This is an interview of Dr. Nathaniel Berlin, who played key roles in NCI, including the Head of the Metabolism Branch and Clinical Director of the Institute, taken on March 12, 1995. The interviewer is Dr. Carl G. Baker, former Director of the National Cancer Institute.

Baker: Nat, would you start out by giving us a little bit of your background?

Berlin: Sure, Carl. In June, 1947, I went to Berkeley as a graduate student of John Lawrence's in medical physics, housed in the Donner Laboratory on the Campus of the University of California, a part of the Physics Department, a part of the Radiation Lab, and at that time my efforts were largely centered around the application of radioactive isotopes to study biological problems in man and experimental animals. After six years there, I went to London as a Special Research Fellow of the National Heart Institute, now the National Heart, Lung, and Blood Institute, in the laboratory of Albert Neuberger at the National Institute of Medical Research, more familiarly known as "Mill Hill." Drafted into the Navy, I spent approximately 2 years at the Pentagon in the Armed Forces Special Weapons Project, but shortly after I got out of the Navy, Bo Mider renewed an offer to me which he made in 1952 of a job in the National Cancer Institute. I went out to see Bo. I was in

uniform. We shared a few pleasantries. He showed me one or two slides of nitrogen balance, and he said to me, "Nat, when are you coming to work for us?" And I said, "The day I get out of the Navy." And he said, "Thank you," and I left. That was the offer of a job and my acceptance. About a year later, maybe 9 to 10 to 12 months before I came to work, Gordon Zubrod asked to see me. He had recently joined the staff as Chief of the General Medicine Branch and, I think, the Clinical Director, although which came first I don't know, and asked me if I would take the position as Head of the Metabolism Service, at that time one of four units in the General Medicine Branch. There was the Metabolism Service, the Dermatology Service headed by Eugene Van Scott, the Clinical Pharmacology Service headed by David Rall, and the Experimental Chemotherapy Service headed by Emil "Tom" Frei. I may not have the right titles. Somewhere along in 1959, Gordon asked me if I would become Chief of the General Medicine Branch, and I did. About a year later, with Bo's moving to Building 1 (known as the friendly front office), as Jim Shannon's Deputy for Intramural Research, a position which had a number of titles, and I think Bo's was Director of Laboratories and Clinics, Gordon became the Scientific Director with the title of NCI Associate Director for Intramural Research

and I succeeded him as the NCI Clinical Director. In the mid-1960s, Gordon, Sol Schepartz, Lou Carrese, and you, Carl, spent 6 weeks reorganizing the NCI Cancer Chemotherapy Program, and, during his absence, I acted in his behalf. With a later reorganization of the Institute, Gene Van Scott succeeded him as the Scientific Director for that piece of the Institute's Intramural Program that became General Laboratories and Clinics. Gene stayed in this about a year, maybe a year and a half, or two, and after he left I succeeded Gene as Scientific Director for General Laboratories and Clinics. And then, when the Institute became a Bureau, our titles were changed. Each one of us who were Scientific Directors became Division Directors, and I became the Director of the Division of Cancer Biology and Diagnosis.

One important aspect of the Clinical Director's job which has not been widely appreciated was that the Clinical Director was listed (and, probably has in the job description) as having a direct link to the Director of the Institute and establishing him as what I used to think was, a Principal Advisor to the Director, a role not often played. Jack Masur, Director of the Clinical Center, used to call the position the Physician-in-Chief of the National Cancer Institute. About that time, for the review of contracts, there was created in the Institute, a Scientific Directorate (later called the

NCI Executive Committee) whose chairman was Gordon Zubrod. The Institute had set up a system for the review of contracts that was layered, much the same way as grants. Grants were reviewed by a study section. The study section reviews were reviewed by a council or later, a board, and that was the model that was used by Ken Endicott. There was, parenthetically, not many know, a conflict between Ken and the various members of the outside community, including Mary Lasker, over the review of contracts. We did report in some fashion to the Council, but I don't think they had any statutory authority, or requirement, to review contracts in the same manner that they had a statutory authority to approve grants, but the final decision for funding, of course, rested with the Director. I think it was my service on the Scientific Directorate that gave me a broad view of what was being done under the direction of NCI staff both internally, but more importantly what was done on contracts. We received, not the contract itself, but an adequate précis of each contract, together with a summary of the budget and often a presentation by one of the scientific leaders internally of the substance of the contract.

Baker: And you left NCI when?

Berlin: I left NCI on March 31, 1975, almost 20 years ago.

Baker: And you became Head of the--

Berlin: I became Director of the Cancer Center at Northwestern University and the Tuton Professor of Medicine. I stayed at that 12 years and, in September, '87, at Gordon Zubrod's invitation--Gordon had become Director of the Comprehensive Cancer Center at Miami, which has undergone a series of name changes from the Comprehensive Cancer Center to the Papanicolaou Cancer Center to the Silvester Cancer Center at the University of Miami--I was asked to join him, and I did. At that time I no longer wanted the responsibilities of a directorship--I wanted to do staff work for the Director--and I took the post of Deputy Director. It turned out that Zubrod left early. I was the Director for about a year to a year and a half, and then reverted to what I would like to call my "permanent" position, Deputy Director. Parenthetically, the salary was independent of the title, and I did what I thought was appropriate.

