Gary Kelloff

This is an interview of Dr. Gary Kelloff, who played key roles in various areas of the Cancer Virology Program, partly working with Bob Huebner, taken on April 19, 1995. The interviewer is Dr. Carl G. Baker, former Director of the National Cancer Institute.

Baker: Dr. Kelloff, I appreciate your willingness to talk with us. Could you give us, first, a little bit of background, where you went to school and who you worked with and so on?

Kelloff: Thank you. Yes. I graduated at the University of Colorado, the Medical School there, in '67, and was fortunate, at the University of Colorado, that Don King, the Head of Pathology, had built a very strong multidisciplined Pathology Department, and you found people in the Path Department that you didn't often find in Path Departments at that time, in the '60s. That is, he had tumor virologists, DNA biochemists--Richard Franklin--and in the tumor virology area he had Peter Vogt, who had come out of Harry Rubin's lab in the late '50s, and a handful of guys came out of that lab in the avian tumor virus area, which is where the retrovirus field was strongest at that time. And I was fortunate, as a student, to go to Dr. King in the Path Department, and he suggested that I go around and talk to these different people. He had 20 or 25 senior staff, all kinds of specialists, in the Path Department. It was pretty unusual at that time. I talked to Peter Vogt. He had a project all figured out for a 2-year eager medical student, and he was so well organized--he then showed me what to do--that in a few months, under his guidance I had a published article in *Virology* on the avian tumor viruses, looking at what was then called the group-specific antigen, but it later became one of the key structural proteins of the virion itself. And there was a lot of question about what the significance was of the group-specific antigen, because people were finding it in the embryos without necessarily having viral particles, and it was one of the findings of interest for having people realize that there may be expression of virus in the embryo

that wasn't in whole viral virion form. And Dr. Huebner was very interested in that because he was thinking hard about the vertical transmission of the viruses at that time. So, I was lucky, with that publication, to get a commitment as early as 1965 from Dr. Huebner for a 2-year postdoc that was 3 years hence in mid-'68. So I was finishing my training and I called Dr. Huebner to ask him for another year so I could get my medicine boards, and he said, "We've got a lot of work to do here. The trouble with you M.D's., and I'm one, is you get a stethoscope around your neck and then we can't get you away." He says, "You'd better get down here. We've got work to do." So I came and started in the Virus Cancer Program. And I came into town on July 3, 1968 assuming that I was going to get the weekend to unpack and he said, "Well, come out to the ranch." He says, "We've got work to do and I want to talk to you." So I drove out to his ranch on July 4, and he gave me about 7 hours of continuous monologue on what had to be done in the Virus Cancer Program. He was at the National Institute of Allergy and Infectious Disease at that time and, as you know, Dr. Baker, he was very close to a transition to move to the Cancer Institute. Building 37 was being finished, and he was working very closely with Wally Rowe and Janet Hartley, and there was a research base, so there was some concern about moving, but he certainly, in his typical self-confidence, just assumed that it would be right, and he moved. And that's how I got started with him. I came when the group was not the size that it came to be in the late '70s and early '80s. The number of people that were trained in some of the techniques of retrovirus assays and cell culture and immunoassays, there weren't that many of us, and so in 1968 I was fortunate to come. And basically, at that time, it was pretty clear what research was needed. With the DNA tumor viruses (the SV-40, polyoma and adenoviruses) Maurice Green and Sol Spiegelman had finished the adenoviruses story clearly showing, here, that you had a DNA tumor virus, oncogenic in animals and, in

the case of adeno, clearly causing infections in people. Many investigators felt that this has got to be it, and they did a very strong negative with seroepidemiology and DNA hybridization on the adenoviruses. At that point you were absent another candidate, and so the direction of research automatically turned to the RNA retroviruses, at least as seen from my perspective, looking at it from my perspective. So, the activity in the tumor viruses on the RNA side picked up. What gave it a lot of impetus was in the murine system you had new isolates on the leukemia side from Rauscher, Moloney and Friend. But you also had the work of Wally Rowe who had developed a focus assay where you could do the quantitative virology that's needed in order to make real progress, and he had transforming viruses, because he had rescued the Moloney sarcoma virus and put helper virus with one of these other viruses--Friend or Moloney. With that kind of assay, we could do neutralization tests and work out the immune reagents and stuff. So, that's all late '60s.

