Holdenried, Robert 1995

Dr. Robert Holdenried Oral History 1995

Download the PDF: Holdenried_Robert_Oral_History_1995 (PDF 167 kB)

This is an interview of Dr. Robert Holdenried, who played key roles in the Viruses Cancer Program, taken on April 12, 1995. The interviewer is Dr. Carl G. Baker, former Director of the National Cancer Institute.

Baker: Bob, would you start us out by giving us a little information on your background, of where you went to school and so on?

Holdenried: Well, I got my undergraduate degree from Chico State University in Chico, California, and a Ph.D. at the University of California, in parasitology.

Baker: At which campus?

Holdenried: The Berkeley Campus.

Baker: Well, that's interesting, because I went to Berkeley for my biochemistry and I somehow didn't realize you were at Berkeley too. When was that?

Holdenried: I got my degree in 1950.

Baker: Well, I'd already left.

Holdenried: I didn't attend graduate school during the war, and I was with K.F. Meyer and had the responsibility of keeping the mice going that were used for the plague vaccine that was being made there at the Hooper Foundation. And we needed a strain of mice that was fairly uniform in reaction to the strain of plague that they were using. And so, after the war ended, I asked Dr. Meyer whether I could go to graduate school then, and he was all in favor of that, and so I then started to graduate school. And I must say that I spent a good deal of time with my classes that probably should have been devoted to the Hooper Foundation, but he didn't seem to object.

Baker: He must have been an interesting fellow to work with, from all I saw of him.

Holdenried: Yes. He was very stimulating at times. And he was known all over the country, all over the world really. After I got my degree I spent 6 months with a Mosquito Abatement District studying the biology of *Aedes aegypti*--not *aegypti*, gosh I've forgotten the name now--that's responsible for transmitting some of the encephalitides in the Central Valley of California.

Baker: Was this with the Army?

Holdenried: No. This was with the State.

Baker: State of California?

Holdenried: I had the opportunity to join the U.S. Public Health Service and was assigned to the Plague Lab at San Francisco with the understanding that I was to develop a field study of rodents and try to figure out any relation that the rodents had to maintaining plague and to tularemia in their populations. After touring the Southwest trying to find a place for locating the station where the studies could be done, we selected Santa Fe, because the State Health Department was very anxious that we come there. And we started out with an entomologist and myself and two field people and an excellent secretary. And we spent 3 years there, and that was long enough, and the study was closed. I was assigned as the Liaison Officer for the Public Health Service to the Dugway Proving Ground in Utah, the place where they tested biological agents in the countryside outside the laboratory. My main function there was to assure the Director of State Public Health that the Army was conscious of the civilians that lived in the area and were making a supreme effort to keep them from being exposed to any of the agents. Fortunately, during the time I was there, nothing untoward happened. We also had an extensive study of the ecology of the area, the Dugway Proving Ground and the surrounding area, under contract to the University of Utah, and I was put in charge of that study. After 3 years I was transferred to Ft. Detrick, where the principal research and development of biological agents occurred, and I was Liaison Officer there for 3 years. Then, in 1960, Harvey Scutter, who had been Executive Secretary of the Viruses and Rickettsiology Study Section, was heading a grants program on viruses and cancer at the National Cancer Institute, and said he would like to have somebody come in and take over the program on the animals to be supplied for these studies and asked if I would do that. I was happy to be able to be free at the time, so that's how I got in the Cancer Institute. That's about it.

Baker: Very good. I realize that some of the questions we've drafted here as a basis for interviews don't always fit your situation, but we can use them as kind of an outline of the interviews. So I've been asking for names various people who come to mind when we ask who were the leading scientists and what main contributions did they make in this period of 1950 to 1980. As you recall, in 1950, nobody thought viruses had anything to do with cancer at all. About the only thing that had happened before that time was the Rous discovery of virus-producing chicken tumors which people said couldn't be tumors, real cancers, because it was caused by a virus. And then Shope had done some work with some of the other animals, including rabbits and swine, and Ray Bryan sort of kept the flame alive during this period when nobody paid much attention to viruses and cancer. Joe Beard, at Duke, was another one. And then you had the Bittner virus which seemed to be involved somehow in breast cancer, and that was about it in 1950. So, we had a change taking place a few years after that. Who comes to mind from your perspective of some of the outstanding people?