Baker: Very good.

Berlin: And then, when I completed that, I came up to the Cancer Institute, was a Guest Worker in Al Rabson's unit, and spent much of my time in the Library of Medicine in a carrel that Al had arranged for me, reading, writing, and studying, making rounds, attending meetings, and rejuvenating myself

scientifically.

Baker: Well, we've certainly had an interesting career, both of us, and are fortunate to have met and worked with so many interesting people. I realize that you were not directly involved in the management of the Viruses Cancer area, but we're interested in having viewpoints of those who were not only directly in the Program, but those who observed the activities from outside, and you were involved in review of contracts, as you say, some of which, of course, were from the Viruses Cancer area. So, if I may, I'd like to turn to the questions that we put together.

The first question relates to your impressions of the main scientific results that were highly significant in this area during the period 1950 to 1980, and who were some of the key scientists involved in those results.

Berlin: I think you could summarize it that the field was largely driven by the fairly substantial number of viruses that in pure culture, or probably in pure culture, could produce either leukemia or a tumor in the experimental animal. And my understanding--and this may be simplistic--is that the underlying notion at that time was if these viruses in pure culture could produce leukemia in the experimental animal-- I don't recall that any could produce solid tumors, but I just don't recall.

Baker: Well, Moloney sarcoma virus did.

Berlin: Well, close to being--

Baker: And then the polyoma, of course, produced all kinds of tumors and Rauscher virus, and others.

Berlin: The polyoma. Sarah Stewart.

Baker: But earlier, they started out with leukemia, and the Program was originally called the Special Leukemia Viruses Program.

Berlin: And I think the underlying thought, if you'll permit me to say so, which may be simplistic, but it was one that could be understood by those outside the field, and even understood by laymen, was that if you can produce leukemia--let's keep the conversation to leukemia for simplistic purposes--if you could produce leukemia with a virus in animals, we should search for the virus, or viruses, that produce leukemia in man. I think you mentioned the polyomavirus, and one cannot dismiss Sarah Stewart's contributions, nor can we dismiss Lloyd Law's contributions in those days. Or Ray Bryan's. From Ray Bryan I learned the notion that there was something called helper viruses and Type C virus particles. I think, as I look back at it, scientifically, the major problem that we may have faced early was that the electron microscope was the only tool available for detecting oncogenic viruses, and you either saw particles or you didn't see particles.

And then, I guess, I got my introduction to some of the serological aspects of viral investigation from Huebner. But I must say that when I listened to him it wasn't long in his delivery before I became thoroughly confused.

Baker: He was very interesting. He was always stimulating, but sometimes he was very difficult to follow, and other times he was clear as a bell. And I could never figure out whether intentionally he was clear when he wanted to be and confusing when he wanted to be, or whether that was just his style.

Berlin: As I said earlier, as someone on the periphery, who went to either the National Advisory Cancer Council or later the Board meetings or to the Scientific Directorate, or a scientific meeting, Huebner did leave me thoroughly confused most of the time.

I think the next event, which turned out to be a non-event, was--and I don't recall who did the work--but it became apparent that it was possible to find some particles in human blood. And at that time Carl Moore was on our advisory apparatus, whether he was on the Board, or the Board of Scientific Counselors, I just don't know.

Baker: Board of Scientific Counselors.

Berlin: I just don't recall. That was the year Carl Moore was President of the Association of American Physicians, better known as "The

Old Turks," a very limited membership, prestigious organization, largely professors of medicine. And Carl Moore donated--gave up--the time for his Presidential Address for a scientific presentation on these particles. I think it was about that time that Ken Endicott made one of his--and I will say it, Ken is gone now and others are gone--end runs to the Congress, and out of that came the Special Virus Leukemia Appropriation of, whatever it was, $10 or $20 million dollars.

Baker: $10 million.

Berlin: I remember Ken going downtown. I ran into him shortly after he came back and he said that he caught hell from the Secretary, Mr. Celebrezze. Whether Shannon ever said anything to him, or Bo ever said anything to him, I just don't know. It would probably not be out of character for Bo to say something but, since Shannon was the "Master End-Runner" of them all. I just don't know. And that's not a pejorative with respect to Shannon. He was the architect. He knew how the system worked.

Baker: And I can clarify that for you.

Berlin: Thank you.

Baker: There was a special memorandum prepared, partly with Ray Bryan, Dick Rauscher and myself, and I think Gordon reviewed some of it, for Ken to send to Shannon to request that we be

allowed to ask for a special appropriation. So Shannon demanded an accounting of, "Why do you think this is justified? He approved the action on the basis of that memorandum.

Berlin: So this was an approved end run? It wasn't an end run?

Baker: No, no.

Berlin: It was an approved action.

Baker: Well, we did not look at it as inappropriate, but maybe they did at the Secretary's level. That is always a complex issue.

