Paul Kotin, M.D.
Oral History Interview
Special Virus Cancer Program, NCI
August 12, 2000

This is an interview of Dr. Paul Kotin. It was conducted on 12 August 2000. The interviewer is Robert E. Stevenson, M.D.

Stevenson: I'm not sure how much he's planning to cover. The last time I talked to him, he was going back through a lot of the early science, to Peyton Rous and stuff, to try to get a background for the first concepts of viruses as causes of cancer, started the whole intellectual process going of what kinds of viruses, what species, what this, that, and the other. I mean, he was trying to trace both that and he also wanted a history of cell culture and the concepts of cell culture and how it was applied to virology, so it could be rather extensive. He's written an autobiography of these periods through, and so I think he's been cranked up and writing fairly prolifically. We've gotten interviews with at least 20-25 people that were in the virus cancer program. At NIH Victoria Harden, who is in the Office of History, has transcribed the tapes and has made this, then, available to him for use and reference in terms of the writing. Now, I should inform you that the tape that I will make here will go to Carl and he will turn it over to Victoria, who will then transcribe it, and you are going to be asked to sign a release so that the National Library of Medicine can have this. It's fairly available to scholars.

Kotin: One thing you can be sure of, and that is the availability of this material is not going to be unknown to attorneys, and you can be absolutely sure that this is going to be scrutinized by attorneys. Let me give you an example. There was really nothing that is as obvious as the relationship of asbestos exposure to mesothelioma. We really know of very few other things that can cause mesothelioma, and those that do are related to asbestos in the sense of obeying the laws of inhalation toxicology, the rules of inhalation, deposition, and translocation of particles. But there's such a thing as a fact, mesothelioma is responsible for 99 percent--maybe not 99 percent, but the largest majority of mesothelioma. All of a sudden there is now some very active research going on in which SB40 is being implicated. Lawyers for the asbestos industry are glomming onto it in ways that, charitably, are ludicrous, being less charitable, cynical. And how did SB40 get into the picture? Some contamination. So, that's just a gratuitous bit of information.

Stevenson: Okay. Let me start out here with identifying you and your work. This is August 12, 2000. And we're going to have a discussion of activity with the Cancer Institute and the virus cancer program and any other, then, subsequent things that you want to talk about. But this interview is being conducted in Dr. Kotin's home in Santa Fe, New Mexico.

Kotin: Let's get to the questions.

Stevenson: Okay. The first question was, please give us your views as to the five or

more most important scientific results highly significant to the virus cancer field during the period 1950-1980, and indicate the scientists involved and each result.

Kotin: Well, I guess 1950 was big because that's when... You mentioned Peyton Rous. Somehow or other, Dick Shope always falls by the wayside, but Dick Shope did for DNA viruses in experimental species what Peyton Rous did for experimental species. Dick Shope was working with mammals and so on, and using DNA viruses as Rous. The first, I think, most important of the scientific discoveries would be Renato Dulbecco and Howard Temin of reverse transcriptase. And a lot of other people were involved as well. And this, of course, put a whole new picture in terms of how RNA would fit into the cancerization of cells. But equally important, and how I can't say, but also very important was Mike Epstein and the Epstein-Barr association or etiology in relation to mononucleosis. Huebner wrote the whole reverse…

Stevenson: Hartley? Janet Hartley?

Kotin: And Janet Hartley, of course. Oncogene lysogeny, the history of viruses, you almost have to go back to non-neoplastic diseases, you know, where lysogeny was developed. Then I think that enough attention has really been paid to the work of clinical cancer, herpes, in relation to carcinoma of the cervix. Names like Joe Melnick, the whole group of virologists that at one time chaired meetings with virologists along with Al Sabin and

"the high priests". So those would be the ones that I can name, but certainly those would be the names that stick out and I think that pretty much covers the area. I should not forget one other name, Ludwig Gross, because I don't think anybody substantively made a contribution to understanding viral oncology that added more than the basic observations that Ludwig Gross did. So I kiss off the Rauscher virus, the Moloney virus. I think that what they were--they were not major; they were important but not major. And I think he uses the word major. They were not highly significant to my way of thinking, not a level of a Rous or a Schultz, or a Gross.

Stevenson: You had Gross producing a lot of work over a fairly long period of time, and it wasn't until Charlotte Friend arrived on the scene that this leukemia virus in mice that seemed to catch everybody's attention.

