CHEMICAL HERITAGE FOUNDATION

DAVID BALTIMORE

Transcript of Three Interviews
Conducted by

Sondra Schlesinger

at

New York City, New York; Cambridge, Massachusetts; and Boston, Massachusetts

on

7 February 1994, 13 April 1995, 29 April 1995

(With Subsequent Corrections and Additions)

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DAVID BALTIMORE

1938 Born in New York City, New York, on 7 March

Education

1960 B.A., chemistry, Swarthmore College
1964 Ph.D., Rockefeller University

Professional Experience

1963-1964 Postdoctoral fellow, Massachusetts Institute of Technology

1964-1965 Postdoctoral fellow, Albert Einstein College of Medicine

1965-1968 Research Associate, The Salk Institute for Biological Studies

Massachusetts Institute of Technology
1968-1972 Associate Professor of Microbiology
1972-1990 Professor of Biology
1994-1997 Ivan R. Cottrell Professor of Molecular Biology and Immunology
1995-1997 Institute Professor

American Cancer Society
1973-1983 Professor of Microbiology
1994-1997 Research Professor

Whitehead Institute for Biomedical Research
1982-1991 Member
1982-1990 Director

The Rockefeller University
1990-1991 President
1990-1994 Professor

1997-present President, California Institute of Technology

Honors

1970	First recipient of the Gustave Stern Award in Virology
1971	Warren Triennial Prize from the Massachusetts General Hospital
1971	Eli Lilly and Co. Award in Microbiology and Immunology
1974	United States Steel Award in Molecular Biology, National Academy of Sciences
1974	Elected Member of the U.S. National Academy of Sciences
1974	Elected Member of the American Academy of Arts and Sciences
1974	Gairdner Foundation Annual Award
1975	Nobel Prize in Physiology or Medicine
1976	Honorary Doctorate, Swarthmore College, Swarthmore, PA
1978	Elected Member of the Pontifical Academy of Sciences
1980	Elected Fellow of the American Association for the Advancement of Science
1985	Honorary Fellowship, American Medical Writers Association
1987	Elected Foreign Member, The Royal Society (England)
1987	Honorary Doctorate, Mt. Holyoke College, So. Hadley, MA
1987	Honorary Membership, Alpha Omega Alpha Honor Medical Society
1990	Honorary Doctorate, Mt. Sinai Medical Center, New York, NY
1990	Honorary Doctorate, Bard, Annandale-on-Hudson, NY
1990	Honorary Doctorate, University of Helsinki, Helsinki, Finland
1988	Elected Member of the Institute of Medicine
1991	Honorary Member, Japanese Biochemical Society
1992	Fellow, American Academy of Microbiology
1997	Member, American Philosophical Society
1998	Fellow, California Council on Science and Technology
1998	Honorary Doctorate, Weizmann Institute of Science, Israel
1999	Fellow, Association for Women in Science
1999	Honorary Doctorate, Cold Spring Harbor Laboratory

ABSTRACT

David Baltimore begins the series of interviews describing his interest in biology as a high-school student and throughout his college years at Swarthmore. During college, he spent a summer at Cold Spring Harbor where he met Cy Levinthal and Salva Luria, both of whom encouraged him to go to graduate school at MIT. As an undergraduate, Baltimore held an interest in viruses. Knowledge and study of animal virology were still very limited, and when he decided to devote his PH.D. thesis to this topic, he moved to Rockefeller University to join Richard M. Franklin who was working with mengovirus. In his graduate work, he discovered that cultured animal cells infected with mengovirus synthesized an enzyme that catalyzed the synthesis of viral RNA. This was the first example of a virus coding for an RNA-dependent RNA polymerase. He then began working with poliovirus, work that continued for many years. In 1965, Renato Dulbecco asked Baltimore to join him at the Salk Institute for Biological Studies. There he initially focused on the replication of poliovirus RNA. With Mike Jacobson, a graduate student, he also began studying viral protein synthesis. Their work contributed to the recognition of the importance of proteolytic processing in the synthesis of eukaryotic proteins. Baltimore left the Salk Institute after two and a half years and returned to MIT in 1968 as an Associate Professor of Microbiology. He continued to focus his research on poliovirus, but also began work on vesicular stomatitis virus [VSV]. He and his wife, Alice Huang, who at the time was a research associate in his lab, discovered that VSV carried an RNA-dependent RNA polymerase within the virus particle. This work provided the insight that led to his discovery of reverse transcriptase—the enzyme in retroviruses that transcribes DNA from RNA—and won Baltimore the Nobel Prize for Physiology or Medicine in 1975 along with Howard Temin and Renato Dulbecco. Baltimore's work with retroviruses was the beginning of his interest in and work on cancer and tumor biology. In the mid-1970s, Baltimore expanded his research interests into the field of immunology, specifically into the areas of B cell development and antibody diversity. Baltimore concludes the interviews with a discussion of the discovery of reverse transcriptase, and thoughts on his research on poliovirus, retroviruses and immunology at MIT in the 1980s.

INTERVIEWER

Sondra Schlesinger is Professor of Molecular Microbiology at Washington University School of Medicine. She received her Ph.D. in biological chemistry from the University of Michigan and spent three years as a postdoctoral fellow with Professor Boris Magasanik at the Massachusetts Institute of Technology, where she worked on enzyme induction and regulation in bacteria. She joined the faculty at Washington University in 1964, where initially she continued her research in the field of microbial genetics and physiology. In the early 1970s, she began her research work on the structure and replication of animal RNA viruses, which continues to this day. Dr. Schlesinger has over one hundred publications spanning these areas of microbiology. She was President of the American Society for Virology in 1992-1993, at which time she began her present interest and work in the history of virology.

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INTERVIEWEE: David Baltimore

INTERVIEWER: Sondra Schlesinger

DATE: 7 February 1994

LOCATION: Rockefeller University, New York

SCHLESINGER: Let's not start at the beginning but just at the end of college, the beginning of graduate school, and tell me a little bit about your major and how you got interested in biology.