Baker: From then on, how did you get into your present position?

Kelloff: I spent all of the decade of the '70s working, the avian was there, the mouse was there, My first work was to isolate the hamster retrovirus. There was not an infectious isolate and everybody was interested in looking at the other species to see if this virus was everywhere, and the hamster was a good one because, unlike the mouse and chickens, which were inbred--avian flocks for commercial reasons, mice for genetic testing reasons--you had some susceptibility that was bred into some of the strains and you could get a lot of virus out. In the hamster there wasn't a lot of virus. In fact, you couldn't find it. There was some question about C type particles in some chemically induced tumors, but nobody had an isolate. So, the first thing that Dr. Huebner wanted me to do: we isolated the first hamster retrovirus. We were kind of excited about it because it was "a low incidence species," and therefore, if it was that hard there, then

maybe humans had it and we just hadn't looked hard enough. A lot of people had obviously looked at human. And in my own lab we did some human tumor isolation attempts. We didn't get any bona fide isolates, nor did anybody else. And there were some isolates that didn't stand up as human isolates. About then Bob Gallo, in '77, between having the right substrate, the T cell, the right cell substrate and T cell growth factor, had enough virus being made to be able to get an isolate out of those human cells. In the early '70s too then, after my postdoc, I worked very closely with Ray Guilden, a CalTech trained immunologist, and Steve Roslind, and a lot of that work was just making the antibodies to the different viruses and the different peptides so that if you had a new isolate you could tell whether it was something new or something you had seen before. So, a lot of the '70s we were doing that. And then I spent a lot of work with Dr. Huebner directly in the '70s. We actually developed retroviral vaccines that would work in mice, that you could immunize mice and prevent them from not only exogenous challenge to virus, but also prevent them from having spontaneous cancer that was coming up from the endogenous virus. So we could actually immunize them. So, in the '70s it was very exciting. The immunobiology of the viruses was being worked out, isolates were-- And then the cat came early in the '70s, the late '60s, early '70s, the cat virus. Dr. Huebner had a Public Health Survey in California which had, as I understood, 8 million people and about 4 million cats, and there was a good household survey done by the California Public Health Department under contract, 60 questions, that went into households to see if there was any kind of link between pet cancer and household human cancers in the cat registry. There were about 6 questions buried in 60 that really was the main purpose of the questionnaire. We didn't find anything, but what was interesting about the cat was that the cat virus moved in cat populations. That is, it would infect other cats. And we had data where we could infect human lymphocytes

with feline leukemia virus. So we knew that it could infect human cells. I published that with Dr. Hampar, who is at the NCI. So it was exciting. There were isolates from different species. Everybody thought it might be just a matter of time for human. As time went on and so many efforts were made you sort of felt, well, if it's there in humans, it's not there in a very infectious form, and it probably isn't being spread in an infectious form. But Dr. Huebner, even as early as when I first came to NCI, was thinking about the oncogene hypothesis. He had to postulate some way by which this virus was probably vertically transmitted.

Baker: Vertical instead of horizontally?

Kelloff: Yes. And then there were little pieces of information that came in from different peoples' work. Some of the stuff that I did with him, which I thought was interesting (and we published it in the *PNAS*), was the observation that you couldn't immunize adult mice with murine viruses of the wild type. That is, they just wouldn't respond immunologically. And there was some question of, well, are they tolerant to it and, if they're tolerant, have they seen the virus in their embryonic period and then you just couldn't get it in the adults? And we were using low incidence strains. And it turns out when we looked at the embryos by EM there were viral particles in some of the low incidence strains. So there was actually viral expression going on in the embryonic period and, at birth there was no virus, and then later in life it came up again. And it sort of added to the whole thinking set about oncogenes and vertical transmission because, in a lot of cases, you couldn't find the virus in the embryo but you could find one of the antigens, but you couldn't get isolatable virus and you couldn't find particles. And so then we started to say, "Well, maybe there is partial expression of genome," and, you know, it all sort of-- It's virogene, oncogene. You sort of visualize that there was genetic information that coded for viral structural proteins and there must be other

genes that come with the virus that were responsible for oncogenesis. He didn't quite have the whole concept.

