh-huh. Sure.

Baker: Well, he's been very active with that group.

Anderson: Complexity.

Baker: Yes. So this complexity idea is kind of a fad, perhaps, but I think this is basically what our problem is here with living organisms, and it may take a whole different conceptualization of how you deal with complexity than simply learning all of the coding. That's a step that's necessary, I think, but that's not at the high enough intellectually organizational level to get at this.

Anderson: When you're done and you have all the genes and all the gene products characterized, you still don't understand how it works.

Baker: I think you've got to conceptualize this at a different hierarchical level. But that's a matter of opinion. Now, how you ever get funds for this sort of thing, you know--

Anderson: I think we've done all the things we can to get funds for little pieces in biology.

Baker: Well, the superconductor--super-collider I mean--

Anderson: That was a bridge too far. The super-collider.
That was a bridge too far.

Baker: But it's, to me, very sad that that's been stopped and it's cost a hell of a lot to stop it. But it illustrates the great difficulty. And a lot of the difficulty, as you say, the wagons were shooting at each other. A lot of physicists killed that because they thought that that money should go to individual physicists, which doesn't necessarily happen if you don't have the other one. And Moloney was pointing that out with the Viruses Cancer Program. He calls it the "demise" of the program. The money didn't go from there to grants.

Anderson: Now, you're raising a whole bunch of other problems as to where we go from here, and I think, to change the subject a little bit, I think that's one of the things that ought to be done by the Cosmos Club is to begin to work on central issues, not--

Baker: Well, these recent creativity symposia at the Club were interesting and I was all for it, but I think you've got a twist on here that might be worth pursuing.

Anderson: For example, we've got now this attempt to cut out the ATP programs and other programs which apply technology. That's a very fundamental

issue. We're spending, I think, \$70 billion on research in this Government, and the idea is that that is going to give us new jobs and get us ahead of the rest of the world in high-tech. Yet we have a missing piece where we attempt to apply it. The questions are, how much of the fundamental research is really useful as fundamental research?

Baker: Don't know.

Anderson: Don't know. But, you see, between 30-40 percent of research papers are never referred to, which tells you--

Baker: Yes. I'm the author on a couple of those. Even on my planning paper I only got one request for it.

Anderson: One request?

Baker: Yes. But I only got one request for the planning program.

Anderson: Well, xerox machines had come in by then. Before, you would have. Didn't I send you a request?

Baker: No.

Anderson: I apologize for that. Because I read it. But, anyhow, that's one thing that I think should be done seriously and should involve the players in Government and in the Congress.

Baker: Well, the Cosmos Club did that sort of thing, of

course, in World War II, and that's why I'm kind of sad that the Cosmos Club is not anything like that influential now as it was in those days.

Anderson: It could be, if it would do these things. Where else are they being discussed?

Baker: Well, not very many places. I don't know.

Anderson: Not very many places, that's for sure. I would like to see them take the bull absolutely by the horns and say, "We're going to have a series of symposia in which we ask the question, 'Why are we not able to cure AIDS?'"

Baker: Well, why don't you write a letter to this guy that's the chairman of this creativity business. He's got this Hungarian name that's not pronounceable. Do you know who I mean?

Anderson: Uh-huh. Yes.

Baker: It starts with a "U." Because I made some suggestions on this creativity area, and they've sort of been in line with--I'm not saying that my letter did anything about that--but the first two symposia were very much what I suggested, and this new one is similar to the idea of trying to relate cultural differences--

Anderson: Uh-huh. These are important things.

Baker: Yes. But what you're suggesting is a different idea. Yes.

Anderson: Present Government policies. Why are we doing

this, or why are we doing that?

Baker: The key to this also is getting the right people involved because, as you say, a lot of people don't think this way.

Anderson: But not only that. You see, you would immediately have a lot of "defensive" presentations. Anybody who feels that their ox is about to be gored.

Baker: Well, you ought to let them speak too. Yes.

Anderson: Sure. Let them speak too, but it can't be just those.

[Can I get you some coffee or anything, Carl?

Baker: Well, if you've got time.

(Whereupon, there was a brief recess.)]

Baker: We've been touching on items in the tenth question here, but let's see if we can crystallize this a little bit more. How do you think the political climate and public knowledge and opinion may affect scientific progress and funding, and how it affected the Viruses Cancer area in 1950-1980 and today?

Anderson: Well, I think that was, in some respects, the golden period in that science was held in much higher esteem and there was much greater expectation of concrete results. Now, for a variety of reasons, especially public scrutiny of

unethical conduct in science, or the appearance of it, has rather clouded over really large funding prospects. But I think what's more important, we haven't had leadership that projected programs that at least looked as if they could be really effective. I don't think we've had--maybe we wouldn't allow--really effective leadership in the biomedical sciences.