Kotin: It sure did.

Stevenson: I remember at the time that she discovered that, I was in a pollution program with the Public Health Service in Cincinnati, and my colleague there, Norman Clark, had been a classmate of Charlotte's. He got very excited and said this is something that really is new, different. And at that point the classical virologists began to take notice, because I remember Ray Bryant used to say that the tumor-virus people, particularly the Rous sarcoma and everything, were looked on as a bunch of freaks. Sort of separate from the human infectious disease virologists, because over there,

what the hell do they amount to, and why are they important? Nobody really put much emphasis or there was very little financial support for them.

Kotin: You're right. Maybe I've been unkind to Charlotte, but, as I say…

Stevenson: The thing I'm trying to elicit from you is, what do you think all of a sudden, at that juncture, caught the imagination of the virologists and got people interested enough that they wanted to go out and establish a virus cancer program?

Kotin: Well, it was a mammalian species. It was obvious counterparts in terms of human leukemia. I really don't know because, as I say, the genesis of the viral oncology program starts as much, in my way of thinking--and I'm maybe a minority of one--with the general frustration of the indifferent progress in cancer research. About this time was the time when the biochemistry of cancer, Jesse Greenstein and so on, were looking for what doesn't exist, and that is differences between the normal cell and the cancer cell that may be, but there was a lot of discussion. I remember at Wisconsin, it was on a symposium that they do with Nobel Prize [unintelligible] a great picture about where cancer research was going because of the fact that they're looking for what really didn't exist. And when it was all over, [unintelligible] came up and said, "I guess the conference is over. There's no point in anybody saying anything anymore--a very eloquent presentation, but I don't believe a word of it." I

knew the point he was trying to make. So maybe that was... I really don't know because, in the '50s, there were three things that were entering their long phase of growth, if you will, on public involvement of cancer research. It moved from the laboratory in the academic health center and research laboratory and began to have people like Danny Thomas on advisory councils. Mary Lasker picked up the research. So there was great pressure and a fantastic amount of misinformation--that the world is changing to a guaranteed cancer environment. Well, cancer is guaranteed, I agree, if you live long enough and nothing knocks you off the floor, because, let me give Carl Baker a laugh as he listens to this, and that is, I do not believe cancer is the logic entity, biologically speaking, that we pretend it is. It's a biological inevitability. It is the end stage of the zygote, the embryo, the fetus, the neonate, etc., etc., etc., through biological senescence, and ultimately, as I say, if you die of nothing else, you'll die of cancer. This isn't just idle speculation. There is a fair amount of data, lots of data to say this.

The important thing is, as I say, the invocation of viruses as a substantive cause of human cancer came at a time when looking for causes of cancer became in the public awareness. And I really, so far as the Cancer Institute is concerned, I didn't show up there until '60, and, basically, viral oncology was the domain of the Huebner shop and NIAID. In fact, I even got involved with, before I came to NCI, microbiology at Penn State.

Researching the pathology of the influenza virus and recombined flu virus with hydrocarbons and got some C57 black lung cancers. This was done in the '50s. What's his name? It will come to me. This was his thesis work. So it wasn't that I kissed off viruses particularly, in view of the fact that, as a young pathologist, I'm positive I would have called some of those changes seen in the lungs of people who died in the influenza epidemic malignant neoplasms. I fought with Red Stewart [Harold L.], I remember. We got into an argument at an AACR meeting. He was chairman of the session. And I said, "Put that slide back," and he would say, "Sure." I said, "I really don't care what you say, but that's not malignant." And he says, "Well, Kotin says it's not malignant. The truth is, he's ignorant"--but, again, with a big smile on his face. And so I think, that the search for the causes and a corollary with cancer gave birth to the rapid growth in viral oncology. Virologists were good salesmen, and virologists, compared to the quality of people in chemical carcinogenesis, etc., had inordinately high fine reputations, deserved in the sense of the quality and integrity of the work they were doing.

Stevenson: What do you think of the key administrative [unintelligible] affecting the virus?