Berlin: You know, again, Carl, you have to remember I was watching, and it's now almost 30 years later, and you tend to either embellish or under-estimate or confuse yourself.

Baker: That is part of the fun of history.

Berlin: I thought Ken had a good sense of relationships with the Congress. But if he had the approval of Shannon, I give Ken credit now where I might not have. Ken was a master at his interpersonal relationships and he understood the workings of the Federal apparatus, although Ruth Mider, who is still alive, once said, "Ken is purple prose." So, that's where I perceive it. And out of this the decision was made that most of that money would be spent using the contract as the main instrument of support. It would be an NCI staff-managed program. And I can't recall, but probably they had an outside advisory group to review it. They

probably had internal review groups and, of course, we had the equivalent of a board in the Scientific Directorate. I think this is approximately correct. Carl, you were closer to it, so you can give the inside view. I give a proximate view.

Baker: Yes. That's fine.

Berlin: So these are the people, Ray Bryan, Sarah Stewart, Bob Huebner, Ken Endicott, Carl Moore, who in different ways played major roles.

Baker: Okay. Fine. That pretty well covers the second question as well, which dealt with the key administrative or management decisions.

Berlin: I think, Carl, I'll amplify it, and I can amplify it on the basis of my later experience. In a broad way, the National Cancer Institute is in two parts, intramural and extramural. The scientific content of the extramural part is almost entirely dependent on what investigators in the universities and research institutes submit, and here the Institute Director has a small role. He can make Program Announcements the Institute is interested in, but he makes no commitment. A request for applications can be made, and again NCI can define the field, but the details are dependent. But I would guess 80-90--or maybe more--percent of all the activity is purely--the phraseology used is--investigator-initiated and the program of the Cancer Institute, or any of the other

institutes that are grant supported, comes from outside and, as a program it is synthesized *post hoc* by staff. On the other hand, with the intramural part, at the time when the contract was an accepted method of support, the Institute could issue a Request for Proposals in very specific ways, defining specifically the research, and it could review a set of proposals and accept what a review group thought was the best. Early, of course, before Leon Jacobs stuck his oar into the process--again I'm being pejorative and personally you may want to edit these out eventually--as I saw it, he played a major role in preventing us from sole sourcing contracts with educational institutions by virtue of the fact that they were just educational institutions and we could go directly to them. I believe that I certainly did take the initiative in selecting the institution, subject of course to appropriate review. We did have a rigorous review, but it gave us an opportunity to mold the program in a way that I don't think you could have in the grant supported program. Furthermore, because we were not bound by study section review of grants where they are unable to deal with large budgets, we could put a substantial amount of money into a project--a sufficient amount of money--so that it would work and not constrain the science by budget.

Baker: I think the other important difference is the integration of the

different projects into an overall program, which is very difficult to do in the grant-supported arena.

Berlin: What you and others in NCI management did was to hold, periodic--whether it was annual, or semi-annual, or biennial--meetings of the contractors. And when I ran the Breast Cancer Task Force the contractors and the advisory committee and we would meet annually and there would be a scientific program so that everybody knew where he fitted in and what the others were doing. And I did the same in the diagnostic field. And I know that there were virus meetings. I don't remember ever attending any one of the virus meetings.

Baker: The same thing was done, very much. My point was that you needed both kinds of approaches, not "either/or."

Berlin: I don't disagree with you, Carl.

Baker: I didn't think you would.

Berlin: Let me provide now, at this point, my commentary about Huebner. There is no question that Huebner was a distinguished scientist. He came to us from NIAID and I think he'd already been elected to the National Academy of Sciences. So this gave him credibility. I was critical then, and I'm critical today, of two things, or more particularly just one thing. Huebner, in large measure, or to some measure, used the contract mechanism to

support his own work or to broaden fields that he had opened up. But he made one major mistake in my opinion. In a comparatively short period of time he published, as a coauthor, a large number--and I don't remember the time interval, but in a period of maybe 3 or 4 years at the most--he published somewhere around 100 papers with contractor-scientists. And when this came to the attention, in one way or another, of the Scientific Directorate, we took note of it. Some of us spoke about it. Some of us were opposed to it. And I think, if anything, the academic community said Huebner had too much money to foster his own research. Later I asked Bob Berliner, and Bob sort of acknowledged that, but he gave me the impression, however the effort was made, it was good research. So I fault Huebner, more than anybody else, for giving the academic community an excuse to criticize the use of contracts by intramural scientists.

Baker: Well, when I was Director, I found that when Huebner's name was on a paper, he had contributed to the research and often was clearly the senior author. But I'd have to agree that this heavy publication with contractor scientitists played a role in the Zinder Committee's deliberations, I think.

Berlin: And the Zinder Committee, as best as I recall, came in and they weren't critical of the science.

Baker: Well, in their Report they didn't even particularly review the science output of the Program, which I thought was a great mistake, and I almost wrote a critique of that but, since I was out of the game, I didn't. Okay. I think you've answered number three. You were observing all this and taking action on final review of contracts as a member of the Scientific Directorate of the NCI, so that, I think, covers the third question. I guess you've touched pretty much on the fourth question, on the main leaders who influenced the direction and course of events.