Holdenried: Well, I'd say the one I was most closely associated with was Bob Huebner. I guess he was one of the more vocal ones also.

Baker: A very interesting fellow.

Holdenried: And he was, of course, extremely interested in trying to standardize the animals that were used for study, for research, in the virus in cancer programs. He fully realized the disadvantage of using mice that had untold viruses of their own and he was one of the first supporters, really, of trying to develop mouse facilities and mouse colonies that were fairly well virus-defined. Of course, Ray Bryan, I was personally associated with, and he also was very interested in these programs. From the outside, who was the fellow that played the piano? He was a Nobelist, I think, and what he did with his money, he bought a grand piano the first thing. He was from CalTech, I think.

Baker: I'm not sure I know that story.

Holdenried: It was Dulbecco. We also tried to develop reagents for detecting viruses in these animals. The reagent field was particularly bad because most of the reagents themselves had so many components in them that trying to absorb some out so you could use them didn't work out too well.

Baker: Yes. I kidded some of the virologists from the polio area by telling them they were excellent in exchanging samples with each other to check on the quality but, by the time they'd done that, they used up all of their virus preparation and didn't have anything to work with, and we needed to get larger volumes, and that's what led to the contracting in that area.

Holdenried: Yes. Well, we were lucky to get Carski. What was the company? The Baltimore Biological Laboratories. And he made polyomavirus antisera in goats, and we had gallons of antisera. And that's where this fellow up here in CalTech, he was a very big supporter of our program because he worked with the polyomavirus and a lot of his studies were in this, and he could get this antisera and it simplified his work a great deal.

Baker: When you started working with Huebner, had you been working with Moloney and Rauscher before that and Bob Stevenson?

Holdenried: No, I don't think so. You see, we were started with Scutter, whose program was--

Baker: Was grant-supported.

Holdenried: --grant oriented. Yes.

Baker: So Scutter is the one who recruited you to come to NCI?

Holdenried: Yes.

Baker: And so you worked in the grants area for a while?

Holdenried: Actually, Endicott assigned me there and I think I was with the postdoc training program in grants, and I kept telling him I wanted to work on this other program, that I was spending too much time with this postdoc, and he kept ignoring it. But I finally wrote him a letter, I guess it was a memo, so he relieved me of that duty, and that was the last that I had with that.

Baker: I gather Scutter was a little unhappy when--and I gather it was Endicott's decision--to convert a lot of the program from the grants area into the contract-supported area?

Holdenried: Yes, he was. And I think part of it might have been the way--though I'm not sure--Endicott used a very abrupt method of doing it, and it did certainly stop the Virus in Cancer Program that we'd started. In fact, we were sitting around for several months wondering what was going to happen.

Baker: Well, I got to know Scutter a little bit when I worked in Building 1 with Dr. Smadel for a while. There was a million dollars in NCI grant funds earmarked for cancer viruses work and we were trying to interest some of the people from the polio field, which was drawing to a close from a research standpoint, into coming into the cancer field, and we had some success with that. The V&R Study Section reviewed the proposals that came in at that time and I got to know Harvey Scutter through that a bit.

Holdenried: Well, I guess that V&R Study Section continued to play a part in the whole program, individually as contractors and certainly as people to discuss the programs with.

Baker: You never had anything to do with Ludwig Gross and Sarah Stewart on the polyoma side?

Holdenried: Well, Ludwig Gross, we did supply him materials, but never directly.

Baker: But you ended up in the Special Virus Leukemia Program, didn't you, at one point?

Holdenried: What's that program?

Baker: Well, do you recall there was a request for $10 million dollars for a Special Virus Leukemia Program, which was in 1964, and that is what formed the nucleus when Scutter was unhappy about moving some of the program activities into this Special Virus Leukemia Program.