Baker: But it was in the DNA of the chromosomes?

Kelloff: Yes. He didn't have all the molecular biology terms, being an epidemiologist.

Baker: Well, nobody did at that time.

Kelloff: And so he was absolutely on the right idea. And John Bader was here too. I interviewed with him as one of the persons who was interviewing before I got the job, and he had shown that by inhibiting DNA synthesis in cells infected with RNA tumor viruses that you don't get RNA progeny. And that was not the usual situation, because polio, the only other RNA viruses that had been looked at, their RNA viruses and they replicate off of an RNA strand. They don't need a DNA intermediate. So, you could inhibit DNA replication and it wouldn't hurt poliovirus replication. Here was John Bader and he had these data. It was right there. And, God bless him, he's still here. He's still upstairs.

Baker: Yes. I ran into him the other day.

Kelloff: So, that was a key finding and I think, in fairness, I'm sure that that was one of the pieces of information that allowed the right conclusions about the life cycle of the virus.

Baker: And you're no longer in the lab?

Kelloff: At about the first of the '80s, it was pretty clear that that whole field was changed from immunobiology and virology to molecular biology, and I spent half of the '80s making monoclonal antibodies and looking at the immunobiology. We looked at monoclonals to the proteins that the oncogenes were encoding and we made monoclonals to the feline oncogenes. Ed Skolnick was really the first with that. He had antibodies to the *ras* proteins, which were the first antibodies to the oncogenes that were defined. And by '85, I felt that this field was really turning into one of gene modulations. The

oncogenes are there, Bishop and Varmus had shown. And again Dr. Vogt, in Colorado, whom I started with, had made mutants of Rous sarcoma virus that allowed the labeled probes of *sarc* to be obtained so that Bishop and Varmus, when they went back into normal DNA, they found the *sarc* gene wherever they looked for it. So, the field had clearly become: you're born with a gene, the genes are activated with time. One of the approaches would obviously be modulation of those gene functions. And I had an opportunity, looking at this field I'm in now, of evaluating chemical inhibitors of gene function, which is what we're trying to do in chemoprevention, and I thought it was a good chance to--

Baker: A good direction to go?

Kelloff: Yes. Develop drugs for early intervention to prevent cancer. Our Chief, Dr. Greenwald, is a very, very good epidemiologist and clinical trials person, and he said, "You know, we need a systematic means of identifying candidate chemical agents that might become drugs." In '85 there was published literature of inhibitors out there with nothing going on clinically except some of the vitamin studies.

Baker: Well, I was just looking at one of Chuck Boone's papers on trying to get an endpoint well before you get full-blown cancer, which certainly, if you can do that, it would be very important.

Kelloff: Yes. It's a real challenge for us that if we can shorten the time frame of evaluation we'll--

Baker: Because even in chemical carcinogenesis, there are the same kind of problems. So, when I was Scientific Director for Etiology, I got wrestling with definition of cause and effect, which is not a simple subject at all.

Kelloff: Yes. I'd say that that's our challenge in chemoprevention is the long-term nature of the studies. If we can shorten them, that's good.

On the positive side, where we think we have an advantage to conventional treatment is that our intervention is timed early enough in the disease that you don't have clones of cells completely out of control that--

Baker: You've got to do it early if you're going to do it.

Kelloff: Yes.

Baker: Well, it's an interesting field. I'm sure you're enjoying it. You may miss the lab a little bit but--

Kelloff: No. We're excited about it.

Baker: I got out of the lab because I got asthma from lab animals, otherwise I'd have stayed a little longer, I think. So, that's how I became an administrator.

Kelloff: Really?

Baker: Well, let's turn to the set of questions. We've already discussed some of the people involved. But it seems like there was a radical change. In 1950, nobody was interested in cancer virology at all. You had Bryan keeping the flame alive and Joe Beard, and there was the Bittner factor. Nobody believed Payton Rous had cancers because they were caused by viruses and therefore they couldn't be cancer! Shope added knowledge. So, what happened to make that change from no interest to suddenly having lots of people doing cancer virology work? How do you see what led to that?

