

This is an interview of Dr. Harold Varmus, Director of the National Institutes of Health, taken on August 31, 1995. The interviewer is Dr. Carl Baker, former Director of the National Cancer Institute.

Baker: Dr. Varmus, we certainly appreciate your taking time to tell us a little bit about your views about the Cancer Viruses area. As you know, there was quite a change of outlook, around Ludwig Gross' findings, and Sarah Stewart and Bernice Eddy's *Polyoma* findings because, before that, nobody thought cancer had a bearing on viruses or vice versa.

Varmus: Peyton Rous did.

Baker: Yes, except for Peyton Rous. And Ray Bryan and Joe Beard kind of kept the flames alive during that period. So, my first question, which you've already received, dealt with the main four or five findings in this field and who made them and who you thought the outstanding scientists were. Obviously you and Mike Bishop are included in that list, but who else would you indicate as key scientific persons and their findings?

Varmus: Well, I'll have to say I don't remember receiving a list of questions from you, so you'll have to just ask the questions again.

Baker: Well, the first one dealt with what were the five leading findings in this field from 1950 to 1980, and who made them?

Varmus: Well, okay. I didn't actually think that through.

Baker: This came with the letter, I think.

Varmus: I may just not have read it, once I agreed to do the interview. Let me see. One of the things that's, of course, difficult for someone like myself who is not an historian of science, but simply a player, is that we tend to think about the great moments as being moments that occurred when we were active players in that field. So, you know, the significance of some of the earlier findings I only appreciate the way anybody would, in

retrospect, and what really had an impact on me were things that happened while I was working in the field.

Baker: Yes. One reason we're interviewing several people is to get a balance of that.

Varmus: Right. Sure. So a certain amount of stuff that seemed important--a lot of the things that seem important to me--are things that occurred just before I entered this field of viruses and cancer, or just afterwards. Perhaps a couple of words of my own background are pertinent here since you're phrasing the questions in this way. I had been trained as a medical doctor, and began medical school with an interest in psychiatry. I gradually moved more and more towards internal medicine and then laboratory research. I came to NIH very naive about science, never having done any significant scientific work until I was 28 years old. I worked in Ira Pastan's laboratory on regulation of the *lac* operon by cyclic-AMP and, during that period at NIH, took a lot of courses in science and was exposed to many things I knew very little about. And in the course of my exposure to a variety of things I was quite excited by my readings in one course that was given by John Bader that concerned virology fairly broadly and cancer viruses only in a minority of the lectures and in another course given by Michael Potter. Both of these courses raised questions about the molecular basis of cancer that seemed to me highly approachable through some new techniques that I was using in the study of bacterial molecular genetics.

Baker: So, most of these courses were taken here at NIH?

Varmus: Oh, yes. These were NIH night courses. I think they had a big effect on most of us who came to NIH in that period. I think in those days the courses were particularly energized because the students were people in their late 20s who had been through medical school, very smart people, who were somewhat under-supplied scientifically and were as excited as high schoolers about things that suddenly were more meaningful

to them because they had a very strong medical background. In any event, the prospect of using techniques of molecular hybridization and other molecular avenues toward the exploration of genes was an energizing influence. And I think what drew people like myself to viruses as a means to explore cancer was the fact that viruses were simple organisms. Although I wasn't around when *Polyoma* was discovered to induce tumors, one of the things that energized a lot of us was the fact that the viral genome had been shown by Jerry Vinograd and others to be very small and unlikely to harbor more than a few genes. There was also increasing evidence from the work on the RNA tumor viruses that their genomes were also pretty small. So, this seemed a very attractive way to get into the problem. I certainly started working on it without any illusion that viruses were going to be a major cause of human cancer; but they were dramatic experimental tools for trying to simplify the problem of cancer. All of us who had training in genetics were very wary of trying to do what had been done on a very large scale traditionally, that is, to compare the metabolic properties of cancer cells versus normal cells. Instead, we went and looked for simplifying principles. And the ability of a virus to transform a cell through the use of a very small number of genes was the electrifying aspect of viral oncology.

Baker:

But I think you said you didn't think of it as cancer research at the time. You sort of--

Varmus:

Well, I thought it was cancer research. I just didn't know whether or how it was applicable to human cancer, but I definitely thought it was cancer research because, just as I had learned from work on bacteria that one could begin to understand at least one of the ways in which cyclic-AMP controls gene expression by looking at a heavily studied gene like the *lac* operon in bacteria, I hoped that by looking at cancers in chickens and mice that were induced by viruses that we'd learn something about how cancer was caused more generally, whether it was viral in etiology or not.