Berlin: These were largely the intramural, or the NCI or NIH scientists. You know, there were a goodly number of virologists who were not in the Cancer Institute who may have been in our advisory apparatus, whether it was Wally Rowe, Bob Chanock, or some of the others in NIAID--Zinder--and I don't know whether Spiegelman ever considered himself a virologist, but Harry Rubin at the University of California, Wendell Stanley, of course. We should never forget Wendell.

Baker: No. He was very instrumental in getting this going.

Berlin: Wendell Stanley, in the late '40s, maybe '50s, was on the--I'll use a common word--the "bandwagon" postulating viruses as a cause of cancer in man, with little or no evidence. But the Nobel Prize carried a cachet with it.

Baker: The fifth question--

Berlin: And I guess we must never forget Peyton Rous, in 1911.

Baker: Yes. Amazing. Well, I consider that Ray Bryan kept the flame alive during all that period when everybody said that viruses had nothing to do with cancer, and that Rous didn't have a real cancer.

Berlin: He had a tumor, didn't he?

Baker: Yes. Which, of course, literally means a swelling.

Berlin: Okay. You asked a question-- I think we've largely dealt with Question Four, or do you agree we've largely dealt with four? And now, if you synthesize it, you start with Payton Rous, Ray Bryan, Wendell Stanley, Bob Huebner were the early movers in one way--

Baker: There was one man, who headed one of our committees, which a lot of people don't seem to realize how much help he gave was Chuck Evans from the University of Washington.

Berlin: I did not know him myself.

Baker: Yes. I don't think you had any connection with him. But he was another one of those very helpful outside consultants and advisors.

Berlin: I think, as I look at it, I don't think we ever reviewed at the Scientific Directorate the membership of the committees. I think, in large measure, they were distinguished people who made very

substantial contributions, and I viewed the committees as--in current terms--sounding boards. From time to time they may have even been contractors selected later. If there was conflict of interest, I didn't see it. But they were a mechanism for widening our ability to capture information and, more particularly, for discussion and, in the scientific community, finding out who was doing what and particularly what was coming down the pipeline before publication. So they were an information gathering, a review mechanism, and, I think, extraordinarily helpful.

Yes, even if there were enough staff internally to do the reviews, it would have been a mistake not to add outside scientists to the committees. By widening the net, I think we enlisted a large number of good people. And once it became known that money was available, we were able to bring scientists into the cancer world, whether it be the cancer virology world that we're talking about today, who might not otherwise have moved their research in that way.

Baker: Of course the timing was related to the polio field, because a lot of very good virologists were sort of looking for something to do since the polio problem had been solved, so we purposely tried to interest--and succeeded in interesting--some of those polio virologists into coming into the cancer field. I think this was very

helpful.

Berlin: I don't know that Salk or Sabin ever did.

Baker: Sabin was very active with the Program; Salk was not. Salk was pretty much of a loner. But Sabin was very active throughout the whole Program. Any political figures come to mind? And I define politics here broadly, such as scientific politicians, or politicians who were in the field, as well as general politicians.

Berlin: Certainly, I don't think Sidney Farber, who was probably the major medical cancer politician, was involved. I just don't think so. I don't know. Sidney's game was chemotherapy. I have no idea, but I suspect Mary Lasker had her fair share, a woman for whom I have great respect in her ability to mobilize the Congressional leadership. And then there was one politician who was on the Republican side of the House, Paul Rogers, and I can't recall--you'd probably have to refresh my memory and I might comment on it--but I don't recall any others. But, you know, if anyone deserves a lot of credit on the political side, it's Mary Lasker.

Baker: No doubt. Well, she was on the Council at that time, and so was Farber, and they were very supportive when we presented these programs for expansion, and believe that the planning that we had done provided a good communication device. I remember after

Rauscher and I presented the plan for the viruses area, Sidney Farber's comment, when Ken asked for the Council comment, was: "Well, Carl, what else is there to say?" So that was kind of interesting. Okay. The next question turns to a slightly different cut, and this deals with the resources question. As you know, a lot of the contracts were let in order to produce needed quantities of well categorized resources such as tissue culture cell lines, virus preparations, antibody preparations, animals of special types and so on. How important do you consider that aspect of the program, or not at all, if you feel that way?

Berlin: I'm thinking, Carl, how to answer. I'll answer you from the standpoint of one who once worked at the bench and worked at the bench again in 1980 when I was at the Walter and Eliza Hall Institute in Melbourne. When I first went to Berkeley comparatively little was available commercially of the tools to help us in the laboratory.

Baker: Greenfield and I made our own ATP from rabbits, and we counted radioactive samples one at a time.

Berlin: Right. And so, today-- When I went to Australia I learned that there was something called "kits," and I wanted to do a translation of genetic information. And you could have a kit. You had to extract the messenger. But they had another kit that you could put

together that had all the ingredients to do a translation. I forget what I attempted to translate. Whatever it was--

Baker: Well, this is a step in producing a--

Berlin: So, availability of resources. When I went to Australia--

Baker: What year was that?