Kotin: I don't know what to say about that, it is a big question mark. I don't know because I was suddenly greeted with this as more than just an embryo, as a full-blown thing. The rest of it can be real brief because, as I

look at the questions, management decisions, how do you think they, what do you think were key administrative or management decisions affecting the cancer field? Well, first of all, I guess the Viral Cancer Task Force. Again, these were things that I was not involved with except peripherally as a part of the whole cancer causation program at the Cancer Institute.

Stevenson: Well, when you came there, they created a whole new division for you.

Kotin: Right.

Stevenson: And that was called Etiology.

Kotin: Exactly.

Stevenson: And Etiology embraced mainly the viral and the chemical carcinogenesis, but I think there was even a minor amount of radiation carcinogenesis.

Kotin: Yeah, they were all there. But when I came there, it was still the...

Stevenson: Mainly epidemiology was what you started with as a nucleus, and then they took the Virology Research Resources Branch that I was in and they added that to your portfolio. I don't know... When you first discussed with Ken Endicott coming to the Cancer Institute, what kind of a big picture did he spread out for you? What did he ask you to do?

Kotin: Well, my coming to the Cancer Institute--this is history again--the role of Huebner in chemical carcinogenesis, the role of Ray, who was associate director for field studies, Public Health Service, and then moved to California--again, the name is not critical to what I'm going to say--in talking to Ken, my feeling was, as it is now, that communication between

people in the field of clinical cancer, epidemiology, the natural history of cancer, and laboratory aspects of cancer were less than ideal. And I said, "With the resources of the Cancer Institute, we ought to be able to set up some programs in which the crude science or discipline of pathology, if you will, becomes a major factor in, first of all, verifying cancer; number two, doing epidemiologic studies based on understanding the disease of cancer. I can remember saying, "Look, if your Bill Haenszel is making these important observations, the migration of, the effects of migration on cancer risk...."

Stevenson: The Japanese women.

Kotin: Yes, and also, not just the Japanese, stomach cancer in general; and prostate cancer, the differences between some of the NCI-supported studies in Ecuador and in South America. You see, these changes that are occurring have to have some form of pathological reflection, and I'm wondering, because basically what I was trying to do was not out-Murray Shear or out-Mike Shimkin, but what I was trying to do was put the mosaic of cancer on a flat, on a level field so that the basic biology of cancer was not restricted to the biochemists. This was before the days of the molecular biologists, the pharmacologists, and the toxicologists. It was a total picture in which a lot of clinical resources were being used to study the biology of cancer. The CCNSC made major steps in that direction. There's no question about it. But, again, I talked--I hope he's

still alive. Is Zubrod still alive, Gordon Zubrod?

Stevenson: I don't think he is. I think he died a couple years ago.

Kotin: But Zubrod and I used to kick it around because Zubrod really recognized that, being associate director for therapy or whatever his title was, recognized that the clinical resource that the National Cancer Institute could make itself was not being utilized maximally in research on the basic level. I'm saying it awkwardly because it's all so far back. I can remember a big player in all of this, in my mind, because I would go and talk to him frequently, is the guy who is still alive, Al Rabson. Al was a rare combination of a fine pathologist and a real student of neoplastic diseases and so on. But Ken had said, "Okay. Set up a program."

Stevenson: Back in the days when this all occurred, and sitting where I was sitting, I got the impression, after going to a number of meetings, that the Cancer Institute was very, very insular, and that all of these various people, the Mike Shimkins, the other people and so forth, each had their own agenda for what they thought was the right way to approach the study of cancer. And there was very little intercommunication between the members of the Cancer Institute at those levels. They each took their bone off in the corridor and chewed on it and so forth, but very seldom did you ever get them together in one room and look across all of these fields and look at the common denominators.

Kotin: Exactly right.

Stevenson: And I thought basically that the kind of portfolio that you had was to try to bring in some new bug and to take a look across the fields and not be so parochial in terms of saying, "Well, we're going to go after the chemical, we're going to go after the radiation, we're going to go after just epidemiology and look for common factors like and so forth." You said, take all these things, pretty much, and mix them up, and I'm trying to find out, was this something that Endicott perceived that needed to be done and persuaded you to do it, or vice versa, did you persuade Endicott that it was a reasonable approach and he bought it?