BALTIMORE: Do you mean graduate school or when I became interested in biology? I did well in science in high school and my mother, noting that, asked whether I wanted to spend the summer at the Jackson Labs where they had a program for high-school students. So I went there between my junior and senior years in high school and had a wonderful experience in learning about science, biology, genetics, and doing experiments with three wonderful people—which is how they set up those programs—Elizabeth [Tibby] Russell, Will Silvers and Don Bailey. Actually, I first met Howard [M.] Temin at the Jackson Labs that summer. Then, when I went to college, the biology at Swarthmore [College] was terrible. It was extremely rote. The head of the department felt, almost ideologically, that it was inappropriate to have any biochemistry or molecular biology, although molecular biology didn't have a name then; it was not really thought about. He said those things were for graduate school. It was important for an undergraduate to learn embryology, anatomy, and things like that. So I took those things, a little bit and I got sick of them. Actually I ended up a chemistry major because they let me do research. They were much more forward-looking people. But the reason I wanted to do biology was because of my high-school experience. Then in college I spent one summer—again between my junior and senior years—at Cold Spring Harbor with George Streisinger. That was a wonderful experience. There is a whole story about how I happened to do that, but it's interesting. Actually I had even spent an earlier summer doing research at Mt. Sinai with a guy named Bob Lideen. So I knew what I wanted to do right from the start. I mean, by the time I was on my way to being a senior in high school.

SCHLESINGER: So you knew that you wanted to do research not medicine?

BALTIMORE: Right. Well, I sort-of took a pre-med curriculum in case I decided I wanted to go to medical school because that was one of those open options, but I never really thought about it terribly seriously. In the summer that I was in Cold Spring Harbor both [Salvador E.] Luria and Cy [Cyrus] Levinthal came through Cold Spring Harbor and approached me about coming to MIT [Massachusetts Institute of Technology] because at that time they were just getting the program going and they didn't know where they were going to get students from.

Here I was interested in the kinds of things that they thought somebody should be interested in. I did well in George's lab so, basically, I never applied to go to graduate school except to go to MIT. It was a different world.

SCHLESINGER: Before we continue, what year is this?

BALTIMORE: I started graduate school in 1960, in the fall of 1960.

SCHLESINGER: Was this now in the spring of 1960 that you were accepted at MIT?

BALTIMORE: The summer before that I had been at Cold Spring Harbor—the summer of 1959. I guess I applied during that year and I was accepted.

SCHLESINGER: Did you actually fill out an application?

BALTIMORE: Yes, I think so.

SCHLESINGER: So you started graduate school at MIT in 1960?

BALTIMORE: That's right.

SCHLESINGER: At that point were you in someone's laboratory?

BALTIMORE: Not really. The MIT program had you starting in a laboratory only after you'd been there for awhile—and today it's very hard to get into a laboratory, which I fight with them about—but I went to Cy because I had kind of known him from Cold Spring Harbor and he was one of the couple of molecular biologists who were watching over the students. He said he'd give me a spot in the lab and that we could do some things. Actually, it was in a laboratory with Dave Friefelder and Peter Davison who were kind of working with Cy. They were physical chemists and they had gotten interested in the size of DNA [deoxyribonucleic acid] molecules, and they were running Model Es. I had a little room back there that year and I plated out some phage. I don't actually remember what I did that year, it wasn't terribly significant.

SCHLESINGER: So at that time you didn't have a particular area of biology in which you were interested?

BALTIMORE: Well, I was attracted to viruses from the very beginning. You know, I hadn't ever thought about this. When I was an undergraduate—I said I wouldn't tell you this story about how I ended up in Cold Spring Harbor, but I will because it becomes relevant. I was taking a microbiology seminar, I guess in my junior year, and was reading all about phage and bacteria and I said, "Could we just look at a phage plaque?" I just wanted to know what we were talking about and the guy who ran the course actually worked on diatoms. This was at Swarthmore and the faculty all had little research programs. He didn't know anything about bacteria or phage but he said, "If you can get the materials, we'll do it." He was a wonderful man. So during Easter recess of that year I went to Cold Spring Harbor, because I lived on Long Island. I lived in Great Neck and I knew Cold Spring Harbor because we used to go to the fish hatchery there as a weekend outing from home when I was a kid. So I connected the name. I'll just go find a lab and talk to somebody and the only person I knew to talk to was Helen Gay who didn't work on bacteria or bacteriophage but her name turned up a lot in cytology literature. I was kind of interested in cytology. So I sought her out. I just drove out there or maybe I called and she said, "I can't help you but I think George Streisinger could," and I had never heard his name before. George is one of those enigmatic figures to most people because he was so much a scientist. He published almost nothing. So I went upstairs and there was George sitting behind his desk in leather thongs, drinking Coca-Cola, and looking like something that just came off the moon. I was both amazed and enthralled by him. Sure he would give me the stuff. We started talking and I guess I must have impressed him because he said to me, "Would you like to come out here this summer and work with me?" I said, "Yes, I would love to." But I had already made a commitment to go to Mt. Sinai to continue working with the people I had worked with before. They worked in parasitology. I can't remember which one. I think that was what the commitment was. So I called whomever I was committed to and said, "They have offered me a job in Cold Spring Harbor and I don't know what to do about." Whoever it was said, "Go to Cold Spring Harbor. You'd have a wonderful time here, but that's a rare opportunity." And so I did. It was the first year of the URPP [undergraduate research participation program] but the reason George asked me was they had this money from NSF [National Science Foundation] and they didn't have any students yet. They had the money to train college students and so I was in the first URPP class.