Holdenried: Scutter was long gone by then. He didn't last more than one or two years. He must have been gone by '62 or '63.

Baker: Well then, I may be wrong on the date, because he was still there when the Special Virus Leukemia Program was set up (1964), and that's why he was unhappy that some of the program activities were moved into that area. And this was a special request for $10 million dollars which, in those days, of course, was quite a big bite to add on top of the budget. And Endicott is the one who really made the decision to go request that, and he had to get Shannon's approval first, and Shannon insisted on our documenting the factors that would make justification for requesting that special appropriation. And so Rauscher, Bryan and I, and I think Zubrod reviewed some of the documents, put together the justification for this request. And Shannon bought that idea, but he wanted some more data, which we sent him, and that was the beginning of the Special Program which Bryan headed at first, and he didn't take to the administrative side too well, so Rauscher became the head of that program, and Bob Stevenson was in that program heading up the resources developments.

Holdenried: Oh, yes. You see, Bob Stevenson came along several years after Scutter was gone.

Baker: At least two years, I guess. Yes. So, what happened to you then along in here?

Holdenried: You see, through all this turmoil my program just continued as though I was still working with Scutter.

Baker: So you were still in the grants area?

Holdenried: No, no. It was in the Program.

Baker: So they moved it in?

Holdenried: Yes. They just took the whole thing over and I just worked the same.

Baker: So you just did about the same sort of thing, except the funding was different?

Holdenried: Yes. Except not working for grantees entirely; it was largely now with the people that were working as--

Baker: Contractors?

Holdenried: Contractors. Yes.

Baker: Did you feel there was a big difference there?

Holdenried: Not really. Not really.

Baker: Yes. I'm not sure I saw all that big a difference that a lot of people assumed.

Holdenried: All through the Program I tried to do things that seemed to be useful and that seemed to work, seemed to get a positive response from the researchers. I didn't try to build any empire or anything. I just tried to please them. And it seemed like it worked.

Baker: Well, I think you did a good job.

Holdenried: I was surprised when you had that meeting a couple of years ago and so many of the people came up and spoke to me and said how much they appreciated what I had done for them, and I could hardly remember who they were.

Baker: Well, I wish they would have made that more public, because there are a lot of people who think the areas involving contract support are somehow at a lower level than the grants activities, particularly the academic community, and my feeling is we need both kinds of things, not one or the other.

Holdenried: Amen.

Baker: So you were concerned primarily with animal production?

Holdenried: Yes. And animal viruses. In all these shifts and things I sometimes also had human tissue resources to take care of, and sera, and things like that, but it was all in the same line.

Baker: Well, I think we've already talked about some key administrative or management decisions that affected this, and I think people who were down at the working level didn't always appreciate Endicott's key decision-making in some of these things because they were far enough removed they weren't always sure who made the decisions, I suppose.

Holdenried: Well, in retrospect, it would have been of less concern for the staff if it had been a clearcut shift where a little piece of paper comes along and says, "This is what we're going to do." I guess maybe he didn't know either.

Baker: Well, once this got started, he came to me and said, "You and Carrese have been talking about planning, plan me a $10 million dollar program," since it looked like we were going to get the $10 million dollars, and that set fairly clearly what the program was all about. It didn't clarify any administrative relationship particularly, but it did the scientific ones.

Did you have any thoughts about the planning of the Viruses Cancer area?

Holdenried: No, I didn't. I think, in order to really think about that, I'd have to understand more about what the people were doing in cell biology, which is kind of beyond me. The terms were hard for me to understand, and sometimes I'd come back and wonder what in the world the people were talking about. Now, the funny thing is, when I came back and talked to the people who were supposed to know, they didn't seem to know either.

Baker: Oh, really? I wonder who that was. Do you have any remembrances of some of the advisors, either as individuals or as advisory groups? We had plenty of meetings we had to go to with an awful lot of committees.