Baker: Who is "we?"

Anderson: We as scientists. It may be that we don't allow that any more. That's a sad state of affairs. But if someone comes up with a program and suggests a course of action which would get a lot of funding, he would immediately get a lot of flak, I think. So it may be that we have people who could be leaders, but maybe they don't feel that it would work or be supported.

Baker: Do you think the political influences on positions of leadership are such that this makes it less attractive for people who might otherwise be willing to provide the leadership?

Anderson: Uh-huh. I think that's true. I think that's true. One becomes a target. And in the present news climate it's very difficult to escape without injury.

Baker: The question of the public's understanding of science. There is a lot written, and some press

activities have been pretty good in trying to convey some of the scientific findings in lay terms. But do you feel that the knowledge of science on the part of the public is worse than it was in 1970, or the same, or better?

Anderson: I think for part of the public it's getting much better, partly due to public T.V., so that we hear a lot more about results. What I think is missing is an exposition of what the problems are. We're happy to go on T.V. and show what we've done, present some particular new or important, or trivial, advance. But we need somebody who can state what the questions are. And I think the examples of why that's important are obvious. NASA convinced us that we wouldn't understand the origin of the universe, or much else, if we didn't have some Moon rocks. They posed the questions before they gave the answers. We constantly bombard the public with new answers to questions that we've never raised. I don't think that gets us very far.

Baker: The other thing I'm getting at is whether college graduates, for example, are taught science well enough to really make most college graduates understand science.

Anderson: No. No.

Baker: And why is that?

Anderson: I think what they've been taught to be is "concerned," whatever that is; that they haven't been given a good enough background in hard science--mathematics, chemistry and physics.

Baker: Why not?

Anderson: Because these haven't been considered important.

Baker: Do you think the science departments have focused so on educating and training those who are going into science that they've neglected teaching science to those who are not going into science? It's a loaded question, perhaps.

Anderson: I think you have to do both. And I don't think you do a good job of teaching the general public unless you're doing a good job of training some scientists at the same time.

Baker: Are the teachers willing to do both?

Anderson: Oftentimes they're not because they don't see any reward in the more general kinds of things. But this is changing. Now, to give you an example, Maynard Olson, who worked out ways of amplifying human DNA in yeast, gave a lecture last week at the NIH on how he would organize the Genome Project, and surprisingly he ended up his lecture by showing a group of high school students that were working in his lab and he said that he believed that every scientist should take part of his grant money to help educate and interest

young people in science, and that was what he was doing with part of his time and part of his effort.

So, if that can be made a generally accepted form of human behavior, I'm all for it. This was an interesting example of somebody who is worried about that problem.

Baker: Yes. Who was trying to do something about it.

Anderson: That's right. So it can't be-- We can't give the problem off to somebody else; we've got to worry about it ourselves.

Baker: Well, I'm well aware that my teaching science to non-science majors isn't going to do much to solve the problem--

Anderson: It helps.

Baker: --but it seemed like something I could do as a retiree.

Anderson: Tell me what your estimation of the response is.

Baker: To that kind of teaching?

Anderson: You're in contact with these students. They're not science students. How do they respond?

Baker: Well, this was in University College, so these people were coming at night after having worked all day, nearly all of them, so they were motivated, at least to get their degree, so it would probably be quite different if I were teaching in a daytime ordinary campus. So I

would say they were motivated. They almost invariably had great fear of the formulas and any mathematics, but I still thought it was essential that they be exposed to the whole idea of why you need formulas which show the relationships, so I started with very basic physics. I even talked about measurement and all that on the first lecture. And most of them tolerated it pretty well. I went in and put a lot of stuff on the board before class and I tried to not give them too much of that, and I only gave a few problems, and I only expected the better students to really solve them. And that was true. Most of them didn't really work on the problems. I was not trying to make scientists out of them, so I pretty much told them what was going to be on the exams. And so, if they really studied, they could certainly pass. And so, as usual, I had bimodal curves, which was the same thing when I was teaching a Sociology course. I didn't get a bell-shaped curve at all; I got a bimodal curve. Some were pretty good and some were pretty bad.

Now, one problem, of course, was language. We had a number of foreign students and the language was a problem for some. But my main objective was to at least make them sympathetic to science and have some grasp of what the main

points were in the different areas of science, including evolution and behavior and neurophysiology and developmental biology and physics and chemistry. And you can do it.

I was surprised. A number of my friends said, "How could you teach all that?" I said, "Well, I hadn't had physics for 40 years, but I went back and reviewed it a little."