Kelloff: Well, a lot of my experience was directly with Huebner, and he was a believer--certainly in the late '60s--for sure. In fact, even the Shope papillomavirus, he said, "Gee this thing occurs in nature. It's not a lab experiment. And somebody ought to be looking hard at the papillomavirus." Well now, in the '90s, we realize that HPV is pretty active in cervical cancer and maybe in nasopharyngeal with EB virus. So, at least in that--the Bittner agent-- think a lot of the problems were--possibly some of the lack of interest--was the difficulty in even studying the viruses if you were interested.

There was not a good infectious assay for the Bittner agent. There was not a good *in vitro* assay for the papilloma. Tissue culture methodologies for even studying things were just getting started. I know you probably remember--I don't go back--but Eagle worked out his media, and a lot of the work in the '50s in the avian viruses was done by Harry Rubin. They were using chick embryo fibroblasts for the first time when Dulbecco had established the media. But before that they were growing virus on chorioallantoic membranes and eggs and, you know, it was difficult.

Baker: I think one of Bryan's contributions was at least quantifying results so you could show there was a dose relationship.

Kelloff: Yes. Right.

Baker: But then, after that though, the field blossomed, and what brought that about?

Kelloff: Well, quantitative methodology to study the virus. For good virology you need dilution experiments to prove, you know, that what you're looking at is caused by the virus, as you said, and the quantitative methodology came out of-- In the RNA viruses in the Rous system, Harry Rubin had a means to quantify virus by the interference assay. They could take a stock of viruses and wanted to know how many infectious particles were present. They would do serial dilutions out as far as they'd go, infect cells and then, if the cells were pre-infected--if they were infected--you couldn't challenge them with another virus, so you could get an endpoint titer. It was an interference assay. And then, with the Rous sarcoma virus they had pathogenic effects where they could count foci. They'd overlay with agar and they could actually quantify. When you could do that, then you could make antibodies. If you show a neutralization antibody, you can do plaque reduction. A lot of those assays for the Bittner agent wasn't there. It wasn't there for Shope papilloma. So, I guess, like anything in a new field, different findings--Dulbecco, and Eagle's media, the EM was being used more and--

Baker: I agree with all this on advances in methodologies, but I think one of the additional things that was important was Ludwig Gross's finding that you could get leukemia from cell-free extracts. Now, nobody believed him for a couple of years, and then Sarah Stewart and her polyoma. So, once that work was confirmed, coupled with the fact that a lot of the virologists in the polio area didn't have anything to do because the polio problem was pretty much solved--and we tried to talk some of them into coming into the cancer field with some success--and those things, I think, were also very critical in opening up the whole blossoming of cancer virology which became the main way of thinking about it until the molecular biology shift, which came much later.

Kelloff: Dr. Huebner told me that initially he got isolates from Gross and he couldn't get the infection to pass and he was--

Baker: Yes. Nobody could confirm him for a while. So they didn't believe it. He was this crazy guy up in the VA hospital in Brooklyn.

Kelloff: Huebner said there were some other pathogens in the mice. Not that the pathogens were causing it, but he thought perhaps they might be altering the susceptibility a little bit. He believed him; it's just that, initially, as you said, he couldn't reproduce the results.

Baker: A lot of people didn't believe him because they had trouble matching his system. They had to be very young embryos was one thing.

Kelloff: Yes.

Baker: Well, do you have any grasp--knowledge--of the key administrative or management decisions that affected the viruses cancer field throughout, let's say, '55 on up? Perhaps not. You weren't in a position to know much about that, I guess, in those days.

Kelloff: I came in the late '60s, but the Virus Cancer Program, I guess, was just starting.

Baker: In '64 it started.

Kelloff: Yes. It was just starting. I talked to your colleague on this history, Bob Stevenson, who, I think, was one of the persons I talked to when I came here to interview also. I remember that. I remember the pictures of the retrovirus and the EM pictures and the tails on the viruses and it was similar to phage. It looked like phage. I know that later it was found to be part of the fixation. Let's see. Late '60s? Yes.

Baker: Well, you probably weren't aware of how the Special Virus Leukemia Program got established?

Kelloff: No, not in '64. No, from then, no.