Baker: You started this before Baltimore came out with his reverse transcriptase or right after that?

Varmus: No. I'm actually coming to that now. I took the courses I mentioned in the late '60s, mainly '68 and '69. I felt I wasn't going to compete very effectively in bacterial genetics in the long run, I didn't have the right kind of training, and frankly, with my medical background, I wanted to work on a problem of vertebrates. So I began looking for postdoctoral positions that would allow me to work on tumor viruses. I considered actually quite a few types of tumor viruses. I wrote to Dulbecco, who was working on *Papovaviruses*, and I thought about *Adenoviruses*, and I was interested in RNA tumor viruses, as they were then known, and went out to see a lot of people, especially in California, because I was interested in moving to California. Just at the time that I made my move from NIH and from bacterial genetics to California to work on tumor viruses, two incredibly important things happened: One was the isolation by Steve Martin, who was then in Harry Rubin's lab at Berkeley, of a mutant of Rous sarcoma virus that was temperature-sensitive for transformation but without any effects on replication. This, to me, was an extremely important result -- both at the time and in retrospect -- because unlike DNA tumor viruses, which do exhibit TS mutants, but mutant for both replication and transformation, these mutants dissociated the growth of the virus from the oncogenic properties of the virus. That, I thought, was remarkably important. The second thing, of course, is the better known phenomenon of the discovery of reverse transcriptase providing proof--or something tantamount to proof--that retroviruses replicate through a DNA intermediate. Now this was, in a sense, a disappointment to me, because one of the reasons I had decided to study RNA tumor viruses was that I felt that molecular hybridization technology had improved sufficiently that it would now be possible to test Temin's provirus hypothesis with a

new tool. So, on the one hand, the discovery of reverse transcriptase provided a better tool for making probes for molecular hybridization, but, on the other hand, it pretty much established in the minds of most people that Temin was right all along and the provirus hypothesis was correct. Now, one could argue that the discovery of this enzyme was not proof that the provirus existed; you still wanted to demonstrate it by physical and biological means. The existence of an enzyme that could make the provirus wasn't the same thing as finding it. But, I think all of us understood that that was the seminal finding. People who came after Temin and Baltimore, as I and many others did, to characterize the provirus would be playing an important, but secondary, role to this seminal discovery. So, in this discussion I've named a few things that I think were really important. One, of course, was the work by those pioneers who actually found some of the viruses that we all cared to work with, and that was Peyton Rous, Wally Rowe, those who were instrumental in finding the *Papovaviruses*. Unlike some of the other viruses that proved to be very important in human oncology--hepatitis viruses, *Herpesviruses*, and *Papillomaviruses*--it was the experimental viruses that drew a lot of us into this field.

Baker:

When you were still at NIH, did you have much to do with Huebner and his group?

Varmus:

No. None actually. I was interviewed by Huebner before taking my position with Pastan. I interviewed with about 18 people when I came for that early visit. But I had essentially no contact with Huebner when I was here. My orientation was all toward basic biochemistry, molecular biology, and I had much more contact with people in Nirenberg's group and with Gellert and Todd and with many people who were in my lab Branch -- Ed Rall, Jack Robbins, Ira Pasten, and Jesse Roth. In addition to the people who made these pioneering discoveries of the viruses themselves, Harry Rubin, Steve Martin, Temin, and Baltimore were the key players in subsequent discoveries that

influenced my choice of problems to work on. Now, the work that had been done with endogenous viruses by Todaro and Huebner did prove to be of some use in my thinking--and in Mike Bishop's thinking--about the origin of transforming genes. Mike and I disagree a bit about the extent to which those ideas influenced us. Mike thinks they hardly influenced us at all; I think that one of our intentions in doing the experiments we finally did to demonstrate the existence of cellular proto-oncogenes was in response to a desire to determine whether or not Huebner and Todaro's ideas about viral genes and oncogenes were correct.

Baker: So their paper, even though it wasn't quite right, had some maybe influence on thinking about that?

Varmus: It certainly had an influence on my thinking, and whether it had any influence on Mike's I'll leave for him to judge. But, you know, I think it was actually not a matter of being not "quite right". I think the fundamental proposal was wrong, and wrong in a perfectly legitimate way, but I think you have to say it was wrong in that what I saw as the most important aspect of the model was simply incorrect, but a perfectly legitimate proposal to have made.