Berlin: 1980. I think one of the things we must never forget is the enormous contributions that Wilton Earle, Katherine Sanford and someone whose name I can't recall--the two ladies--made, together with George Guy of Johns Hopkins, making the technology of tissue culture what it is today.

Baker: I think we have to add Harry Eagle, who simplified it considerably.

Berlin: Mostly in the Cancer Institute. Harry Eagle was in the Cancer Institute, Wilton Earle was, Katherine Sanford. Was the other lady Todd?

Baker: Katherine Sanford and Virginia Evans.

Berlin: And we certainly couldn't live today without the media that were prepared, the concepts of tissue culture, and how to do it. And I did learn the tissue culture principles and technique, and I actually did some tissue cultures. When we started, I learned from Ray Bryan that there were highly selective strains--highly inbred strains To make a long story short, it's possible now to do very

sophisticated research at the bench with instruments and, more particularly, the wet resources, whether they be viruses or reagents, whether they be chemical reagents, nucleotides, polynucleotides, proteins, or monoclonal antibodies, that you can get from a catalog. And you can imagine what it would be-- I can imagine what it would be if you wanted to make your own monoclonals. You can do it. People do it. They are still searching for a new monoclonal for this, and there are probably people who are fusing cells and growing them up. But for specific purposes there are large numbers of monoclonals, and it's very impressive to see the reagent catalogs. Now it's very impressive to go back and see that the Cancer Institute, particularly in its Frederick apparatus, was instrumental in building resources, or understanding the processes needed to produce a large number of reagents. I think this has been fairly successfully taken over by industry and whether the Institute needs to provide this kind of resource anymore I don't know. The other resource, in the instrumentation hardware, I don't think we ever did very much. The people who built instruments were mostly in commercial enterprises, whether a Beckmann centrifuge, or radiation scintillation counters, now scanners for looking at gels, or the gel apparatus.

Baker: Norman Anderson was at Oak Ridge developing the special centrifuges, and the NCI did put money into Oak Ridge for some of that development. So, on the instrumentation side, that was one contribution. I interviewed him last week.

Berlin: I don't recall. I knew Norm when he was at Oak Ridge and I knew him when he came to Chicago. I haven't seen him in maybe a decade. I think he turned his attention to analyses, attempting to find spots on one of his chromatograms, or with his analytical techniques, that were different in tumor cells from those of benign cells. This sort of goes back to Jesse Greenstein's era of searching for biochemical differences between normal and a malignant cells. There are differences, but they're pretty subtle.

Baker: I might mention one thing about resources. When we interested some of the virologists from the polio game into coming into the Program, I pointed out to some of them that they were great at exchanging information very early and sending each other the resource materials for confirmation but, by the time they had sent it around to all their colleagues they didn't have any left to work with, and that was one reason we needed to produce large quantities of whatever materials were in order. And I'll never forget, we were over the hump, when John Moloney came in one day and said that Pfizer had produced a viral preparation which

was as good as anything they'd ever done and that, "We've got buckets of it," he said. So, he was a converted member at that point, I think.

Berlin: Well, I think, if nothing else, the science has emerged, the science has evolved. The concept of resources, those resources that the Institute made available, may be the underpinning that was long neglected in our historical view of what's happened, because the research couldn't have been done--much of it couldn't have been done--without those resources.

Baker: You probably don't have too good a grasp of the relative amounts of funding for Cancer Viruses in grants compared with contracts?

Berlin: My guess is, Carl, certainly in the early days, maybe for the first 10 years, the ratio was probably 8 to 9, or more, contracts versus grants because it wasn't a popular area in the scientific community. How correct am I?

Baker: Well, pretty much, except the first appropriation funds earmarked for viruses at $1 million, went into grants first, before we had the Special Viruses Leukemia Program. So it got a boost in the grant side before the Program was started. Later on then the contract dollar amounts got greater, and then they flattened out with the new Cancer Act, so that the increases were no longer made. I will be looking up the actual amounts on this question later.

Number eight. Would you like to have seen anything changed from what happened? Again, I realize you're sitting on the sidelines on the program itself.

Berlin: The only thing that I would have liked to have changed and, as I intimated earlier, I would have liked to have had the intramural staff be forbidden to be coauthors of papers for which the research was done under contract in which they played a part in either the award or the management. I realize that we haven't discussed the role of the Project Officer, because I think, if anything, this was the thing that gave ammunition to the critics of the contract mechanism, and I do think that the Institute, in the long-run, suffered from not being able to use the contract mechanism, particularly when it was apparent that there is a high priority piece of research that should be done, particularly when it was very costly. And I think I can think of one example.

Baker: I think I disagree with that a bit, because in most of the contracts, the Project Officers were very much involved as scientists in formulating what was to be done, and that's probably the most important part of a project, getting it steered right, and therefore why shouldn't he be able to publish? Moreover, the job of Project Officer is difficult because the person needs to understand the science and also be a good manager.

Berlin: I don't disagree with you, Carl.

Baker: Oh, I thought you would.