So I went out there for the summer and I worked with George asking whether T4 [bacteriophage]—T4 I think—required DNA synthesis in order to recombine. I believe that was the question and we were blocking replication and were looking at whether recombinants came out. I don't even remember what answer we got but I do remember the last thing we had to do was some P^{32} experiments to see if we were really blocking replication with—I think was drugs we used—and that was kind of messy. I had no experience with that but I managed to get some numbers out of it. The last day, I was there and George said, "Well I don't know if we'll get to publish this or not"—it was never published like most of what happened in George's lab, but the key was to go downstairs and to present the work to [Jun-ichi] Tomizawa, who was then in [Alfred D.] Hershey's lab, because Tomizawa was the smartest man in the world. If Tomisawa

thought the experiments were good experiments, then they were good experiments. So we did that. Tomizawa, I think, liked the experiments—I'm not sure he understood them.

SCHLESINGER: Did you go to the lectures that they had in conjunction with the courses?

BALTIMORE: Oh, sure I went to lectures all the time. By that time—this is between my junior and senior years of college—I knew a fair amount of molecular biology, almost all self-taught. I mean, we haven't discussed college, but actually, in my senior year of college I taught a molecular biology course because there were so many undergraduates who wanted to know something about it. As I said, the faculty was more or less opposed to it. So I just did it for interested people and we would meet once a week. I knew more than they did, but only barely. And what I knew was, of course, very unsystematic and very unfiltered by anybody who really knew what they were talking about and therefore confused and spotty.

SCHLESINGER: As long as we're discussing Cold Spring Harbor and Swarthmore, did any of the people you taught later become molecular biologists?

BALTIMORE: Well of the group there, I don't remember who exactly. What I don't remember is how many of them were the senior people. You would have to ask them, but my class at Swarthmore had Dave Denhardt; Ellen Glowacki [now Strauss]; Dave Teller, who is at Seattle; Davida Young who is in psychology, and there is somebody I'm missing. It was a fairly notable group.

SCHLESINGER: At Cold Spring Harbor, in the undergraduate research program, were there other students who continued in science?

BALTIMORE: There were other students. I haven't kept track of them. There are a couple of them I run into occasionally but I really can't place them. I was interested in viruses, which is how we got to this. Well, I had gone to Cold Spring Harbor because I was interested in viruses. He [George Streisinger] gave me the stocks and we went back and played with them and saw phage plaques. I don't think we ever did a serious experiment but at least we convinced ourselves that we could look at phage plaques and count them and that these were real numbers. I had this interest in viruses, I guess from the first time I saw a virus and it is something about their smallness. I mean it's that incredible insight that Mueller had in the 1920s: the basis of life is in viruses because they manage to live, they're the tiniest of things, and you should be able to learn from them. Of course [Max] Delbruck and company had proved that.

SCHLESINGER: That was something I was going to ask you: if at that time you were already influenced by the statements of Delbruck and his group.

BALTIMORE: Well, I was interested to the extent that I was reading the stuff that was coming out. A lot of it was phage and a lot was based on the logic coming out from working on phage. So I was reading a lot of phage experiments. I was never directly influenced by Delbruck, and whether I was even aware of his name or not, I couldn't tell you. I probably was—the Luria-Delbruck experiment—so I was.

SCHLESINGER: Luria was at MIT; was he influencing you as well?

BALTIMORE: I was in a kind of an untutored situation until that summer at Cold Spring Harbor, where suddenly I began to see people and they had faces and names. I heard lectures from them. I guess I certainly was brought up in the mystique of the phage group there. George was very meticulous himself. He was moderately young; he was even younger than the core of the phage group, although he died very young. So when I came to graduate school, which was where we were, it was with an idea that viruses were the right things to study. I had no doubt about that. I had done it already, Cy gave me a place to do a little work but nothing came of that. Now I did get involved in one serious experiment that was important and that was with Cy. I did a lot of the counting of the last-star experiments. In fact, I ended up with tennis elbow from focusing the microscope up and down. I'd go over to his house at night and count stars. What he wanted was people who counted the stars without knowing what the data were or what you were looking at because he wanted an objective set of numbers. So I was a pair of hands or a pair of eyes.

SCHLESINGER: You were doing the counting at his house?

BALTIMORE: Yes, he would bring the slides home with him. He had a microscope at home. I would go there at night. I don't know why it worked that way, I guess because I was taking courses during the day. So I stayed at MIT for one year. The reason I stayed there for one year was again these wonderful people. Somewhere around midyear I was taking a biophysics course. I was actually learning a tremendous amount. I was finally getting things in place because I was learning from people who knew what place they were.

SCHLESINGER: Do you remember who was teaching it?

BALTIMORE: Well, there was a terrible biochemistry course that Buchanan taught. They almost threw me out of MIT because I was so nasty to him. I was a terror, but I thought I knew

what was right. I guess that is still true, but it was really bad. I wouldn't let anybody get away with anything.

SCHLESINGER: But were you usually right?

BALTIMORE: Yes, I mean certainly on that. Everybody on the faculty knew how bad the course was but nobody said, "The emperor had no clothes." I don't remember who else—I only remember the bad ones. Why don't I remember the good ones? I must have learned something.

SCHLESINGER: What microbiology did you take?

BALTIMORE: Well first of all there was Boris' [Magasanik] teaching in Bio 721, which was something I'll never forget. I mean that was like listening to a bacterium talking to me. It was so stunning, and Luria who also taught microbiology, and what else did I take?

SCHLESINGER: You mentioned a biophysics course.

BALTIMORE: I was a biophysics major, which meant that I learned a lot about spectroscopy, about machines and Model E equations. I studied for the prelim exam out of [John T.] Edsall and [Jeffries] Wyman, Volume 1, but there never was a Volume 2 (1).

SCHLESINGER: I think they are both still alive.

BALTIMORE: Edsall and Wyman are both still alive. Then came my oral exam. I'll never forget it; someone asked me about Raman spectroscopy. That was something I had skipped over. I didn't understand it at all. They quickly asked me more and more. Anyway, I passed the prelims in one year.

SCHLESINGER: Was that unusual?

BALTIMORE: Yes, it was.

SCHLESINGER: Besides Cy, who was in biophysics at MIT at that time?