Kotin: Actually, the two meetings that were crucial in my coming were meetings with Endicott and Jim Shannon. And Jim Shannon, of course, was--the Institute was still--NCI, not NIH--was still smarting from all of the accusations of Huebner being published in the *Gazette* and to congressmen about how the Cancer Institute is not interested in etiology because of the support that he's not getting, etc., etc. The omnibus approach, the umbrella approach, was discussed, and I indicated at the time, if I were to leave, I would need some kind of a--the question you asked. Just what was off limits for me? And essentially I was told that nothing is off limits as long as it relates to the etiology of cancer, because I had a big stake in going to NCI. You know my history. A big stake in NCI. I had an endowed chair at the University of Southern California, professor of pathology. And if I never got another penny in research, it would have

made no damn difference. Mr. Pierce, in those days it was $5 or $6 million--this is in the '50s--which would have paid me, Hans, Marilyn Thomas, and all of the people that were part of the group, and I really didn't have to apply for grants, even. So I was sacrificing a sure thing. And as it so happened, the president of the university at that time was a man by the name of Norman Topping, and Norman Topping at the time--this was a half century ago--told me I'm crazy. And he says, "What's more, I'm so convinced you'll come back that I'm not going to fill the chair, the main chair, for a year." He said, "Somewhere between Omaha and Cleveland, Ohio, you're going to call and say, 'What a mistake I made.'" Well, obviously, that never happened. You're asking crisp questions to an amorphous situation.

Stevenson: Well, the point is that there's no one who can answer those questions probably precisely, because you get in an environment and there are many factors that play on the decisions. What I'm trying to tease out in the discussion are, what are some of these key factors that played a role? You can't say, well, I went there because (a) it made me A through Z that influenced your decision. But I think the thing that Baker particularly is trying to get out of these interviews is, what was the climate? What was the stuff? Now, for example, Endicott made the decision to bring you to NCI, but he didn't have any space on the campus to give you. So you had to go out and rent buildings and create laboratories out of office buildings,

have what you might call a distributed empire with a little bit here and a little bit there. You had the two buildings and I don't know what all. But all the people that you hired and everything were in leased space that you had to make do.

Kotin: That was the sort of the history of etiology, because the animals were all kept at Georgetown Medical School.

Stevenson: But then the phenomenon of contractors came in, so you had Microbiological Associates and people like that, Melpar and so forth, who would take animals and house them and provide the staff who would feed and water and clean the cages and everything else. So the key element in all of that was money. Endicott went out and got money, and the money was then converted into things and services and hiring people.

Kotin: Right.

Stevenson: But without somebody feeling that this was all worthwhile and it was something that ought to be done, it never would have gotten off the ground. And I think that's what we're trying to figure out, is, you know, who had the perception of the need to do this and then convince the people who held the purse strings that this was a job worth doing, and then the feedback that reinforced the continuing support?

Kotin: Well, let me just think for a second and put it as truthfully as I can. I think that a scientific--and it's almost a platitude--a scientific base for the public health aspects of cancer control was lacking, and it would be nice, I felt, to

have, whether it was tobacco carcinogenesis or whether it was, in later years, methyl herbicides, Agent Orange, carcinogenic hydrocarbons, what have you, it would be nice to incorporate all of this into the concept of risk, which really had never been crystallized. The concept of risk is something that was perhaps the past few decades. It doesn't go back a half century. And the question--there are many, many scientific questions I asked that I knew could only be pursued under the umbrella of a cancer institute. The whole issue of the relationship of biochemistry, pharmacology being a better word, to cancer risk was something that was just beginning. Why do dogs get bladder cancer from aromatic amines but rodents didn't? Why does man get aromatic amines, urinary bladder cancers that rodent species don't? These things have always intrigued me. The idea of why the whole issue of dose response. I know that I've said and I will repeat it, that if you're talking at the molecular level, the reaction between a proximate carcinogen and a base in the DNA chain, there is no threshold. I'm willing to buy that. But the idea of there not being a threshold for exposure to carcinogens in terms of the total animal is ludicrous because of the fact that we know, if there were no threshold, everybody would die from mesotheliomas because of the ambient concentration of asbestos in the air from the earth's surface. And then, of course, dose-dependent metabolism I think has reached its heyday, with vinyl chloride or, indeed, with a carcinogen. Environmental carcinogen