Berlin: Now, was Huebner ambitious for the Nobel Prize? In terms of the accolades that a scientist can get, and the recognition, what more, you know, can you expect? What more should you expect, in terms of recognition, by your colleagues and the Academy? It shows how ambitious you are.

Baker: Yes. Partly. That's part of it.

Berlin: And if Huebner had stepped back--

Baker: If you are too aggressive, you can step on toes.

Berlin: Carl, I don't think I ever had my name on a paper for work on a contract funded investigation. Yes, I did. Later, after I left the Institute, there was one paper published from the early Lung Cancer Program that I set up, and that's probably it, and it was a summary paper of the study, and it was published after I left the Institute. And I didn't put my name on it; the coauthors did.

Baker: Well, we belong to an old school there, I guess. The next question is probably a loaded one. Do you think the viruses cancer field laid significant foundations for the development of molecular biology and, I might add, biotechnology?

Berlin: Well, I would separate them. There is every reason to believe that a lot of the reagents that we used, and a lot of the thinking of

the early molecular biology, came out of the Virus Cancer Program and the Chemotherapy Program. And I think, if you go back and look at it, you can develop a scientific evolutionary tree that shows this. Certainly Gordon had this view, I had this view, and I think the others who know the history of this field well have that view.

Baker: I agree, of course.

Berlin: Now, your question is in two parts. Significant developments. For the enlarged National Cancer Program, certainly, Carl. The enlarged National Cancer Program, as I look at it--you and I talked about it recently--when you and Gordon got together with Lou in the mid-'60s, a decision was made that had two subparts: one, we would pursue vigorously the development of new drugs to cure cancer; and, that we would pursue vigorously the viral etiology of cancer as the best potential scientifically, at that time, for the prevention of cancer. So, if the Institute succeeded in curing cancer, or if the Institute succeeded in preventing it, it would have been wonderful. And you didn't put all your eggs in one basket. And Rauscher left Gene Van Scott with a basket which I inherited, which turns out to be one of the great baskets, but it wasn't when I inherited it.

Baker: Well, I was going to say, I have been amused at a lot of the

younger people who think that the advances started with the new Cancer Program, but it's really a continuum and you have to look back at the accomplishments achieved before the passage of the National Cancer Act of 1971.

Berlin: I can well remember coming in, early in my career, coming into Bo Mider's office where he had a microscope out and he was reviewing some pathology slides of some of the work that Sarah Stewart had done before she published it.

Baker: Yes. I remember.

Berlin: So, it goes back that far, that I can recall and observe.

Baker: And it's really a continuum and not sudden changes. Let's shift the direction again here. The tenth question relates to how the public perceives science and biomedicine and whether the support and sympathy for science by laymen is better now than it was 15-20 years ago, or the same, or worse, as you see it, or no difference?

Berlin: Carl, do you remember when Kenneth Cole of the White House staff came out after the National Cancer Act of 1971 passed, and I had my political naivete confirmed? Cole said that the White House had a private poll that showed that cancer was amongst the most dread diseases. The American Cancer Society had a comparable poll. But it impressed me that in the White House,

the Nixon White House apparatus, there was sufficient interest and sufficient effort in getting a private poll that showed that cancer was a dread disease. I think what's happened, for which I'm critical--you can see this in *The Wall Street Journal* when I was quoted a couple of years ago--we appear to have promised much and delivered less. I think that my friends still tell me, people that I meet for the first time, "Nat, Dr. Berlin, is there still hope, or is there hope?" I don't see--and I don't know of any evidence for it--any diminution in public interest and, as a matter of fact, the American Cancer Society continues to be an effective fundraising apparatus. I think the women have learned from the AIDS people what I call "strident advocacy," with respect to breast cancer, which has resulted in that curious phenomenon of a $200 million dollar appropriation to the Defense Department for breast cancer research, which caused conflict between the Institute and the Army. I don't know what the current Congress is like. John Porter, who is a Republican who plays a major role in the NIH science appropriations, or authorization, I think, is supportive and said to be a friend of NIH. Whether we have other friends, I don't know. You may, or may not, have seen that Committee on Science, et cetera, that George Brown headed, their report, which was supportive of science, but I viewed, as

best as I can recall, having a great possibility for hindrance. I don't recall the details. I think they wanted us to justify what we were doing in terms of early practical results. In a ball to ball sense, good science is good science. Don't ask us what we're going to accomplish in any specific way. And I think the Brown Committee, if I read my memory correctly, sort of asked us to justify what we were doing with more applied science. But I may be entirely wrong. I have some of that at home and I haven't read it for a couple of years. There is no doubt, Carl, that if the Institute were to go to the public in a public referendum way and say, "We have the potential, but a real potential"--I don't mean the past potential--"to take $100 million dollars, or a half a billion, or a billion, to prevent cancer. We now know how to do it; we just have to scale up," you'd get it. Or if we had a new treatment that was "penicillin" for cancer we would get it. The fact of the matter is scientifically, as I see it, Carl, we don't have either and we're just going to have to continue to pursue doing good research.

Baker: Why do you think we're not further along with all this effort and money that's been spent?