Holdenried: Well, I can't go over this without mentioning how fortunate we were to get Les Murphy, a veterinarian, from the Army. He was a really smart, conscientious and very nice person to have, and he certainly helped our program a great deal.

Baker: Which Murphy?

Holdenried: Lester Murphy.

Baker: Yes. I didn't know him.

Holdenried: We had him for three years on assignment and he was supposed to go back to the Army then and they were going to send him to Okinawa, he said, to do artificial insemination with the cattle there, and he couldn't see that, so he retired and went to be Vice President of the University of Missouri and ended his career there.

Baker: Do you know Riley Housewright?

Holdenried: Oh, yes.

Baker: I assumed you must. He was, I guess, head of Detrick for a while.

Holdenried: Yes. He was the Scientific Director. Yes.

Baker: Yes, that's right. Anybody else comes to mind that sort of stands out in your memory?

Holdenried: Well, it's sad to say there aren't, but I know there were several that were outstanding.

Baker: Well, you know, there were some people that thought the contract proposals didn't get as good a review as the grants. What is your view on that?

Holdenried: Well, I've sat through both, and I think they got a very good review by the review groups.

Baker: In both cases?

Holdenried: Both cases. Yes.

Baker: Yes. That's my impression.

Holdenried: Both of them were subject to influence by people who had some personal interest in them.

Baker: Well, you can't get rid of all of that. In fact, one of the great conflicts about peer review is how do you get the best people to review and not have potential conflicts of interest? And in the early days of science I think we had enough respect for each other that that really wasn't a very serious problem.

Holdenried: I think the contract work must have been a lot more satisfactory for the staff than the grants because it worked so much quicker.

Baker: Well, it did in the beginning. It apparently doesn't now.

Holdenried: Oh, well, I don't know anything about that.

Baker: Because you keep adding all these regulations on top of the old ones?

Holdenried: Well, we could get contract proposals in and have them operating within 6-9 months. It didn't happen very often.

Baker: Which still seems long.

Holdenried: Well, with grants you couldn't do that.

Baker :Yes. Do any political figures come to mind here that played a role in this area, and I use "political" in two senses. One is the ordinary politician in Washington, but I'm also talking about scientific politicians. Mary Lasker and Sidney Farber come to mind as two very supportive people who I would call working politically primarily.

Holdenried: Yes. I was aware of who they were and some of their influence on the Program but, from my point of view, they didn't have much effect on it directly.

Baker: Well, that's as it should be.

Holdenried: Yes.

Baker: In fact, I worry about political decisions being made at NIH now on scientific matters.

Holdenried: The first time I was aware of the politics of it was at a--what's the cancer research organization?

Baker: The American Association for Cancer Research.

Holdenried: Yes. That's it. They were holding a meeting in Boston and Nixon's daughter Tricia came to address the meeting on something about a change in the Program. Well, it was more than that. It was putting the Cancer Institute under the direction of the President really. And all these Secret Service men came in and I said, "Oh, my God, here goes politics and science." I had a rather odd feeling.

Baker: Well, when you get a budget as big as NIH and NCI now you can't expect there not to be a fair amount of politics involved.

Holdenried: I guess not.

Baker: But, in our day, it wasn't quite so bad.

Holdenried: Well, it was the first time I'd seen anything like it.

Baker: Well, the next question I turn to is how significant was the availability of quality controlled resources? We've intimated that it was hard to get enough high-quality reagents, tissue cultures, animals, antibody preparations.

Holdenried: I don't know how important it was. A lot of people began to think and talk about it though, and how much progress-- Well, tissue cultures particularly. I can remember that fellow that had the big tissue culture lab at Roswell.

Baker: Yes. Roswell Park and George Moore.

Holdenried: Roswell Park. And the trouble he went to keep from contaminating his different cultures, and then the problems that he had in spite of it. And also I learned pretty quick that germ-free mice was a dead field to follow because you couldn't use them because it was impossible to maintain a germ-free colony, yet alone try to do research with it.

Baker: Well, I think they did some nutritional studies that were pretty well controlled, as I understand it.