Baker: Endicott, I think, was the key decision-maker here because he's the one that made the decision to go ask Congress for additional money. And then we had to convince Shannon that we had the evidence to support that move. And we convinced Shannon. Rauscher, Bryan, and I--with Zubrod also reviewing it--put together this information which Endicott used. So I think a key decision then managerially was Endicott's decision to go after special monies, and that started the Special Program. Then, when we got the $10 million dollars, Endicott came in said to Carrese and me, "You guys talk about planning. Plan me a ten million dollar program in leukemia virology." And that led to our laying out those plans, which most of the virologists didn't pay much attention to. The chemotherapy people paid attention to theirs, but the virologists-- we might as well not have done it from their point of view, I think. But it did help get money and help explain things to people. And the *Convergence Technique* was a modification of systems analysis and systems planning to the research environment, and I think that was not a bad job.

Kelloff: Yes. Uh-huh.

Baker: And that's the way we got the Program underway. And then we budgeted pretty liberally in that direction, and that bothered some people. In fact, we might want to

touch on what happened to the Program in the long run, because some people feel that it is ironic that just when the value of the Program is clearly demonstrated, including the commercial availability of numerous resources that were developed in the Program, the Program is pretty much gone.

Kelloff: Yes. I remember Dr. Huebner writing what he called a "Moonshot Memo," to Secretary Finch because a man had just landed on the Moon. Was it June of '68, or July? Or was it '69?

Baker: '69, I think.

Kelloff: '69. A fairly lengthy description of how successful infectious disease approaches were to lessening human disease. And he had a long litany of successes in the bacterial area, of course, and I think it got a lot of attention, or at least I felt that it did. I don't know what the impact was.

Baker: Well, I think it helped convince the Secretary to support the budgetary requests we put in.

Kelloff: Yes. And the National Cancer Act was '72, right? That's when the Frederick--

Baker: President Nixon signed it in December of '71, but it really started in '72. Those meetings that we held at Airlie House, which were planning sessions for the new National Cancer Program. Did you go to any of those?

Kelloff: Yes. I sure did.

Baker: You see, I think we might have gotten a little closer to a moonshot kind of thing if we had been able to continue with that kind of joining together of people, because we had people there who were sympathetic to having an integrated Program. And how do you integrate different disciplines? The grant system is not very good at that.

Kelloff: Yes. Right.

Baker: And that's why we really turned to contracts in addition to the planning.

Kelloff: Yes. Right.

Baker: And, of course, Huebner saw the value of that. He was always able to put different disciplines together, including epidemiology, which a lot of guys, of course, in the lab never paid any attention to.

Kelloff: I wished he were in good enough health to realize what we've done here in the prevention area, because I think it is close to a lot of the thinking about how to integrate a multidiscipline effort, which is really required for prevention, and we realized that as we went into this.

Baker: Have you laid out a systems plan? You might want to do one, if you haven't. It won't be very popular with a lot of people, you know?

Kelloff: We have an Agent Development Committee. We have a Decision-Point--

Baker: You don't want a big committee, at least not more than three or four people. Get a small group who really know the subject; don't get a larger committee.

Kelloff: Right.

Baker: Okay. What do you consider to be the main activities and effects of your participation in the field during this period? Well, you came in the latter part of that, but--

Kelloff: Yes. I was just one of a large number of people that were in this, and there were some very good people in the Virus Cancer Program, and I think their record since then has shown how good this program was at fostering good people. Ed Scolnick left here and he went right up to the top of Merck. He's Chief Scientist at Merck, and he's been there 14 years. George Todaro left. He went--

Baker: I heard that he's now down in Texas. He went to Washington for a while.

Kelloff: Yes. He started the oncogene concept with Huebner. Yes. And he went to Seattle and is associated with the Fred Hutchinson Cancer Center. Stu Aaronson has left to go to Mt. Sinai as head of their cancer center. A lot of people came through the Program, and

they all--everybody--contributed.

Baker: Well, we turn next to the membership on committees, both NCI committees and those at NIH. Does anybody stand out, as you recall, a chairman or acting members of some of these committees?

Kelloff: Well, I thought Dr. Moloney, who ran the Special Virus Leukemia Program, did pretty well in terms of trying to oversee that block of funds and those contracts and, as you say, the review meetings, and then later the annual meetings in Hershey. He did a pretty good job with that.