Baker: Fine. I think that covers that first question. The second question deals with administrative or management decision-making. You probably didn't have much input on how that came about?

Varmus: I would say just about zero.

Baker: That's happened.

Varmus: You know, my collaboration with Mike arose in an interesting way in that when I went out to California--this is an important part of our own interaction, the way our joint laboratory arose--I went to California looking for postdoctoral positions and I'd never heard of Mike Bishop. I'd never heard of anybody in that group in California, except

for Leon Levintow, whose name I knew because he had recently left the NIH. And when I went out to California and visited Harry Rubin in Berkeley, I realized that I would have trouble trying to work in Harry's orbit. First of all, I didn't want to live in Berkeley, I wanted to live in San Francisco. Secondly, Harry struck me as much too eccentric for my own taste, and I wanted to begin in a relatively conventional setting, maybe having some unconventional thoughts in that setting. I didn't want to start in a setting that was so antagonistic to major themes, especially when the big themes that seemed to be emerging, that is the discovery of reverse transcriptase and the use of TS mutants of *src*, were things that I thought one shouldn't be rebelling against. These were tools that were going to be incredibly powerful and I didn't want to start with a negative mind-set. So I had really very little interest in working with Harry, but I did have a big interest in being in the Bay Area and living in San Francisco. Rubin said I ought to go over and talk to some young folks, including a guy named Warren Levinson, who had recently gotten a degree with Harry and was working in a group with Mike Bishop and Leon Levintow. I stopped by there and it was apparent from just a very brief conversation with Mike that here was a kindred spirit, and I started there as a postdoc. I think I was even officially sponsored by Leon Levintow on some of my applications, but it was clear I was really working with Mike.

Baker: But you really didn't have a mentor? I mean Leon wasn't exactly a mentor. He was--

Varmus: Yes. Leon was a spiritual advisor, and he was definitely a mentor with respect to virology in general, but he knew much more about *Poliovirus* than he did about the viruses I was working with. We were all exploring at that point. Actually, Warren Levinson had the greatest experience with Rous sarcoma virus of anybody in that group, but I think the important issues here were not the virological ones so much as the molecular biology. And, although UCSF was at that point not nearly as strong as it is

now, there were people there like Brian McCarthy and Bill Rutter and Gordon Thompkins who provided a very strong environment in which to do this kind of work. In any event, because I had come there as the most junior of the four of us who became the faculty in that area, I was carried on initially through the grants that had already been awarded to this group, and I really didn't worry too much about the source of funding. It was a good time to be an NIH-supported investigator, and Mike--I believe it was Mike, or Leon--but I think Mike was the PI of a large grant to which all four of us put our names and then, negotiated mainly by Mike, we had a contract through Huebner's program. I always thought of this contract as slightly tainted because it was gotten in a sort of less competitive, more sort of you-scratch-my-back-I-scratch-your-back manner. I was never very happy with it. But it was a fair amount of money. I remember going to some of these contract meetings at Hershey and feeling this isn't the way I really wanted to get my money over the long haul, but it kept us pretty well supported. I also had an American Cancer Society grant. But getting money was not really a problem in those days.

Baker: And you probably weren't very aware of who some of the, shall we call them, "science politicians" were during this area?

Varmus: No. Very little.

Baker: Or some of the committees that we had?

Varmus: Well I was on, actually, the Breast Cancer Committee that was reviewing contracts for breast cancer, and I was quite aware that the quality was pretty low and we were awarding a lot of low quality stuff. But those were different days.

Baker: Well, we might turn to resources. One of the main functions of a lot of these contracts was to produce resources that seemed to be needed and were not available at that time.

Varmus: Yes. I remember we used to deal with Jack Gruber in getting things.

Baker: Well, but this all got started well before Jack Gruber.

Varmus: Oh, probably. Yes. But I mean--

Baker: As a matter of fact, this large grant and the contract that you had, that you were on, at San Francisco provided a number of resources which you may not even be aware of.

Varmus: Oh, I'm quite aware. The main thing was virus, was getting virus every week.

Baker: Among other things. But tissue culture cell lines were kind of a mess earlier with contaminations and it took a lot of work to get that straightened out.

Varmus: Well, we actually didn't make very much use of those. We were mainly working with chicken embryos we made ourselves and we got a lot of our cell lines through Peter Vogt, who was a close collaborator at the time, So we were not major beneficiaries of cell lines. I think the biggest thing for us was getting these major shipments of concentrated Rous sarcoma virus.