BALTIMORE: There was Cy and now I remember one thing I took was the molecular genetics seminar with Cy and we read [Barbara] McClintock's papers. That was why I was never so sure that McClintock was as forgotten as people said because we were fighting our way through her work in 1960 and the color experiments in phage by Edgar and—

SCHLESINGER: Bill Wood?

BALTIMORE: No, Wood is younger than I am. They were real card-carrying members of the phage group at Cal Tech [California Institute of Technology]—[Charley] Steinberg and [Franklin W.] Stahl. There were incredible complicated theories of recombination that we studied, which I couldn't repeat to you now. McClintock stuck in my mind, very abstract. But we read all the Hershey-Chase experiments. Cy ran a wonderful seminar, which he ran until he left MIT. Somewhere around the middle of that year, probably from reading Luria's book *General Virology*, I became aware of animal viruses (2). Maybe not from reading the book, but I remember my awareness of animal viruses was very vague. I may have looked at [George K.] Hirst's recombination experiments with influenza viruses, which were out there. What did you look at when you looked at viruses in those days? You looked at genetics. That was the only thing that anybody did.

SCHLESINGER: That was at the Cold Spring Harbor meeting in 1961, I believe. Did you go to that meeting?

BALTIMORE: We'll get to that—1962 was the animal virus meeting—but I don't know maybe it wasn't Hirst. I can't remember what it was that got me thinking about animal viruses. I may have read about it before I got started. I probably read some of Luria's book on it but I didn't know anything about it. Almost no one knew anything. There really wasn't anything much to know except that they caused disease and that they were small. But I was struck by the analogy that animal viruses might do for animal cells and animal biology what phage had done for bacterial physiology, genetics, and general molecular biology. So for one reason or another—I can't tell you what it was—I was attuned to try get out of bacteria and into animal cells almost from the very beginning, and that animal viruses might be the wedge to do that with.

So I went to Cy one day and I said, "I have this question: I think what I would like to do ultimately is to get into animal cells. It looks like animal viruses might do that. Would I be better off trying to do a thesis in animal viruses somehow"—there wasn't anybody there to do it with—"or should I do a thesis in phage, get the kind of rigor that would be involved in that and then go to animal viruses." I'll never forget Cy's answer. He said, "You know I've been thinking about the same thing." That was a big help! So I went to Luria and I said the same thing. Salva was a big help. Salva said, "There's a guy I know and respect, Phil Marcus, at

Einstein [Albert Einstein College of Medicine], why don't you go and spend a summer with him." Maybe this was in the spring. He said, "Go and spend the summer with him. I can arrange it or I'll try to arrange it and take the animal virus course at Cold Spring Harbor." That, of course, was a brilliant idea. "Then you'll come back and you'll know what you want to do and anyway Jim Darnell is starting here next fall and then you can work with Jim Darnell."

You can see and will see in the course of all the discussions how much Salva had to do with this. So I went to work with Phil Marcus for a month or two, something like that. Then the animal virus course started in the beginning of August roughly.

SCHLESINGER: Now we're at 1961, is that right?

BALTIMORE: The summer of 1961.

SCHLESINGER: Who taught the animal virus course?

BALTIMORE: It was taught by Richard [M.] Franklin and Ed Simon. It was terrific. Phil was then more involved, actually, in cells than in viruses. In a funny way he would study viruses by looking at cell cloning because he came from [Theodore T.] Puck's lab and the big thing that Puck's lab did was to clone cells. So he would infect cells with viruses and then dilute the cells and see when they got killed as a measure of how much virus there was. We were doing a lot of cell-based worked, and I did learn that you could do cell-based work and we did some UV-killing experiments. I remember he was interested in whether the light reactivation of UV damage also occurred in animal cells. We tried to figure out if that was true or not. I don't know if we ever came up with an answer. The techniques of cell culture were pretty cumbersome, but I learned a lot from Phil and a lot of quantitative things. Then I went to Cold Spring Harbor and that was stunning because there were a lot of experiments you could do with animal viruses. That's what I discovered. A lot of people had been thinking about this and I kind of connected with a whole network of people who were thinking about making animal virology into a quantitative science.

SCHLESINGER: At that time, when you were working with animal viruses, was there any worry at Cold Spring Harbor about the danger of animal viruses?

BALTIMORE: No. Not at all. The first time the danger issue came up was at MIT much later. We did focus assays on chicken embryo cells using [Harry] Rubin and Temin's technique and they wouldn't work. We couldn't get the foci to come up and Richard said, "Don't worry, Harry is driving across the country. When he gets here he'll fix it." He got there and he added some magic substance to it and suddenly the foci appeared.

SCHLESINGER: You don't know what it was that he added?

BALTIMORE: Some kind of nutrient, pyruvate or something. Jim Darnell came and Jim didn't know me from Adam. I came up to him—a little guy talking to a big guy—I said, "You know I'm a graduate student at MIT and I really got turned on to animal virology. Do you think I could work with you in the fall?" He said, "Well I don't know, I have other people coming up, when you come we'll have a look at it." He doesn't remember the story exactly but that's certainly how I remember it. I took that as a statement as "I'm not sure." He didn't turn me down, but on the other hand he didn't say for sure I could do that. I was actually convinced and, as August proceeded, I got more and more interested in experiments that were being carrying out by a guy called John Rosner. John Rosner had been in the molecular biology course I taught at Swarthmore. He was a physicist. He had gone to Cold Spring Harbor as an URPP and was working with Richard and they did experiments showing that mengo virus RNA [ribonucleic acid] was made in the cytoplasm. Richard, you might remember, was very much of a cytologist as well as a physicist, a virologist. He was everything—always been his problem. He does too many different things. So he was working using *in situ* hybridization and they, just that year before, discovered that actinomycin D turns off nuclear RNA synthesis. I'm not positive if that's true—whether they used actinomycin or whether they allowed the virus to inhibit nuclear RNA synthesis and showed the viral RNA was in the cytoplasm.

SCHLESINGER: That was the only virology journal, was it not?