Anderson: Yes. That's the only thing to do.

Baker: So you can do it. And I worked the problems myself.

Anderson: Yes. It's refreshing to do that.

Baker: But it's, you know, a drop in the bucket. So it's like trying to treat cancers by treating symptoms. I mean, it doesn't get at the heart of the matter. So your suggestion of a program at NIH that included a certain X percentage of dollars for training young students would be a way to get at it at a bigger scale.

Anderson: Yes. Yes. Because I don't know what the high school students get out of this, but they see a scientist who doesn't seem to have horns and they begin to hear some rational discussion.

Baker: And these problems are interesting if you present them right.

Anderson: That's right. But one problem I have with the general public is a certain loss of faith in

rationality.

Baker: Yes. That's a very fundamental problem.

Anderson: There is--

Baker: Scientology is still surviving. Astrology is still reported in the newspaper.

Anderson: My son Lee got his degree at Cambridge with Perutz in the MRC, and here is a place that's full of Nobel Prizewinners, et cetera, and so I said, "All right, tell me, what is it about the place? Why does it work?" And he said, well, he'd thought about this too, and he said, "A lot of people come and they talk about a lot of things and there are ideas floating all around." He said, "I came to the conclusion that the group, as a whole, was essentially unfoolable." He said they were willing to--

Baker: That's a form of quality control.

Anderson: That's right. They were willing to take any idea and work it through and see whether they were being fooled or not. But it was a very interesting way to put it. My conclusion about it was that was true, but it was also true that there is an enormous effect of being at the center of things, and it was driven home to me so much when one time from Argonne I was asked to go give a lecture at someplace in Kansas, a university. And so I showed up, and here was

their new Biochemistry Building, which was, you know, almost a block long and several stories high. It was just being equipped and had more stuff than--

Baker: Where was this?

Anderson: Someplace in Kansas. And I thought, "Gee whiz, they've got more stuff than I've ever seen crammed into one place, except maybe at the NIH. They must be setting the world on fire here."

And so I was scheduled to go and talk to people, one after the other. And when I got done I concluded I had never heard of any of them before and I wasn't going to hear of them again. Yet, they weren't any smarter or dumber than a lot of people that I met at the MRC. There is something in the intellectual flavor of your environment that has an enormous effect on your expectations of yourself.

Baker: There is a new book out on the history of a mentor-protégé chain (Shannon to Brodie to Axelrod to Snyder to Pert) that illustrates the effects of intellectual environments and who the mentors are as important factors in career accomplishments. There have been some interesting discussion on the genealogy of one's scientific forbearers, and I'm happy to say I can trace mine back to Emil Fischer and Justus Leibig, and van

Hoffman before that even, and it makes a difference.

Anderson: It makes an extraordinary difference.

Baker: In the development of the Ludwig Institute for Cancer Research, we were starting from scratch setting up research labs, and the prime consideration was the same thing that Shannon represented: continual emphasis on top quality. We also elected to pick younger people to head the Branches.

Anderson: What is going to be the future of the Ludwig Institute?

Baker: Well, it's still going strong.

Anderson: Financially it's--

Baker: Well, financially it was set up in a very unusual way. Mr. Ludwig transferred all of his assets outside the United States to the Institute, so the Institute became, in effect, a holding corporation which represented about 60 companies, and all of the funds which normally would have been profit were fed back in and used to set up Branch laboratories. And we have to do clinical research as well as laboratory research, and we have to always associate with a not-for-profit hospital. But we elected to have different branches emphasizing different aspects of the cancer problem. But, by in large, it was to pick

your best young people, give them a good deal of leeway--don't try to manage them from Switzerland--but be willing to get rid of them if they didn't perform, which I think is the key to some of this.

Anderson: Oh, yes.

Baker: Now, how did we pick these people? One element on deciding location was whether the Ludwig Institute owned properties, e.g., in Australia where the Institute owned a lot of coal deposits; so we had two Branches, or did have, in Australia. So, you go into a country and meet with some of the top scientists and you ask them if they can they identify some of the bright young people. And it's amazing how often the same names come up. Now, we couldn't compete with Harvard but, there is a second layer of people who don't go to Harvard who are just about as good, and so we set out to try to hire some of these people of that quality, and we identified them by these suggestions from the top scientists in an area. And then we would talk to these people and as Hugh Butt, our Chairman of our Scientific Advisory Committee, often said, "This fellow is bright-eyed and bushy-tailed, or he isn't," and if he wasn't bright-eyed and bushy-tailed, we didn't hire him. Do you know what

that means? You probably do.