Baker: How about the outsiders?

Kelloff: In my first 16-17 years here as a buried intramural lab scientist, I didn't see too much of that, other than the structured meetings that were part of the Special Virus Cancer Program headed by Dr. Moloney. And we'd have occasional visits by scientists from outside. But I was not involved at all at that point in much in the grant side of things, or what was going on there with grants.

Baker: No. I wasn't talking about the grants. Like Melnick and Sabin and--

Kelloff: Well, we saw them a couple, three times a year, at meetings, and they were leaders. Melnick and Sol Spiegelman was always active, and Ed Lynette, in a quiet way, in California, was a sound, respected virologist.

Baker: Well, I was with Joe Smadel in Building 1 for a while. When I left the lab, I went in grants, and then I went back to the lab when the Clinical Center opened, but I still had my asthma, and so I was going to go back to grants, however, then I got the offer to be assistant to Smadel. He was Deputy Director for Intramural Research. I thought it was a good training experience. And the Cancer Institute had gotten a million dollars in grant funds earmarked for cancer virology work, and so we called up a bunch of the virologists who had been in the polio game to see if they were interested in coming into

the cancer field, and some of them were. The V&R Study Section agreed to review these proposals very quickly; so, that's partly how we got some of the polio people into the cancer field. They were looking for something to do, and there were some funds available, and I think that was helpful to everybody. So, I started getting interested in viruses and cancer, that was 1958 I guess, and so we had good people, both on the staff and outside. One of the joys of our working at NIH, of course, was the interesting people you had a chance to work with.

Kelloff: Yes. And Joe Beard was one that would go back into the '50s.

Baker: Yes. He was a colorful fellow.

Kelloff: He had all the avian myeloblastosis he could grow for many years. Even into the '70s, when we were trying to make as much virus as we could, his AMB system to grow virus was better than any of the others. Still it's much cheaper than trying to do it in tissue culture.

Baker: Well, he sure put in a lot of effort when nobody else was interested in that area. I always wondered why he was in the Surgery Department, but it's just as well.
Okay. I asked a question about whether you were aware of any political figures, and here by "political," I mean both in the sense of Congressmen and that kind of politics, but in science politics as well, and, as you must be aware, there are science politicians too. Sidney Farber would come to mind as one.

Kelloff: Yes.

Baker: Again, if you were in the lab, you might not have had much feel for this.

Kelloff: My experience mostly was, I guess, Dr. Huebner, who was reasonably political, and Joe Melnick. They were always sort of--you got a feeling--of active people that were thinking beyond their immediate laboratory efforts. Spiegelman. But I don't know when Mary Lasker got involved. Early on, I guess.

Baker: She was involved in that, like she was in so many things. Yes. Positive. She could be worrisome sometimes, but on balance she certainly made great contributions to biomedicine.

Kelloff: Dr. Rauscher was the first Director that I knew very well. When did he--Was he in, in sixty--

Baker: '72.

Kelloff: And you were in then--

Baker: Before that.

Kelloff: Right before that.

Baker: Yes. The new Cancer Act made the Head of NCI and the Head of NIH Presidential appointments, which I think is wrong.

Kelloff: Yes. And that was '72. Right?

Baker: So, I was not appointed, and Rauscher was, and that was in early '72.

Kelloff: I see. Yes. The years blur a little bit.

Baker: The hardest thing in this history writing is to get the dates straight. The next hardest is remembering names of people. But we'll try to--

Kelloff: Jim Duff. Do you remember Jim?

Baker: Yes. I interviewed him just last week.

Kelloff: Oh, he's a good guy, and he's interested, and he probably has good information.

Baker: He had the questions ahead of time and he had written out on legal paper all his answers before I even got there. Well, we'll turn next to the question of resources, and here we're talking about tissue culture cell lines, virus preparations, antibody preparations, animals, and that sort of thing. It seems to me the Program made considerable contribution where to start with you had practically no reagents available, even non-commercially much less commercially, and now many of these reagents you can buy

easily.