Berlin: I think the answer to that, Carl, is twofold. We are much farther along in understanding what a malignant cell is, but, if you take as an example: there are mutants--I understand there may be 50-

odd mutations of the p53 region, or the p53 protein, or the basic DNA, or however it gets transcribed--and I just don't think we know, or have any good ideas as to how to translate that into preventing a disease yet or treating it. And so, if you ask me, what we've uncovered each year, if you look back, you can criticize us by saying we were extraordinarily naive about what it is that a living cell is, and we were naive about the difference between a living cell--the fundamentals--not the observed thing, that it can metastasize, or it has too much DNA. "Naive" is the wrong word, Carl, but I think it's become apparent that it's not simple. You know, you and I, when we grew up, we didn't know what a signal transduction pathway is.

Baker: Well, the idea wasn't even there.

Berlin: We didn't know what a receptor was. We didn't know that a receptor had to be transmembrane, or some of them are, and we didn't know there was a receptor and something got onto the receptor, and there was a whole process, and it's obvious that that's not a simple process. There are a lot of controls.

Baker: My one word answer to the question is complexity. Living organisms are just very, very complex and are very adaptable to external changes.

Berlin: Compared to anything that is non-living.

Baker: Yes. And this biological diversity is a fascinating subject as to how that came about, both in the embryological development of individuals and in the evolutionary sense, so I've been trying to read up a lot more on what accounts for this diversity.

Berlin: And you told me about chaos. The other thing, Carl, is I was never able to convince the pharmacologists that they should become physiologists because I was never able to convince them that maybe one of the reasons that they don't get the therapeutic results they want is that the perfusion rate to a metastasis is very low, and the drugs they use are either excreted or catabolized before they can get a therapeutic concentration in a metastasis, and they've never really taken that up research-wise.

Baker: Partly because the circulation of the blood vessels in tumors is inadequate compared to normal.

Berlin: Yes. You know, you and I can devise the requirements for a good therapeutic agent. It ought to have a high extraction efficiency when it hits the tumor cell and have a long biological half-life.

Baker: That's like saying sin is bad.

Berlin: And have a long biological half-life so it can get in and out of that metastasis. This is a principle. And they've never, to the best of my knowledge-- There is a man named Prakesh Jane, who used

to be at Pittsburgh, an engineer--he's now Professor of Tumor Biology, I think, at MIT--who has some very interesting ideas in this field, and he calls it the "microcirculation." Piero Gallino was interested. But if you look at what the current staff of the Division of Cancer Treatment are doing, they get raw material, whether it be from the sea, plants, or animals, you screen it, and you eventually test it in man and then you get a single drug that may or may not have a moderate effect and you attempt to combine them, or you attempt to combine it with another one, and you combine old ones in a new dosing schedule, and I'm very critical of what they're doing because it's theme and variation. And I recently reviewed, for *The Journal of Clinical Epidemiology*, a paper written by two Canadians in which they broke out the elements of multi-institutional trials for lung cancer, and it was apparent, as you look at this, that there are many variants--chemotherapy, radiation, surgery, surgery before, radiation before, maybe a little chemotherapy afterwards--and yet today a patient who comes in with metastatic lung cancer, it doesn't matter much. He may get a little bit of benefit, but not a hell of a lot. So, I wrote a paper, Carl, that's about to be published in *Cancer Investigation* called "The Conquest of Cancer." I'm very sad that despite some spectacular successes in treatment,

particularly in the childhood tumors and in young adulthood, Hodgkin's Disease and testicular cancer (the most spectacular really numerically is testicular cancer), Hodgkin's Disease may still carry with it a 20-30 percent mortality. That is not much less, or approximately, what the mortality was in the great bubonic plagues of the middle ages.

Baker: Let me ask you one question about political aspects on NIH, a question of whether there has been an increase in political decision-making on issues that are scientific questions and perhaps the decision-making should be based on the science but perhaps is being more and more influenced on political decision-making, for example the creation of the Office of Alternative Medicine? Do you have any comments on that?

Berlin: Sure. Jacobs, when he came in to head the Office of Alternative Medicine, had an office next door to Al Rabson's temporary office while Al's was being renovated, and I talked to him once or twice on a very superficial basis. The NIH would never have created that office on its own initiative. It was created by pressure from Senator Harkin.

Baker: I know. That's a political thing.

Berlin: Purely political. We'll come back to the cancer. Another political matter that's interfered with science is the issue of fetal

tissue research and abortion. And, as you know, Bernadine Healy probably waffled on that issue. Varmus didn't, but Clinton did. And I think that is wrong. There was a couple of other political issues that the Cancer Institute got into. One I'll talk about is breast cancer screening. And I have something that may be coming out in Sam Hellman's and Vince DeVita's and Steve Rosenberg's new journal, the *Cancer Journal*, and this has to do with screening of women under the age of 50. There was a meeting in February of '93, February or January, entitled "An International Workshop on Breast Cancer Screening," which focused its attention, either in the title, or in the entire meeting, on women under 50. When I left that meeting and came back and I saw Al Rabson I said, "Al, I have never attended a more biased meeting and," I said, "I would be willing to write an editorial." He probably mentioned it to [Daniel] Ihde, the *Editor of the Journal of the National Cancer Institute*. I was not invited to write an editorial. I've since done it. That meeting led to a report. The Chairperson of the committee, a woman named Fletcher, who at that time was Editor, she and her husband, were the Co-Editors of *The Annals of Internal Medicine*, about a month or so before that meeting wrote an editorial on breast cancer screening that tilted towards physical examination of the breast and