Anderson: Right.

Baker: He had the ability to formulate a program beyond where he was, knew where he wanted to go, had some good ideas on how to get there, and insisted on quality because he'd been trained in a milieu where that was expected.

Anderson: But how is the Institute going to take into consideration the problem of its aging? That's a central problem in any--

Baker: We have closed two or three branches partly for that reason. The Sydney Branch was set up for chemotherapy emphasis, both clinical and non-clinical. The young man we picked was a good clinical investigator trained in chemotherapy, radiology, oncology, internal medicine and the works, and he was also quite knowledgeable of folic acid metabolism which, in those days, was key to studies in leukemia. But he didn't grow with the field. So, he was an excellent clinician but he really didn't keep up with the lab side. So we kept sending him guys down to be the number two man to run the lab side, and he kept turning them off because he wanted to be in charge of everything and wouldn't delegate to them. So, the Ludwig Institute, a little bit before I left, closed that Branch down.

Anderson: How do you deal with the following problem?
People that are supported by Howard Hughes, for example, here's a kind of scenario. You're in a university and suddenly you're not competing for grants, you have a special space, and you're a Howard Hughes investigator, and you're over here and the poor peons in the rest of the place are envious of you, et cetera. And then you lose your Howard Hughes grants. It's known to all the granting committees that you were on that for a while, and now you're coming into the situation, and there is a certain amount of resentment to somebody who has been outside the system living a plush life for a while. Don't they have a re-entry problem?

Baker: Yes. And we had a policy of giving them two years to get back into the stream.

Anderson: That's a good idea. Yes.

Baker: Because, when it was set up in the first place this was discussed with them.

Anderson: How they re-enter?

Baker: Yes. But we would give them two years to get their grant applications submitted.

Anderson: You see, that's what I think should be done with the National Laboratories. What you should do is say--

Baker: Well, if they're going to close them, they ought

to do something like that.

Anderson: Yes. You ought to say, "If a university will take you, you get so much for equipment which the university wants, you get 2-3 years support, maybe on a declining scale, and--"

Baker: But you've got to be tough enough to cut stuff out.

Anderson: That's right.

Baker: And not everybody can do that.

Anderson: Well, it's going to be cut out, so the question is how.

Baker: Yes, in this case, the basic funding is going to be cut. It's bound to produce a reduction. But what worries me is will you cut out the less quality stuff?

Anderson: No. You see, your quality will leave right away.

Baker: You know, how do you determine quality? Well, in a field, the best people know what quality is.

Anderson: Yes. But there is another way to determine it. Look what happened at Oak Ridge. Hollander had a pretty good set-up going. And then there wasn't going to be enough money to keep growing like he wanted to keep growing, so he encouraged, and his successors encouraged, you to go out and get your own money. Like Kenny got his own money, I got funds, other people got funds, and so now you're living on outside funds and the money that comes

inside goes to the second and third-rate people that couldn't get any money. All right? When the outside funds began to become at risk, what happens? Who leaves? The top people leave. You don't say, "Oh, these guys are coming back into the system."

Baker: I think you've got to have a turnover of younger people coming through in a fairly high proportion and, in most places, that proportion is probably not high enough.

Anderson: Well, that can only happen in a university.

Baker: No. You develop programs where the guy comes and he's only going to stay for 2-3 years.

Anderson: Or he's a postdoc which, you know, that's another big beef now, that the postdoc career doesn't lead anywhere. You keep on being a postdoc.

Baker: Well, we probably have trained too many for the size of budgets we've got now. Either you've got to have bigger budgets or stop training so many. Now, I'd prefer to have bigger budgets but, you know, not everybody agrees with that.

Anderson: Well, my general conclusion is that a research activity is usually only healthy when it's growing.

Baker: Well, it's a lot easier. That's one reason I went after bigger budgets, so I'd have more options.

Anderson: Right. You dilute them out.

Baker: It's a lot more exhilarating, as well as productive, I think, if you can grow. But you can't keep growing forever, so you have to change your style of operations when you're not growing, and that is harder to do, and you've got to be tougher.

Anderson: That requires a certain kind of discipline that is very rare.

Baker: Yes. And I suppose you can only stand being a "bastard" a certain length of time before forces throw you out.

Anderson: No. You only get the opportunity to be-- You're the one that's going to go.

Baker: That's what I'm saying. You know, you can only make so many enemies in a given time, so you don't expect to survive forever, and yet some guys are very skillful even at that and they last a long time and still do a pretty good job.

But the key leadership roles, whether it's a lab, or an institution, or a small group, are hard to define, but crucially important.