BALTIMORE: Yes, the only journal. We did those experiments in the course. We couldn't have because he was just doing them with Richard in the lab. I don't know—the course and the lab were interchangeable.

SCHLESINGER: So Franklin would also bring his lab out to Cold Spring Harbor at that time?

BALTIMORE: Well no, Rosner was just there for the summer. No, I don't think he had anybody working with him. It was just he and his technician, Joan Calendar. They had a lab on the fifth floor of Founder's here [Rockefeller University] in Igor Tamm's section. So Richard was a young faculty member in Igor Tamm's department and had no one working with him. I think that's right. So he just took his lab.

SCHLESINGER: In other words, just himself.

BALTIMORE: Right, if I remember correctly. So I got all excited about those experiments. I saw the opportunities of actinomycin and other things you could do and I said, "I like working with this guy, why should I worry about what will happen when I go back to MIT? Why not see if it's possible to continue," and Richard thought that would be a terrific idea if it worked out. There was a graduate program here that was very famous.

SCHLESINGER: But it must not have been very old at the time?

BALTIMORE: Oh, it started in the mid 1950s. It was about five years old. I had thought about applying here and had decided not to because some people who had graduated in the year before me had come here and had a bad time. Bob Cahn had left after a year and went to Brandeis [University] where he got his degree. Art Karlin was here; he had a better time. I think Dave Sonneborn left and he also went to Brandeis. So I was a little leery of the program. But what I had found attractive was that it paid you a lot of money. It was in New York City and by this time my parents had moved from Great Neck to New York City, and I loved New York City. So there were a lot of reasons that moving to Richard's lab wouldn't be bad, and they had a dormitory here so I could live there. It so happened that a guy—actually someone I was talking to the other day—knew this guy, could place him—had dropped out of the program so there was a slot in the program. The way you got into the Rockefeller program in those days was that somebody whom Detlev [Wulf] Bronk knew wrote a letter to Detlev Bronk saying that this guy walked on water. Detlev Bronk said that's the only kind of recommendation that really matters and it has to be from somebody I know and it has to be a first rate recommendation. So I called Salva—this is how brash a guy I was. I found him at Woods Hole and asked if he would write a letter of recommendation. I explained the whole thing and he said, "Look, I want you to be at MIT, I think it's a very important program and everything else, but if this is what you want to do I'll do it." He got me into Rockefeller. So I think it was the 23rd of August when he wrote the letter and I was here in September. It was a fabulous experience because Richard was very supportive and at the same time let me do other things.

SCHLESINGER: Was this 1962?

BALTIMORE: No 1961, the fall.

SCHLESINGER: This was after you took the course?

BALTIMORE: Right.

SCHLESINGER: Right after?

BALTIMORE: Right, and when you came here in those days in the fall, you had to take this course that met every day. I almost got thrown out again; it was really horseshit. First of all I didn't show up for awhile and they let me know you were expected to show up. So I would show up and do a crossword puzzle. People were just pissed off to the point where a great old embryologist, Paul Weiss, didn't invite me to his Christmas party. He invited all the other students, but he hated me.

SCHLESINGER: How did you do in the exam or did they not give you one?

BALTIMORE: Oh, they never had exams and the course was kind of a culture of science thing. There were anthropologists and sociologists from Columbia [University] and I wanted to get out of it. I knew what I wanted to do. I didn't need this thing, and I had already passed prelims.

SCHLESINGER: Did they let the MIT prelims count?

BALTIMORE: No, well they didn't have prelims. In those days here the program was totally unstructured. You just worked out a program. The only course you had to take was this course, which was the apple of Detlev Bronk's eye because it was culture, scientific culture and it turned out cultured people. Other than that, if you wanted to take courses, they taught a few courses here or you went to Columbia. You went somewhere else. You were really much better off coming here if you had had training somewhere else. I did it exactly right, in that sense, because I could never have gotten the formal training here that I needed. Most students—and I think that was part of the problem—were coming out of Swarthmore, where the program is seminar-based and we used to teach ourselves. Anyway coming here was a shock because there was no way to structure your life. The people who did best were M.D.s or Ph.D.'s. The first graduates were mainly M.D.s. They loved it. I was one of the few people who were just a Ph.D. student and I had had one year somewhere else and that helped a lot. There were students who were here forever trying to get straight what they wanted to do. But I came to do something and did it. I worked in Richard's lab while I was taking this course and I really got involved in mengo-virus work, which was what the Rosner experiment had been on and what I ultimately did my thesis on. I think I started looking at whether actinomycin inhibited flu and NDV and other lipid viruses. Richard was one of the first people interested in lipid viruses and actually wrote a very important review on lipid viruses. I remember that. I mean I think I discovered that actinomycin inhibited flu, and we didn't believe it and we didn't know what to do with it. It wasn't necessarily even interesting because you couldn't fit it into anything. So somehow, around January, I started on mengo—maybe when that course was over or something—and on actinomycin and then I just did experiments day after day after day. I'd come in the morning.

SCHLESINGER: Were there just the two of you in the lab?

BALTIMORE: Two of us and Joan Calendar, his technician. Bob Krug came the next year. He was the other student in the lab. Peter Gomatos was sort of Richard's student—he wasn't really a student, sort of a postdoc—working on reovirus. They discovered that reovirus was a double-stranded RNA virus by looking at infected cells, seeing that they were green instead of red. But Gomatos was really Tamm's student. He was a student in the program, but he was Tamm's student. So the first year it was just me.

SCHLESINGER: How much interaction did you actually have with Tamm?

BALTIMORE: Tamm was kind of distant. I mean I knew everybody on the floor. Purnell Choppin was on the floor. He was still mired in eggs. I mean he was an M.D. who was just getting his hands wet in experiments. He was an assistant professor, maybe, by then but I remember my feeling that his experiments were not very biochemical.

SCHLESINGER: So was there a fair amount of animal virology?