can be metabolized up to a given level with relatively innocuous metabolites. But the ability to latch a group onto a carbon chain or something like that is a dose-dependent phenomenon. I was interested in that, and it seemed that, for that, you need enormous amounts of research associates and also access to the clinical disease. And with the imprimatur of the Cancer Institute. I could do this, because at NSC, for the 10 years I was there, I still had ward 10600 at L.A. County Hospital, I still knocked pathology into very reluctant heads of sophomores for over a decade, used my research, our research. And I just felt, on a bigger scale, the questions would be more global, and the likelihood of a response might be global. And somehow or other, viruses really never became a beater in the smaller areas of research or in big program considerations. It wasn't my bag. I understood what happens to a chemical on the basis of its metabolic pathway. I had no feeling for viruses. Immunology was clearly not my long suit, and I guess I just wanted to be able to do what I did, which motivated my going to NIEHS when--it's a whole other story--when I figured an omnibus approach with the Environmental Health Sciences Institute. You know, NIEHS was never meant to be part of NIH. It was part of the Bureau of State Services, and this is where it was, and when I got called downtown. Would I be willing to leave Southern California to lead NIH until I decide I might want to move on. So, with Mr. Cohen [Wilbur] as secretary, Cohen or the guy from California. What's his

name?

Stevenson: Yeah. It's Wilbur Cohen.

Kotin: Yeah. I explained to him, "I will become director of the Division of Environmental Health Sciences"--they didn't call it an institute at the time--"if you promise me three things, Mr. Secretary. Number one, when it's the appropriate time, and you'll know better than I when the appropriate time is, a request for it to be given institute status would be honored," which he said all right. "Number two, that indeed it would never revert to a non-NIH status," and that was agreed upon. "And number three, because of the fact that it's going to be the first institute off campus because Mr. Kennedy owes Governor Hodges a favor for carrying North Carolina for him, that that would be taken into account in the funding of the institute." In other words, it really had no local base, and Mr. Cohen said yes, in the presence of, I think it was Phil Lee and Leon Jacobs still at NCI, because Phil Lee made Leon Jacobs his deputy, remember, because... And that was my first meeting with Mr. Cohen. Later, turn that off. I'll tell you this, and it's a very sad story. Can we go off the record?

[Tape recorder turned off.]

Kotin: It was interesting that--I don't know why I did things really as much as how I planned things. See, that's another thing. When I came, I told Ken, "I'm leaving government in 10 years. What I'd like to do is go back to

academia." And I did leave government to go back to Temple either Michigan or Temple. I'd been offered the two deanships simultaneously and chose Temple for a lot of personal reasons. And we're not helping you with all of this. Who do you think were the main leaders who influenced the direction and course of events in virus cancer field? The names I wrote down were Huebner, Melnick, Ludwig Gross, and then I have undecided; Maloney and [unintelligible]. They were all terribly, terribly influential, and I think that's a fair answer to that question. I've probably left some people out, but I don't know. I mix up my association with the viruses, virologists at the Cancer Institute, with the years I spent on the Armed Forces Epidemiologic Board, which is predominantly a, virtually entirely focus on infectious disease. And of the infectious disease, it was a lot of viruses, so this was what they needed was a token somebody interested in the field of the relation of chemicals to disease.

Stevenson: Key NCI and NIH scientists?

Kotin: Yeah. I can't be helpful on that in the sense that I knew who they were, I met with them. I never got a handle on the universe of the Al Sabins and the Jonas Salks and the Huebners.

Stevenson: Well, Salk never had any direct connection with the virus cancer program. Other than having gotten involved with the SC40 contamination of his vaccine, I think he wanted to stay as far away from that as he could.

Kotin: Yeah. In addition to the names, I do have SC40.

Stevenson: Still, as you pointed out, still rises occasionally to haunt us as to whether that is something that's sitting that integrated into people's genomes.

Kotin: Number five, I have no answers, actually, other than...

Stevenson: One of the things you did mention earlier were the early conferences, where we tried to bring together a bunch of people from disparate institutions and government, academia, industry, and so forth, and try to exchange ideas and information and even results on the research. What kind of an influence do you think those types of meetings and the involvement of a lot of these people in the advisory committees that reviewed contracts had in terms of moving the field?

Kotin: It moved it because basically there were persons like myself who would have had no other focus for meeting these people. The seriousness of the program, I have to be honest--and I'm glad the machine is going--the evangelism of Lou and Carl periodically got to me as I was listening, the functional overlay, if you will...

Stevenson: Positive or negative?