Baker: Well, at first we couldn't get most of the outstanding scientists to agree that industry could produce sufficient quality, but I found that they were giving away to each other, for testing, what samples they had of the virus preparations and they didn't have any left to work with. So it was obvious that we needed a lot more quantity. And we went down the industrial route, and we had to convince a lot of good scientists, including some here, that that quality could be produced. And the point was, "Well, you guys test it. If it doesn't meet your standards, obviously we're not going to expect you to use it."

Varmus: Yes. Well, we used it for--

Baker: So that took more doing than probably is evident now.

Varmus: Well, maybe. I mean, our view of the kind of thing that we got from the Contract Program was that we needed the stuff in such large amount that quality wasn't that much of an issue. That is, we needed viral protein.

Baker: Well, it was with us.

Varmus: Yes. But we did a lot of labeling of virus and that, of course, we had to do ourselves.

And, you know, for high-quality, small amount of stuff we made it ourselves. But there was no way we could grow virus in the kind of bulk that was required for certain things, like making large amounts of viral RNA, or trying to make viral proteins in abundance, so it was definitely useful. On the other hand, I also was working at that time on--as I am now--on mouse mammary tumor virus, and some reagents were forthcoming from the program, but a lot of the stuff we had to do ourselves, or through Jackson Lab, or through other collaborators like Nuvul Sarkar and Bob Nowinski. But, there was a time when I was being supplied with considerable amounts of mammary tumor virus that I certainly couldn't have produced myself, and that was important for us.

Baker: You probably didn't have much input about the activities of the committees and the councils, on how their decisions affected any of this?

Varmus: No. As long as the money kept rolling in, I didn't worry.

Baker: Well, at your stage of things, that was appropriate, I guess.

Varmus: Well, in '76, I became a study section member and, of course that--

Baker: Which study section was that?

Varmus: Virology. Claire Weinstock was the Exec. Sec.

Baker: Who was the Exec. Sec. on that? Do you remember?

Varmus: Claire Weinstock.

Baker: And the Chairman?

Varmus: Well, we had--

Baker: It's hard to remember all these.

Varmus: No, it's not so hard. We had different chairmen. The Chairs while I was there were Bob Haselkorn and Purnell Choppin, who remain very close friends of mine.

Baker: This was all after my days. Yes. You weren't aware, probably, either, of the ratio of

grant monies to contract monies on cancer virology?

Varmus: I would have no idea.

Baker: Well, we'll look that up. So, if you could have changed anything, as you look back on this, is there anything you would have done differently? That's a hard question in a way.

Varmus: Yes. I feel I was very fortunate. I came into this area without tremendous background. I doubt I would have been very competitive in today's market because we were funded with a very large proportion of grants, and it was not difficult for me to get started. And I never really had to worry very much. I had an RCDA that started in 1972, and that protected me from abuse by the medical school, and I was free to do a lot of work on my own because I was in part of this very active group. We had a lot of trainees come to us. It was never difficult to attract people to San Francisco, especially when we had this group effort. So we had, you know, very strong colleagues, postdoctoral colleagues, at a very early stage, even though our graduate school wasn't particularly strong. That made for an environment without which I doubt Mike and I would have accomplished what we did.

Baker: You said you were protected from abuse by the medical school. What abuse?

Varmus: Well, I wasn't required to--

Baker: You didn't have to teach as much?

Varmus: I mean, I did the amount of teaching I wanted to do. I would have been happy to do more teaching, but we didn't have a graduate program to speak of, so there was very little graduate teaching. We gave one Virology course and there were four of us teaching it, so the amount of teaching time was actually less than I would have liked. But I was protected from committee work and other kinds of responsibilities because I had an RCDA. Later on, in the mid '80s, I became an American Cancer Society

Professor and that protected me from the kinds of problems that afflict other aging scientists -- like being saddled with department chairmanships or other tedious responsibilities. So, I've never really had any administrative responsibilities until I came here.

Baker: Well, you're getting plenty now, aren't you?

Varmus: I'm getting plenty now. But now I can handle it.

Baker: The question of whether this Viruses Cancer effort laid some foundations in molecular biology, I think we've already alluded to, to some extent. I suppose Gunther Stent thinks molecular biology only originated from the phage people, but I'm speaking of molecular biology as it moved on into higher organisms. Do you feel that some of these contributions in this area were helpful in developing molecular biology?