BALTIMORE: Well that was Tamm's Department. Animal virology at Rockefeller went way back, starting from the beginning with Rous [sarcoma virus]. There was the whole lab in Princeton [University], the virus lab. That's where Wendell Stanley was and the papova virologist, [Richard E.] Shope [Bob Shope's father]. Shope was in Princeton and then when Princeton closed they moved all the Princeton people here. Stanley went out west but Shope moved in here. Shope was on my thesis committee. He was very old. I remember he said that the abbreviations made it very difficult to read, "What does cpm mean?" That was a different world. Animal virology here had a very long and strong history. Tamm had taken over the department from [Frank L.] Horsfall because Horsfall had gone over to head Sloan-Kettering [Memorial Sloan-Kettering Cancer Center]. Horsfall in turn had taken over from [Tom] Rivers and all the original polio work, but Rivers was the great figure. So this was the virology lab.

SCHLESINGER: Was Franklin the first more molecular person to come here?

BALTIMORE: Yes.

SCHLESINGER: Were there any other young virologists around besides Franklin?

BALTIMORE: Purnell and Igor always had an active lab and people would come through. A guy named [Rostom] Bablanian worked with Igor. He's now at Downstate [State University of New York (SUNY) Downstate College of Medicine].

SCHLESINGER: I'm trying to get a picture of the viral group.

BALTIMORE: There were these people on the floor. Lennart Philipson had been there the year before. He had been there for two years before. He had brought in a certain amount of molecular techniques. He was more interested in receptors and everything on the floor had Lennart's name on it. Lennart had taken over pretty well. He and I laugh about that now.

SCHLESINGER: Where was his previous training?

BALTIMORE: He came from Sweden. I don't know. I never really asked him what he had done before. I didn't fully know what he did there but that was the beginning of his career in biology.

SCHLESINGER: How much did you interact with other groups?

BALTIMORE: Well, I'll get to that because that actually is critical. When I first started out the answer is none. I just went to Richard's lab and we continued what we had been thinking about throughout the summer before. His only really close interaction was with Ed Reich and they together had worked out the action of actinomycin and mitomycin. Ed was kind of a chemist working with a chemical background, Richard from a biological background.

So I just started doing experiments and they started working. I did experiments using cells grown on coverslips and just pulsing them with radioactivity, then fixing them and counting them in an end-window counter from which I took off the membrane. You used to have these Geiger counters with membranes. If you took off the membrane you could count tritium at very low efficiency but you could incorporate a lot of tritium.

SCHLESINGER: Were you using tritiated uridine?

BALTIMORE: Tritiated uridine or leucine.

SCHLESINGER: Could you buy them?

BALTIMORE: You could buy tritiated compounds; C-14 label was too low a specific activity and it was too expensive. You couldn't buy P-32 label, but you could buy the others. So I used lots and lots of tritiated uridine once I learned that actinomycin D turned off nuclear RNA synthesis and allowed viral RNA synthesis. Then I could just do that routinely and study all sorts of things about the virus. It was just like walking though open doors. Everything worked. It was all new. Some things that were already in the literature suddenly made sense. I turned out papers—it was extremely productive. This is now, basically, six months from January to June. Once we knew that actinomycin inhibited nuclear RNA synthesis, you could see the viral RNA in the cytoplasm. What you realized was that if you infected cells and looked at them again by autoradiography, you realized that the virus inhibited nuclear RNA synthesis by itself. You didn't have to add actinomycin. You just watched nuclear RNA synthesis fall. I had a biochemical bent so I said I would take a look at it enzymatically. It was only just then that Sam Weiss had discovered the RNA polymerase in rat liver. Originally it was called the aggregate enzyme. So I made the aggregate enzyme preparations from cells infected with virus, L cells, and showed that you could see the aggregate enzyme inhibited by the virus infection. We published that (3). So in the summer of 1962, I went to Cold Spring Harbor and Richard gave the talk (4). He reported all those experiments and they were a bit of a sensation because they were much more biochemistry than anybody else was doing.

SCHLESINGER: Was this before you were assaying the viral enzyme?

BALTIMORE: Yes, that's what I was going to tell you. When I came home from that meeting I said what the hell. We had been so successful showing inhibition of nuclear RNA synthesis. It was just at the end of that spring.

SCHLESINGER: How did you do that? How did you show that it was nuclear?

BALTIMORE: We purified nuclei. The aggregate enzyme preparation was a kind of "gemisch" from the nuclei that incorporated nucleotides and was sensitive to actinomycin D. But you needed to do something quite different, and I would have to go back and read the papers to remember what that was in order to see the cytoplasmic RNA synthesis. So I came back from Cold Spring Harbor and said, "What the hell I'll look for the cytoplasmic activity"—and there it was, as soon as I made a cytoplasmic extract and added the right precursors. Now we did have to synthesize our own precursors, as these were triphosphate precursors, I actually made some triphosphates.

SCHLESINGER: Did you make them labeled?

BALTIMORE: Alpha-P-32 labeled. We used various sorts of things, but in order to really show incorporation you wanted to show transfer of phosphorus. Basically the methods were all things that had been worked out by [Arthur] Kornberg and then that other people had picked up to look at other polymerase systems but Kornberg had discovered it with DNA polymerase. He was the key figure. All through that time the reason I was able to do these experiments was that I got tremendous help from the people in [Fritz] Lipmann's lab. So here was where the graduate program was wonderful because we all lived together. We lived in the dormitory, we ate together; that's how I got to know some of the graduate students pretty well. I was pretty much of a loner and some of them had come in together and I came in my second year. They had known each other from the first year so I was not really a part of the crew but I got to know them pretty well and I think it was my friendship with Jimmy Schwartz that led me to Lipmann's lab, Jimmy was then a student in Lipmann's lab and the guys there showed me how to do in vitro biochemistry and it's not that it's hard but if you don't know what size test tubes to use or how to use a vortex—I had never had even seen a vortex before I went there—and micropipettes. We used to use glass micropipettes. The guys would help me were with Jimmy and particularly Dan Nathans who was a postdoc in Lipmann's lab. I still have friends—in fact, I just got a letter—I have to answer it—from Jorge Allende who wants me to visit him in Chile. He was in the lab at that time. Jim Ofengand was in the lab at that time.