Kelloff: Yes. There is a segment, of course, you know, the Resources and Logistics group of contracts that were set up specifically for reagent production contracts and Dr. Moloney, early on, had put Jack Gruber to oversee the administration of that. I was on that committee for 4-5 years looking at contracts to make antibodies, contracts to make virus, contracts to make peptides, and it worked pretty well. And, of course, a lot of the initial effort at Frederick, once Frederick came on-line, was in the resource support and reagent area. That was early on.

Baker: I was aware of the significance of all of this, but I think I should point out that two people preceding Moloney and Gruber played major roles in developing the resources and logistics areas. Harvey Scudder initiated these activities and Bob Stevenson developed the Program area further. In tissue culture in particular I think Stevenson, himself, played the key role. Before coming to NCI he was at the Navy Tissue Bank, where they were preserving bone tissues for bone surgery. And in those days we didn't even know how to freeze and thaw cells so they survived. So we put money into the Navy Tissue Bank along those lines before Stevenson even joined us. And a lot of developmental research was done to get the right conditions, which wouldn't have been funded through grants at all because it was development; it wasn't "really research." And the same thing with animals and animal husbandry. We didn't even know what the normal blood counts were in most of the primates. It turns out we almost overdid primate production, but at one time, you know, it was very important to evaluate specimens in primates. And we finally got so we could produce all the monkeys we wanted to in captivity and so, if we ever need that again we know how to do it, if everyone doesn't forget history. The other thing that I think was kind of interesting with the virologists from the polio field: I said, "You guys are great about exchanging your

virus preparations for checking on quality but, by the time you've done that, you don't have any left to work with. We need to make large quantities of it." "Oh, but industry can't do that. They won't be good enough." And I said, "Well, you don't have to use it if it's not good enough, but you can apply your same tests to it, but we need more quantities of it." And I remember when Moloney came in one day all excited. He says, "Hey, Pfizer has just produced wonderful virus stuff, better than anything we've done, and they've got buckets of it."

Kelloff: The Rauscher plasma virus. Right?

Baker: No, Moloney sarcoma virus. So I figured I was over the hump at that point.

Kelloff: Oh, that's great.

Baker: And Huebner influenced me, to some extent, on reagents. He was always pushing, "We need more of this kind or that kind of reagent," and I listened to him.

Kelloff: And Joe Beard was key in production of AMV at that time. Joe Beard. Yes.

Baker: So, I think people tend not to think about these types of items. This is not research, so it doesn't get the attention that the intellectual level of research does, but I think it's very important for helping the advances to be made. And the quality standards are essential.

Kelloff: Oh, yes. And to have people doing it that are interested in doing it to keep the standards up. That's important. Yes. You know, the people producing reagents were as important to Dr. Huebner as people doing other things, and they were always included as a collegial group in the meetings and everything like that. That's very important.

Baker: Well, we agree on that.

You probably have no grasp of the relative funding between the grants and the contract supported areas on relative funding?

Kelloff: Today or--

Baker: Then. I doubt if you do today either.

Kelloff: Yes. It's hard. I guess the Virus Cancer Program grew at its height to, what was it, $40 million?

Baker: I think it got up to almost $60 million.

Kelloff: Yes. That would be about 1973 or so.

Baker: Yes. When I was Director I funded it faster than anybody else, and then that's partly why I think it got killed. And we might as well talk about this a bit. A lot of people were concerned that Huebner had too much money; that these contracts were for his own personal research, which I think is an exaggeration. Do you have any comment on that?

Kelloff: Well, I think there were a few things that were going on that were a little bit of a concern. One is, as the program got large, where are the results for humans? And human investigation was begun possibly earlier than the science might possibly have warranted. And so, like anything, with that kind of pressure, he started funding things that maybe weren't ready and I think that caused some problems. There was a lot of pressure to do human studies when you didn't have the right human studies to do. You didn't have the isolates. It led to some isolates from humans that weren't human and it caused, I think, some problems. As far as centralization of resources in too few hands, when you have a grant situation of people on small grants and they see these large blocks of dollars under one person's, or five people's, control, that Dr. Moloney and others had, that's a natural reaction.

Baker: The quality and value of the output of the Program seems to have been obscured by these emotional reactions. The question of review of contract proposals compared to the review of grant proposals. Do you think that one was better than the other, or they were about the same?