Varmus: Well, I think molecular biology had to move into the vertebrate setting, and it wasn't easy before molecular cloning. One of the things we have difficulty teaching students is what it was like to be a scientist who understood the principles of molecular genetics in the pre-cloning era. So, when people look back at the work that Mike and I and our colleagues did on the discovery of the cellular *src* gene, it looks awfully easy in retrospect because people have a hard time thinking about molecular genetics without cloning. And, you know, cloning was a revolution of the most extraordinary sort. It too originated from bacterial genetics, not necessarily just with phage, but with phage, and plasmids, and the bacterial tools. I'm a great supporter of the idea that many of the most important things we do originated with the simplest systems. And the fundamentals of molecular genetics did arise from bacterial work. But a lot of inventiveness is required to move those tools to the point where they are useful in exploring problems that are closer to the problems of human health.

Baker: Well, I think we need to give a little more history to the younger people. These days

they just stand up and start right off, "First slide, please.." and they don't seem to have much grasp of how the field got to that stage.

Varmus: Well, I was that way too. People get more interested in history as they get older.

Baker: Yes. Well, part of it is the strong competition for grants so that you haven't got time for history, I guess.

Varmus: I don't think that's what does it. I think that when you begin working in a field, unless you're particularly fond of history, but you tend to plunge into the field. Life was less competitive when I started working in this area, but my interest in the historical origins of it became much more powerful after I'd been working in the field for five or ten years and began to see the history of the field develop under my own eyes. Then I became more curious about what the steps were earlier on.

Baker: Well, I notice people have seemed to be unaware of previous events. They think things started with their starting in their career.

Varmus: Sure. I felt the same way.

Baker: And it happens over and over in various fields. Well, since you were not in on some of the higher echelons in those days, I guess we don't have to spend a whole lot of time in this interview in that direction.

Varmus: Good.

Baker: So, a question of--

Varmus: I think that's good. I wish that young investigators starting out these days could be similarly oblivious and that the NIH system would be working effectively for them -- so effectively that they didn't have to worry about the politics of science.

Baker: I agree. Certainly at that level you don't want to bother them with all these problems.

Varmus: But I'm amazed that people in my own lab are fixated on some of the mechanics of funding and issues of appropriations. They really shouldn't have to worry about it at this

stage.

Baker:

Well, as money got tighter, I think the more attention was being paid at that level.

That's not necessarily good, but understandable. Now let me turn away from the viruses cancer area, even away from cancer, and look at science in general. And the question deals with how you perceive the public's appreciation of science, their sympathy for funding it. Is that any different now than it was in, say, 1955, 1960, along in there?

Varmus:

Well, I really can't tell you about those earlier days. I was oblivious. I'm very conscious now of public attitudes, and I think public attitudes are fairly positive toward science. Scientists are still respected. People are excited by developments, especially in biological science, despite the fact that we've come in for a few public slammings over fraud and indirect costs and so forth. I think, in general, the public still endorses what we do and is proud of American leadership in these areas, excited about biotechnology and opportunities to improve health, in understanding the basic genetic components of disease. I think we have a challenge to educate the public so it's more able to understand the implications of things they read. That need is going to be enhanced tremendously in the very, very near future, as we ask people to make decisions about their lives that are influenced by our advances in genetics. For example, within the next couple of years, people will have decisions to make about whether they're going to be tested for genetic risk assessment for cancer. That's very different from prenatal assessment for cystic fibrosis, for example. This is something that every individual will have to think about, and I'm not sure that people are prepared to do so. I'm not sure we, as scientists, are prepared to offer clear advice about when someone should be tested and what you should do in response to a positive test, because now we're talking about risk assessment, not about the inheritance of a disease.

Baker: Well, may I say your book with Bob Weinberg, I think, is an excellent example of educating the public who is willing to spend the time to read it.

Varmus: Well, I appreciate that. I think it's difficult to convey some of these ideas in anything less than book-length form, but then it's also hard to expect people to read a book about an area like this.

Baker: I understand the President took it with him on his vacation. I don't know whether he read it or not.

Varmus: He did. But he probably spent more time camping and horseback riding, and I don't blame him.

Baker: Fine. Are there any additional comments, or questions, that you want to raise?

Varmus: Not that I know of.

Baker: Well, we could cut this short and not use up any more of your busy time. So, thank you very much for your willingness to do it, and we'll run off the transcript of this and give you a copy in case you need it.

Varmus: I appreciate your doing this.

*Whereupon, the interview concludes*