SCHLESINGER: This is all in Lipmann's lab?

BALTIMORE: Yes, all in Lipmann's lab. It was the most active biochemistry lab.

SCHLESINGER: Were you the only lab that was looking at *in vitro* RNA synthesis at that time?

BALTIMORE: You mean at Rockefeller?

SCHLESINGER: No, in the country?

BALTIMORE: Oh, I think so.

SCHLESINGER: Now, I'm trying to remember what the story was with the RNA phages.

BALTIMORE: Oh, I can tell you that I was first. I did it before they did. They were beginning to look for it. RNA phages were discovered here. In fact, whomever I was talking to the other day said that the guy who had left the program was actually the guy who was in sewers and isolated the RNA phage in [Norton] Zinder's lab. Zinder was always convinced that the RNA phage would wipe animal virology off the map because the only thing interesting about animal viruses was that they were RNA viruses, and when there was an RNA phage, who needed to study RNA viruses? He believed that for a long time.

SCHLESINGER: There are some people who still believe that.

BALTIMORE: Well, I don't know about that because the styles of replication issues are so different, but I had moments of hesitation on that issue, but I never let it bother me, thank God. The people who were doing the biochemistry on the RNA phage were at NYU [New York University]. Actually, I had some connections with them because Richard was friendly with Jerry Hurwitz and when I had done all these experiments and we were going to write up the first paper on the inhibition of the aggregate enzyme Richard said why don't we go down and show this stuff to Jerry Hurwitz. He'll be able to help us and Jerry was terrific because he helped me reformulate the data in a form in which other people would be comfortable with. There wasn't anything wrong with what we had done but everything was in counts per minute. Nobody knew what the specific activities were. I didn't know how to write a paper that would match with what the scientific world expectations were for a biochemistry paper but Jerry knew how to do this so he helped me. It was a matter of ordering the data. He may have even suggested some control experiments that we did. I think he did but I don't remember what they were. But when the paper came out we owed a lot to Jerry for making it sensible (3).

SCHLESINGER: Where was it published?

BALTIMORE: *PNAS* [*Proceedings of the National Academy of Science*], I think, I'll have to look it up myself but I believe the first paper was in *PNAS* and it was submitted by Lipmann (4). I remember because I had to go to Lipmann's office to talk to him. I mean all the time I was in Lipmann's lab I had never met Lipmann who was in the classic way the German Professor, sitting in this big office, more or less by himself, and then the people would come to him. Everybody venerated him because when you did come and talk to him, he was so clear and so quick. He was very nice. He actually helped me. Until the time he died, he remembered that extremely well. So he was probably much warmer than I would have thought he was but I was kind of frightened. He was already a Nobel Laureate then. There were a lot of great men around here in those days; there weren't many women. A lot of great men.

SCHLESINGER: In 1962, the Cold Spring Harbor meeting was, in retrospect, certainly revolutionary. Did it make that kind of impact on you?

BALTIMORE: Absolutely. I came back from that meeting starry-eyed by all the progress, all the interesting science that came out. I don't know who organized it. It would be interesting to look back and see. Whoever it was really knew what they were talking about and got an incredible group of people. It was very interesting. It was wonderful for a second-year graduate student to find himself part of this world. That's of course a great moment in everybody's scientific career—to discover that all these people you've been reading about take you seriously.

SCHLESINGER: I am trying to remember, and maybe you can try to remember too, what the major issues were at that time. How was your work treated? What were the questions being asked about it?

BALTIMORE: All I remember really was this kind of feeling that biochemistry was coming into a field where it had never been before—that you could begin to look at DNA synthesis by DNA viruses, RNA synthesis by RNA viruses—turning on enzymes and turning off enzymes.

SCHLESINGER: Were there criticisms of your work? Do you remember? Was there anybody who didn't believe it? Now were talking about 1962.

BALTIMORE: That's right, and a lot of work on actinomycin and timing issues. No, I don't remember any. I don't think there was anybody who could criticize me. The only people working on picornaviruses from that perspective, the only person was really Jim Darnell and he wasn't involved in the same issues. I don't know what he was involved with.

SCHLESINGER: In polysome distributions?

BALTIMORE: No, this was earlier than polysomes. Polysomes were only discovered the next year. I think the discovery was in Rich's lab by John Warner and then I found myself at MIT two years later.

SCHLESINGER: Let's go to that later. What you said was that it was 1962 and you came back from Cold Spring Harbor.

BALTIMORE: Right.

SCHLESINGER: Let's spend a little more time on that.

BALTIMORE: All right. So I started looking at the RNA dependent RNA polymerase and the experiments were basically modeled on what I had learned to do with the aggregate enzyme incorporation studies. I knew the issues and it was easy because mengo sets up a really powerful ribonucleotide-incorporation system in infected cells and there is no real background if you work with normal cells. So you add actinomycin as a proof that it was RNA dependent.

SCHLESINGER: So the animal virus RNA polymerase was discovered before the phage polymerase?

BALTIMORE: Right, as I said, at NYU. Charles Weismann was working on that at NYU, I knew about it, and [Sol] Spiegelman was also working on it but we published before them (5, 6). Of course we couldn't do as much with it as they because they could then purify it. They had a soluble enzyme and they could really work with it and we were blocked in doing anything until years later when I discovered how to solubilize it.

SCHLESINGER: Did you try at that time to purify the enzyme, after you made this discovery?

BALTIMORE: I characterized the activity but it was a particulate activity. I knew it was particulate and it was really a problem to work with.

SCHLESINGER: So this was done with mengo?

BALTIMORE: Yes.

SCHLESINGER: Did you then follow it up?