Holdenried: Well, you could work and keep certain agents out, but you couldn't keep a colony of mice going without getting something from the outside in very soon.

Baker: How long are we talking about? Weeks?

Holdenried: In the matter of a few months.

Baker: I guess I didn't realize it was that difficult.

Holdenried: Yes. It was. We tried to develop what might be a commercial colony of germ-free mice with Carworth Farms and it just wasn't possible.

Baker: Well, I notice this book we were talking about here earlier has the biohazards symbol on it. Do you know the origin of the biohazards symbol?

Holdenried: I know I did, but I can't tell you now.

Baker: Well, most people don't know the story. But there was a contract, a small contract, in the Program to develop a hazard warning signal for biological materials, which we didn't have. We already had the radiation hazard symbol. So, this small contract evaluated about 60 different symbols and did some field trials for measuring which ones people would recognize and remember. The biohazards one that we all see everywhere was the one that won in that competition.

Holdenried: Who was that?

Baker :I don't remember. It was some little firm, small business firm.

Holdenried: Oh, it wasn't anybody from the--

Baker: No. It was psychologists, primarily, that were in this firm that did this sort of thing. So, that's a little side issue that a lot of people don't know about that is kind of interesting.

Holdenried: It's well distributed now.

Baker: Oh, very much. So, do you feel, or not, that the Program--I guess this is a loaded question--that the Program provided reagents that were of high quality that were not available before, some of which were eventually moved into commercial production?

Holdenried: Yes. I think it did. One of the problems, I think, is that so few of the laboratories were equipped really to fully utilize this kind of material, and they looked toward some of the labs here as being able to do things that they couldn't. I tried to arrange one time for one fellow who claimed he had the virus for human cancer to come and work in Todaro's laboratory. I thought maybe Todaro would do that. He said, "Sure, I'll do it," but the fellow who wanted to do it says, "I don't want Todaro to get the virus until I get this all put together and published." And Todaro said, "Well, he can't come and work for my lab."

Baker: Well, I can see either side of that one, I guess. I think that a lot of the biotechnology of today really rests on some of the developments that were made in the Program. Is that a fair assessment from your point of view, or am I feeding you loaded questions too much?

Holdenried: No. That's right.

Baker: How about molecular biology?

Holdenried: Well, that's kind of beyond me. I've heard a lot about it, but not in the Program.

Baker: Well, we certainly shifted, with particularly the Temin and Baltimore findings of reverse transcriptase, but to some extent some of the work in the Pprogram made a real transition from interest in viruses and cancer to interest in the genetic coding and cancer. But, of course, Bishop and Varmus made the link there by showing that the genetic coding in some of the cancer causing viruses had the same, or approximately the same, sequences in the genetic code in mammalian cancers. So you really shifted the whole outlook by making a marriage, I think, between biochemistry and genetics which really gave you the foundation for the switch to molecular biology. There are still a lot of biochemists that say there is no difference between molecular biology and biochemistry, but there is a difference, I think, on the melding of genetics with biochemistry to form molecular biology. Were you aware around '55 to '80 of the relative amounts of funding in grants compared to contracts in the Viruses Cancer field? Few people seem to be aware of this.

Holdenried: That was something I wasn't really faced with.

Baker: Yes. Not many people know the answer to that question and I'm going to have to look it up in detail, if I can find the proper information. You already mentioned one area where you thought a little more communication might have been in order for creating certain changes. If you had the power, and you looked back, is there anything you would have done differently from what you did in those days, or that you thought the program should have done differently? That's a tough question.

Holdenried: I would have probably not succeeded at all, but I would have tried to get the scientists to be more cooperative.

Baker: Get the who?

Holdenried: Scientists.

Baker: Well, I thought another accomplishment of the Program was it improved the communication among the scientists via the annual meetings and what not. It still was hard?

Holdenried: Yes. When you see scientists get off in the corner and whisper to each other. Oh, gosh.

Baker: Well, they're humans too. You know?

Holdenried: Each one of them were thinking of Nobel Prizes.