Kelloff: I was an intramural scientist, but we had research support contracts that helped us with

a lot of our basic research, and I felt that we were site visited and reviewed about as much as anybody. So I felt as long as there is a system of peer review I think it will work, and did work. The argument against objection to too much money in too few hands is that if you need an organized program to follow a research plan, then somebody has to--or a handful of people--have to be overseeing it, and it is going to put a lot of power in a few hands. And that happened.

Baker: And in wartime that's usually the way we do it because we haven't got time to fool around with less efficient means, and I felt we were in a war against cancer and we should act accordingly. I may have gone a little too far in that direction.

Kelloff: When you look at how streptomycin and some of the antibiotics were produced in World War II, it was because you had a national emergency and--

Baker: And a few people controlled the thing. Yes, I admit, I thought we had a war on and we ought to run it like a war, but we didn't quite win it all, but it was a good time. This is an interesting question here, I think. If you could have changed anything, as you look back at all this, what would you like to have seen done differently? It's not an easy question.

Kelloff: Yes. That's tough.

Baker: Well, that's fine.

Kelloff: Yes, it's a tough one.

Baker: I guess we've already concluded that the Viruses Cancer Program laid the foundations for molecular biology and for biotechnology. Is that correct?

Kelloff: Absolutely. I think the reagents and the science produced in the '70s have had implications. The oncogene field is everywhere in cancer research, whether you're in therapy with drugs, or whether you're in prevention with drugs, or screening for cancer risk and early detection. A lot of that, out of the science of the '70s in the Virus Cancer

Program in the oncogenes has had consequences for the whole thing. I think even the AIDS situation, without the isolation techniques and the hard science of how to isolate retroviruses; I think you might still be looking for an AIDS isolate, without the '70s data in the retrovirus area. As far as doing things different, I don't know.

Baker: Okay.

Kelloff: I think it's important to get leaders that are multidisciplined, or are at least humble enough to listen to thirty experts, because there are at least--I don't know how many subspecialties of cancer research there are--but there are a lot of them.

Baker: Lots of them. That's why cancer is somewhat different than a lot of the other areas.

Kelloff: Yes, sir. And I guess I think in some ways the Virus Cancer Program was dismantled a little quickly, relative to--

Baker: Why do you think that is?

Kelloff: Well, it may have been this critique of too many resources in too few hands. I don't know what all the reasons were.

Baker: That was part of it, I'm sure. And then there is, of course, widespread belief in the academic science community that planning is bad in any form. And then the third thing is that most would like to see that money in grants. And those funds don't necessarily go into grants just because you cut them out, as people should have known by now, but don't seem to remember.

Kelloff: Yes.

Baker: Well, one final question is a broad question that relates to science in general, not even necessarily just to biomedicine, and that's the public's appreciation of science. Is the public better informed about science and understands science better now than in 1960, or less so, or about the same, in your impression?

Kelloff: Well, I think that health awareness and health promotion and prevention, the areas

where we're working, there seems to be a lot of lay press interest, and maybe I'm more aware of it now than I was, but it seems like even the national media have M.D. commentators on every day here, even reviewing *New England Journal* articles in the general news, so I would say there is probably more awareness. Yes, I would think there is. There are also more active groups that are interested in specific areas, I think. At least I feel that there are more.

Baker: Yes. I think that's true. That doesn't mean that necessarily the general public is more informed.

Kelloff: Yes, that's true.

Baker: I don't think it does.

Kelloff: That's true. Yes.

Baker: Television, for example, I think interferes with some of that information being assimilated, but maybe I'm wrong. In terms of funding, is the public more sympathetic to that, or less sympathetic? I think it's pretty clear we're going to have some reductions in Government spending whatever.

Kelloff: I think there is a real appreciation that prevention holds some promise. I don't know what will happen in the budgets.

Baker: Well, we'll see. Well, I've enjoyed the session with you and I thank you very much.

Kelloff: Well, I appreciate your coming and I enjoyed it. If I can help in any way, other people, names, or--

Baker: I intend to get transcripts made of this and edit them and what not, and then, if I can get that done, I'll get a copy back to you.

Kelloff: Thank you. Yes.

Baker: And, if you find something you said you didn't want to say, you'll have a chance to--

Kelloff: I appreciate that.