Anderson: It's like obscenity. You know it when you see it.

Baker: Yes. And so your Cambridge group, they somehow have collected an interesting group of people.

We (at the Ludwig Institute) had a Branch

right in the middle of the Cambridge Lab of Molecular Biology, but the Dean of the Medical School kept trying to get more space for our Ludwig Branch and he never succeeded; so we finally closed that one because we didn't think it could grow enough. And it was originally proposed by them and us. So, the Institute still has eleven Branches turning out good work, and the money is still there because, as I say, it's not just an endowment which gets used up; it's an ongoing group of businesses really. So it's different. It was more like-- Let's put it this way. Howard Hughes used the same area of the law to set up the Howard Hughes Institute that was used for setting up the Ludwig Institute, which is a very different body of law than the ordinary foundation.

Anderson: So it's a loophole in the law, in a way?

Baker: No, just different.

Anderson: Well, originally, wasn't it set up so that a physician could have his little research operation in the hospital as a sort of a tax-free arrangement?

Baker: Not that I'm aware of. I never did get into the business end of the Ludwig Institute operations. That was always--

Anderson: It was explained to me that that was the reason

it was felt that a physician ought to be able to have a special laboratory just for research under his jurisdiction in a medical environment and that that had to be covered by a special type of law. And Hughes snuck his whole operation into that.

Baker: I know that they used part of the same basis of law as we did. And this is why we always had to pair up with a not-for-profit hospital. That was one of the requirements. And we never did get a Branch in Germany because we could never find a hospital that was not-for-profit that was suitable. We found one, but we didn't feel like putting young people in that "morgue" environment. It was dead.

Anderson: Do Government hospitals qualify as non-profits in this sense?

Baker: Well, in Germany that's not the way medicine works.

Anderson: I know, but I wanted to know if they were out? You don't have any in Russia, for example, or couldn't?

Baker: Well, in Melbourne the Walter and Liza Hall Institute, I suppose, is not Government but it's sure got a lot of Government funding. We still had to deal with the hospital of the university. So we usually had a 3-way thing going. We had a

hospital, a university and, if it's there, a research institute. And we always, in setting up this thing, got everybody together to agree that this would be a collaborative thing.

We also always had a local committee of outstanding citizens whom we worked with to make sure we didn't do something that upset the local practices, and that, I think, was probably wise to avoid troubles. And then we, of course, set up our scientific review committees and reviewed the programs every 5 years on how they were coming. Bill Paul of the NIH was on one of our committees, for example. And so I think it seems to be working pretty well. We got up to nearly \$20 million a year which, by NIH standards, isn't high, but that's good to give you a little exercise on how you manage something.

Anderson: You can get a long way, if you really want to, on that kind of money.

Baker: And the Melbourne branch is very good partly because the young man we picked, Tony Burgess, worked with Metcalfe, who is one of the leaders in the area of differentiation and growth control factors. Another Branch Director is Thierry Boon, who worked with Christian de Duve, and he had an interesting phenomenon where he could show that certain mutations of certain tumors would elicit

the immunological response against the tumor, but the modified cells would not go on and form tumors. And so he's been trying to exploit that and so far we haven't got much further than that.

At the Branch at Bern we had a problem with finding the right director there. And at that Branch we had some clinical trials which, even though clinical trials were not popular with some members of our Scientific Advisory Committee, I was a backer of them because I thought we needed trials and they're very difficult to do, and it seemed like that should be part of the program of the Ludwig Institute. But that's been closed by now.

Anderson: What happened to the man that left the NCI and formed a cancer center in Nashville, I think it was?

Baker: Yes. I know who you're talking about but, I don't know, he's still peddling stuff, I guess.

Anderson: He's still going? Tim O'Conner went with him, I think.

Baker: Well, I'm not sure. I don't have enough on the details to know. But I really haven't looked into it enough to know.

Anderson: Well, his basic ploy was that people are getting special treatment at the NCI and, if the NCI does it, it must be something good and new, and we

want to make it available to the general public.

And so whatever they do, we'll do here.

Baker: That was the pitch. Yes.

Anderson: Yes.

Baker: But they charged for it too, didn't they?

Anderson: That's right.

Baker: So it's not quite that simple.

Anderson: Right. Well, it was a way to make money but it--

Baker: I don't object to people making money,
necessarily, but--

Anderson: --it had a gimmick attached to it.

Baker: --it makes a difference how you get the money.

Anderson: That's right.

Baker: Well, this has been a lot of fun, and I
appreciate your time and willingness to talk.

Anderson: I hope something comes of it all.

Baker: Well, I hope we get that.

(Whereupon, the interview concludes.)