accepted the data from the Canadian study which turns out to be a poor study, at least from the mammographic standpoint, which the Canadians acknowledge. Then Sam Shapiro, head of the Health Insurance Plan of New York (HIP), whom you know, was there. Well, Sam Shapiro has the data. Now, the biostatisticians reminded me that Sam Shapiro's data originally came to us in the Scientific Directorate, in the proposal for a mammography study presented by Mike Shimkin, which I think I voted against because it was too expensive.

Baker: It was $3 million dollars. I remember it. That was a big decision for us to make.

Berlin: I might have voted against it, Carl.

Baker: But it was voted--

Berlin: I remember.

Baker: I don't remember exactly how you voted.

Berlin: But it didn't matter. You know, to amplify something, and to have fun in this discussion, I say I may have voted against it. It was designed to study women between 40 and 65, and I've learned from the biostatisticians that it can be fraught with danger to do subset analyses. And his original subset analysis of the women under 50 was that there weren't enough women to draw a conclusion. And when later we set up the Breast Cancer

Detection Demonstration Project, clearly the American Cancer Society protocol, which the Breast Cancer Task Force's Diagnostic Committee went along with, and certainly when it came to my desk for signature I went along with, was a non-randomized study, which Sid Cutler did not approve of, and I went along with the women starting at age 40. Now then, you can trace--which I've done--Sam Shapiro's interpretations over the years. And over the years they've changed. So once he said there was effect, now he says--and he didn't understand it--now he sort of backs away from it. But at that meeting, they forgot. They forgot that they gave the tapes to some Dutch group who wrote a report and said that they did demonstrate an effect on the women under 50, and they said it was approximately the same as the women over 50. That's the HIP tape data with another statistical analysis. Then they forgot that the Institute staff, Chu and Tirone, published a paper in *The Journal of the National Cancer Institute*, saying that there is quantitatively an effect. But they forgot all those and came down hard and fast that there wasn't an effect, or it wasn't sufficient in the women under 50. Now then, the political side. As you probably know, the Cancer Institute, at one time, joined with the American Cancer Society in their guidelines, and their guidelines said, "Women from 40 up." Then

there was a Board of Scientific Counselors, and again I learned from Benno Schmidt, "Tell me the conclusion you want and let me appoint the committee." That Board of Scientific Counselors to Peter Greenwald came in with 50 and over. That recommendation went to the NCAB, and the NCAB overturned it and said, "Let the guidelines stand." Then Sam Broder overturned the NCAB and said it's 50 and over. And, in the meantime, Donna Shalala, quoted in *The Cancer Letter*, said, "In the process of developing these guidelines, we tripped over ourselves. We made a mess of things." I have been told that Sam's attitude may have been colored by the Department. So that's political. Shalala, in print, in *The Cancer Letter*, denies that the Department attempted to influence that age division in the recommendations. The mere fact that people postulated and the mere fact that they deny it means that it may be true. You know what I mean, Carl? You know, you can probably point to those examples, you know, that are plausible deniability.

Baker: Well, I think we've got too much dependence on correlations as though they're cause and effect.

Berlin: Okay.

Baker: And when we get disagreement among experts the laymen have the right conclusion. You guys don't know. We ought to say we

don't know when we don't know.

Berlin: The other place where the Institute recently got in a political mess, or difficulties, is with Bernie Fisher and the misconduct of one or two participating groups in the breast cancer study. With all the publicity, women became frightened, and women got angry. "You haven't told me the truth." And now we have that Breast Cancer Coalition that's a very strident group, maybe rightly so. And there is another area that's hard to describe, and that's the role of the Federated Societies for Experimental Biology and the Institute of Medicine. The Institute of Medicine may be almost apolitical on the science side and so may the Societies for Experimental Biology, but they attempt to influence the political process, particularly that society, often in terms of money, often in terms of the mechanisms of support. Have I answered you, Carl?

Baker: Anything else you'd like to comment on, or say?

Berlin: I've said too much, Carl.

Baker: No, not at all.

Berlin: I've been very candid, a little bit pejorative, and I may have named names, some--

Baker: Well, I'll be careful about that.

Berlin: --some of whom are no longer alive, some of whom are no longer

in positions of influence, but they're personal opinions. I think, when we sat around at the Scientific Directorate, Carl, we were a pretty candid group.

Baker: Yes. That and the insistence on quality, I think, are the strengths, very much, that we had, and NIH as a whole was that way. Yes. We can disagree without getting angry about it. We didn't have to shout at each other like it seems to be more common now.

Berlin: I don't like it either.

Baker: So I feel very fortunate that we had such good colleagues we worked with at NIH. Well, thanks very much.