Kotin: Negatively, because, for heaven's sake, you've got--if a bomb hit this place, virology, viral oncology would be wiped out, I used to think. But the idea of things is new and dear to my heart. McNamara turned out to be a first-class bastard sociologically, but he had his geniuses around him. Why can't you approach understanding and control of a disease the same way that you build a battleship? You can. And this accounts for all the

linear arrays and concurrent arrays and the decision points and so on. Intuitively, they appeal to me. But there were a hell of a lot of assumptions that were treated as though they were more than just assumptions, so on, and in an environment like that, I guess that's just...

Stevenson: You've read Ken's *Scientific Revolutions* and the idea that paradigms are useful up to a point and then you get a new paradigm. Now, how would you put in the context the virus cancer program with his basic thesis that you go along for a period of time until you have a lot of observations that just don't fit the theories, and then you have a new wave front moving? How do you think this program fit into that concept?

Kotin: The program--there's no finite periods for evaluating the program. This is one of the major contributions. He asks that later: How much did it contribute to our understanding of molecular biology? A fantastic amount. How much it contributed to our understanding of cancer is an entirely different question. So that I don't think the paradigm might shift, but even if you start your new paradigm because of the massive accumulations of information, it is not stepwise, it's a continuum. And for that reason, one of the problems, to me--and this is why I felt a stranger, was, how do I test this in people? How do I determine if this is--not I, but how can it be tested in people? How can you use epidemiology, which is even today, I think, to a remarkable degree as much in the art as it is a science. Epidemiology is the darling of the press. On NBC, there's a

breakthrough a week--Bob Bazell is on--and on CBS, there's a breakthrough every month, or whatever it is, on the basis of epidemiologic.observations--biological nonsense, most of them. And I have two dear friends, Dimitrios Trichopoulos, who is at Harvard and Brian MacMahon. He's the dean of American chronic-disease epidemiology. I spent a lot of time with Bob Huebner while he was still active and still see Dimitrios Trichopoulos at frequent intervals. We're members of a committee. And I still keep looking--I know I'm meandering--and it's the same thought I had then: How can you take these observations and utilize the study of population surveys but not test your validity, test their compatibility. Those were things that were discussed and that was exciting. But let's put it this way. I never was an "in member" of the viral cancer program in spite of what my title might have been, what the portfolio included.

Stevenson: Maybe you weren't, you know, with Huebner, but at least you were in a catbird seat at NCI, seeing all this interplay of all these people and personalities and funding and national meetings and positions that were taken and everything. Do you have any overall impression of all of that that remains with you that you think can distill some of that?

Kotin: Well, reduce it almost to an absurdity, and it sounds like it may--tomorrow is my 84th birthday--maybe I have indeed seen a de-emphasis on this. The

cancer cell is, obviously it is indispensable. It's the sine qua non of a neoplasm, a cell. But there's a couple of town-and-country miles between the *cancerization* of the cell and the development of a clinical cancer, and my impression was that there was less attention given to phenomena that were cancer oriented. To this day, I remember, in fact, somewhere in the house here are the two volumes on spontaneous remissions of cancer. It's a reality. Three or four seminal articles on the finding of circulating cancer cells in a senescent--and I mean senescent biologically, not mentally speaking. Those were the kind of things that through my career have always--why haven't they been pursued more? And that reflects not that they're more important in cancer virology, but cancer virology was not my bag. All of my answers to these questions may be completely, not meaningless, but may be going north on an east-west street or something.

Stevenson: The subject that you bring up about some of these phenomena that have not been well studied is, I think, answerable by the fact is that we currently don't have good tools to study them with. Now, here at this point in the evolution of science, we had viruses, we had cell lines, we had the ability to control model systems like we never had before, and all of a sudden you're presented with a bunch of tools. So, in essence, people are doing science because they have tools to do that kind of science.