Baker: I thought they shared reasonably well, those that were very active in the Program anyway.

Holdenried: I had just hoped there would be more sharing than there was.

Baker: Of course, what I was trying to do with the planning on the National Cancer Program, when Nixon signed that into law, with these big meetings at Airlie House included attempts at better sharing of information and at better collaboration--I don't know whether you remember those or not--

Holdenried: Oh, yes.

Baker: That was an attempt to improve the communication and get some sort of *esprit de corps* like that I thought NASA had.

Holdenried: I think it did.

Baker: Well, but I wasn't there long enough. They didn't really have that kind of meeting after I was no longer the Director, so I don't think it ever got pushed the way it should have been.

Holdenried: I wasn't even aware that there was a shift. Maybe I stepped out too before--

Baker: Well, when Benno Schmidt was head of the President's Panel, he was convinced by the academic scientists that he ought to do away with the Viruses Cancer Program planned approach, and go back to using that money in grants. So that's what I meant by the shift. But that was after we'd both left, of course. Well, I'll ask you one general question here. This tenth question is not just about viruses and cancer, but about science, in general, not particularly biomedical science, but science generally, and that's a question of the public's perception and understanding of science today compared to back in, say, 1960. Is it the same, better, worse? Also is the sympathy for science by the general lay public any different today than then?

Holdenried: Well, I can't really tell you. With respect to the people that I associate with and know in the family, I'm amazed at what our grandkids understand about it.

Baker: This is what Dr. Zubrod told me.

Holdenried: And my son and daughter-in-law, what they understand and talk about is certainly more than you would expect since none of them are biologists. But, in general, from what I read in the paper, I would think that it's probably regressing with, for example, the creationists.

Baker: Alternative medicine is one that bothers me.

Holdenried: Oh, yes. That's another one.

Baker: And I'm very sad that NIH has created an Office of Alternative Medicine because of pressure from a Congressman. Does that bother you?

Holdenried: Sure it does.

Baker: Why?

Holdenried: Well, I don't think they ought to be at NIH. Somebody else can do that and leave NIH where it's supposed to be.

Baker: It's not science.

Holdenried: Yes, I agree.

Baker: Well, maybe they're trying to get some science in the review of clinical trials, I guess. I thought maybe it might be a good idea if we had a well-controlled clinical trial on acupuncture. But then, as I looked into it, I found out that there is no good agreement on what constitutes acupuncture. So, if you did a trial and it didn't show any difference with the controls, they'd immediately say, "Well, you used the wrong kind of acupuncture," and so it goes on, and on, and on. And homeopathy, I thought, was laid to rest long ago, but apparently not. I understand they made $13 million dollars' worth of grants in this area already!

Holdenried: Yes. You mean from the Congress, or did they get money--

Baker: It was part of this Office of Alternative Medicine. It's appropriated monies. Your tax monies, as we say.

Holdenried: I can see where some people are very positive about that, "I got cured by doing this, and other people ought to be able to do the same thing."

Baker: Do you think the public is more or less sympathetic to funding science now compared to 1960?

Holdenried: I would say less, just reading the papers.

Baker: As one of the interviewees said, the amount of information available now is better. For example, *The Washington Post* on Mondays have very good science reporting, but that doesn't mean as many people are reading it necessarily. So, we'll see. Well, the last question is a general one. Do you have any other comments or points you'd like to make, or anything you want to say?

Holdenried: Not really. You know, this is far back, but I must say that, by and large, I enjoyed my association at the Cancer Institute. The last two years weren't so good, but I was really delighted with most of it.

Baker: Yes. We had a good time. We met a lot of fascinating people and got to work with good people and the insistence on quality at NIH was, I think, important.

Holdenried: And the reception you got around the country in meeting all these people. In my case it was always very favorable. I was amazed at how much they went out of their way sometimes to talk to you.

Baker: Well, I thank you very much for your time and your comments.

Holdenried: I hope it just isn't wasted.

Baker: No, no.

Whereupon, the interview concludes