Kotin: Well, you're much more of a science philosopher than I am, and I think, at that time, my vision was not broad, it was parochial, and it was parochial

to the extent of, I'm convinced the questions I was asking in relation to cancer were important, and, as you say, the tools necessarily were not there. But I did not take a cosmic approach, and maybe I should have by virtue of the position I had. See, at NIEHS, it was different than the Cancer Institute. Their mission of NIEHS clearly stated, was to "provide"--as glorious and as unachievable as it sounds--a scientific base for every government decision on in the world of regulation and standardization, and I would meet every month with FDA, I'd meet every month with EPA. We three would meet, and it was a growing concern, whether it was Ron Knowle [sp.] at EPA, the guy who became dean at Arizona Medical School. That was different because at NIEHS, I realized I had to move from the microscope and the barometric fraction collector and chromatograph to important decisions that affected the lives of people, the economy, and the political considerations, of course, were the overriding ones. So maybe it was a mistake in sending requests to me because of the fact that I really, despite the title--and I can see where it would be misleading; if one would look at my title, one could say, "Gosh, he was there all the time. He should know more about it than he does," and I really don't know a hell of a lot about it even though, as I say, I sat, I banged the gavel with the world-quality virologists sitting in the room. I guess maybe one of the feelings that I was really basically ignorant of virology. I knew pathology. I knew enough to teach.

Stevenson: Let's go into your field. Back in '67, Morris Pollard at Notre Dame...

Kotin: Oh, yeah.

Stevenson: Came up with the finding that the RNA viruses were integrated into the genome of the mice, and we found that out by studying, under contract, the germ-free mice that had been bred there.

Kotin: At Notre Dame.

Stevenson: For a number of years. Okay. Now, these were the model systems that the chemical carcinogenesis people were using. And I remember some years later, when I was at Frederick and we were setting up the animal bioassay program for Salvetti I asked him... You know, they were defining the parameters of the program. I said, "Why did you choose this particular hybrid mouse strain?" and he couldn't give me a reason. He had no rationale for why we should hybridize these two strains of mice and provide them for the experimental models. And it blew my mind because I had thought that over the years, that they had carefully selected these strains based upon particular types of tumors that they developed or one thing or another as they grew older, and that these things were in the normal mice, a noise level that you were going to have in there no matter what. Whether you just fed them food and water and did nothing to them, they were going to develop tumors, as you pointed out, and sooner or later, you're going to die of cancer if you don't die of something else. And this is, to me, a very interesting phenomenon, as to how well systems are

picked. And then, particularly when you know that you've got a virus that is a tumor virus integrated into the genome, what does your work tell you? But I don't know if in '67-'68, that any of the chemical people changed any of their rationale as to what they were going to use for model systems based on that.

Kotin: They didn't. That I can tell you, because I remember--this was before Purdue, I think.

Stevenson: Was he at Purdue?

Kotin: I think before it. And the whole idea of a germ-free…is not only intriguing, but, as you say, eliminated one other variable of more than theoretical significance. And how crudely. I remembered back in '51 or '52, when we were studying inhalation carcinogenesis, there was an A strain and there was a C57. Look at an A the wrong way, you're going to get pulmonary adenomas or, adenocarcinomas, and the C57 was not. That was really primitive thinking, but it was consistent with the resources that were available at the time. And when we did some virus chemical studies, we used blacks for that reason. The purity of the model systems in the field of chemical carcinogenesis, until very recently, has never... You live with the strains that you got out of Bar Harbor, or if you're dealing with rats, Charles River, wherever you are. But, again, my approach was a little different, and to this day it's that. I feel you can learn as much, perhaps even more, at my level of diagnosis, which is, if you can't see it, it may be

there but it's useless to you in terms of your developing a [unintelligible] and so on. So for the last 20 years I was much more interested in pathogenesis rather than pathology. In fact, one of the nicest accolades I got was at a meeting in Geneva where they said, "Now, Dr. Kotin, a man with a crystal ball on his microscope, will present the next paper," and it wasn't a crystal ball at all, and this has nothing to do with this. But as you follow the pathogenesis of the lung region or the pathogenesis of the liver region, with almost 99 percent reliability, you could predict whether this is going to go become a neoplasm or not. That's got to be insane. But as long as it's on the tape, somebody's going to come with a butterfly net to try and get me. My approach to cancer is entirely different than Carl Baker's or the virologists. Carl not being a virologist, but nevertheless he has a comprehensive understanding of, always had, of cancer. But my wedge of the pie, my piece of the pie was wedge-shaped whereas his might have been square-shaped or something.

Stevenson: Well, looking back over it, despite what you just said, how would you put this in perspective? Do you think it was a useful exercise to have gone through? Do you think the taxpayers got a good bang for their buck, or do you think a lot of money was poured down a rathole?

Kotin: Yes or no. Did important things come out of it? Hell, yes! But on a cost-result basis, I wouldn't know how to quantify it. I spent two years at Wisconsin.

Stevenson: Well, for example, do you think we would have been able to have recognize and deal with AIDS as quickly as we did if this program hadn't existed?

Kotin: No. This is the part I'm getting to. It subsumes under the question that, yes, how much did it contribute to our understanding of not only molecular biology, which is the umbrella, but understanding of the vicissitudes possible in the life of viruses. An awful lot. To this day, I think not enough has been made of the variability--not enough has been made in terms of not looking at the bench. But every once in a while you'll see a breath of fresh air. Jane Brody from time to time will write an article relating to viral diseases and now the big West Nile virus scare in New York. But I'm going back to the variability and mutagenicity, but that's what I'm speaking of--the mutagenicity of viruses. And it's unlike chemicals. A chemical crystal, it's the same.

Stevenson: It stays.

Kotin: Exactly. And to this, the viral program contributed mightily. We learned an awful lot about the variability of viral entities. So, again, I think the questions aren't answerable by me in specific ways.

Stevenson: Well, what additional comments, if any, would you like to make?

Kotin: Well, I think the likelihood of our sequential nucleotides or the mapping of the genome, its impact on cancer control is, I think, going to be minimal. There are certain... In other words, the corollary of mapping the

genome and understanding…should be identifying a target for a magic bullet. I think that's the impression that is around, and it just ain't gonna happen. That it's going to have a beneficial impact, undoubtedly. I'm talking about non-neoplastic diseases where the impact is already being felt--the replacement of inborn errors of metabolism, you know, the causes of inborn errors in metabolism. Of course, a biological inevitability once enough time passes. But neoplastic diseases are systemic diseases in the sense that I envision them. Localization is where environment, to a remarkable degree, such as aromatic amine, it's the bladder; if it is the liver; if it's a polycyclic hydrocarbon, it can be the lung that localizes, you know. Betty Miller once, in a presidential address at AACR, coined a lovely phrase. I think she coined the phrase of all of these things that are necessary but frequently insufficient, all these causes, to cause a cancer by itself. I really, you know, I get incensed at the great hopes that are predicated, really, one foot on the cloud and the other on a rainbow in terms of how, with enough time, they want to be able to control cancer. Sure, we're going to make major steps. But are we going to eliminate cancer? You no more can eliminate it, I think, than you can eliminate the progression of a zygote to an embryo. Now, that would be powerful.. And you're going to find it, I'm sure, relatively useful.

Stevenson: Well, the process is that we'll have this transcribed and send it back to you. And you're free to add to or edit.

Kotin: And I'll leap with horror. Again, I do hope this hasn't been a waste of time for you.

Stevenson: No.

Kotin: Because I should get off my duff and at least Dusty [Cornelius P] Rhoads got his picture on the front of *Time*. Remember when he came out with as director of Sloan Kettering Cancer Research Institute. At last, a unifying concept of cancer. It was on the front page of *Time*. Dusty Rhoads made a major, major contribution to cancer research at Sloan Kettering. But I don't see a quasi-normal or quasi-pathologic process being eliminated by a magic bullet. I remember when Harry Gruber [?] was then in L.A. at the time. He had left Cleveland to become head of pathology in the cancer research program at the then fledgling UCLA. Remember he published his paper on the transformation of fibroblasts? And, what's his name at Stanford?

Stevenson: Henry Capp?

Kotin: No, no. Aging of cells.

Stevenson: Hayflick.

Kotin: Yeah, of course, Lenny Hayflick I remember I was on the West Coast at the time and I had a talk to Lenny Hayflick, and what made me curious of some ideas as to the progression leading to this spontaneous"[unintelligible] He was a terrifically great guy as a person. A very humble guy. Do you know Lenny?

Stevenson: Very, very well.

Kotin: Tell him hello for me, then, please, because I remember this is back in the late ‘50s or ‘60s. We still communicate periodically.

Stevenson: He’s fascinated with the whole field of telomerase and everything, proving all of the stuff that...

Kotin: Exactly. It was nice to have lived long enough to see that. Okay. Want a bagel?

Stevenson: Okay. With that, at 12:24, we conclude the interview.

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