BALTIMORE: I think right then I followed it up with polio. Richard didn't work with polio, but Igor did. Hans [J.] Eggers was in Igor's lab and there is a paper on the polio polymerase with Eggers and Tamm (7). But that was just an extension and very straightforward. The polio infection didn't inhibit nuclear RNA synthesis as well. They got involved in that and Bob Krug's thesis was on inhibition by polio, but it was never as nice as mengo; mengo was much better—mengo and the L-cell system. I don't know why. It depends on the cells. So I worked on that through the fall, perhaps. We published some papers on it. Then I decided some time in there—Richard was leaving, I think he left in the spring of that year to go to Colorado.

SCHLESINGER: 1963?

BALTIMORE: Yes.

SCHLESINGER: Permanently?

BALTIMORE: Yes, he took a job in Colorado and so I kind of finished up on my own and there was no reason to stay. I had enough for a thesis, more than enough. He was gone. I didn't want to go to Denver, and I didn't need to. So I ended up actually doing my thesis in a year and a half, until June, 1963, then I went to work with Jim Darnell as a postdoc.

SCHLESINGER: So you actually came to MIT, but you hadn't gotten your degree by then?

BALTIMORE: I hadn't gotten my degree yet. They didn't want to give me my degree because I had only been in residence for two years and they said it wouldn't look right. It was very flexible here and it wasn't unusual for somebody to go away. So they said, "Why don't you go away for your last year and meanwhile write your thesis?" So I wrote it and actually Igor helped me a lot (8). Igor was a stickler for every word. So that was good. Some time during that previous spring I went out to Colorado once or twice and went over things with Richard. Then after June, probably September of 1963, I went up to MIT and I was in Jim's lab.

SCHLESINGER: What made you decide to go to Jim's lab rather than say to Jerry Hurwitz?

BALTIMORE: I did go back to Jerry Hurwitz later.

SCHLESINGER: But what was the attraction of Jim's lab?

BALTIMORE: Jim did polio research very differently. Richard and I had even tried to use some of the techniques that Jim pioneered, sucrose gradients, in particular.

SCHLESINGER: David, before we leave your graduate career, let's continue a little bit more on the observations that you made. You must have given some talks. Do you remember responses to what you were presenting or what people said?

BALTIMORE: Yes, I gave talks. I even went to the West Coast for the first time in my life. It was set up by Richard. Richard had worked on the West Coast, worked at Cal Tech and knew people there. For some reason Klaus Bayreuther—I guess Richard was a Germanophile and he was friendly with Klaus—took me around the West Coast. It was very nice. Actually it's interesting, now that you mention it, there were two people I met at Cal Tech that made a lasting impression on me because they were the only people of my generation I could find who were thinking like I was. One was Tom Benjamin and the other is now at ICRF [Imperial Cancer Research Fund] , Mike Fried—those two guys.

SCHLESINGER: What do you mean—thinking the way you were thinking?

BALTIMORE: Well, they were thinking biochemically, and they were thinking from a base of molecular biology and genetics. They were interested in phage, trying to see how animal virus systems fit into the more general concepts of virology that were then current, which came out of phage.

SCHLESINGER: Can you reconstruct at that time what were the major issues in molecular biology? This was just about the time when allostery and repression were being described.

BALTIMORE: Of course all those things that were about physiology and bacterial physiology had no effect at all on virology. I knew about all of those things. I remember when I came back to MIT late in the summer of 1961, Cy stopped me and we talked about our summer experiences. He had been at the Pasteur Institute, I think. He told me about messenger RNA. The experiments had just been done that summer—back and forth between Cal Tech and Paris. So virologists had to deal with messenger RNA and with genomes.

SCHLESINGER: That was just the breaking of the code?

BALTIMORE: The code, yes, I think that summer [1961] was the Moscow talk by [Marshall W.] Nirenberg—the polyU experiment.

SCHLESINGER: Did either messenger RNA or the code breaking impinge on your thinking?

BALTIMORE: Absolutely, because I had always been interested—as any molecular biologist at that time. I had been interested in codes. I even wrote a paper—I think either at Rockefeller

or maybe at MIT—about codes, just the whole coding-decoding issue. Could we know what the code was? We only knew there was a code, and it all came from [Francis] Crick. We knew, particularly working on RNA viruses, that RNA could be a genetic material. For many years when I had to give a one-word summary of what I was concerned with, I was concerned with how RNA could be a genetic material. In fact Ed Simon did the experiment that really showed that there was no DNA involvement in replication of RNA viruses.

SCHLESINGER: What did he do?

BALTIMORE: It was a BUDR [bromodeoxyuridine] experiment or something. He showed that you could interfere with all DNA synthesis—and it shouldn't be BUDR but for some reason I think it was. No, it was FUDR [flurodeoxyuridine], that's right. It would block all DNA synthesis and still RNA viruses would grow and that said there was no DNA intermediate in the growth of RNA viruses. Of course it was the dogma until reverse transcriptase.

SCHLESINGER: In fact it was that kind of experiment that I would think Howard [Temin] did with Rous.

BALTIMORE: Yes, actually Howard's experiment was more an actinomycin experiment. It was a key experiment about 1962. In fact, although I wasn't particularly aware of what was going on, it said that it blocked Rous. Remember, I had found that it blocked flu.

SCHLESINGER: I was going to ask you about that.

BALTIMORE: So I wasn't so impressed that it blocked Rous.

SCHLESINGER: In the first edition of the *Microbiology* text [Davis et al.] Harry Ginsberg wrote that actinomycin blocked viruses like Rous sarcoma virus most likely due to side effects (9).

BALTIMORE: That was what we all worried about and although it was very nicely specific in the cases in which we worked with it here, we had this one anomalous result with flu. We didn't have any other anomalous results.

SCHLESINGER: So you put that on the shelf and didn't worry about it?

BALTIMORE: Yes, and Howard never turned up at these meetings. I knew Howard from when I had run into him in high school, so his name was familiar to me. I was aware of his very important work with Rous, but I didn't physically see him for many, many years.

SCHLESINGER: So let's move back to the part where you were talking about Tom Benjamin and Mike Fried.

BALTIMORE: It's not that they had any particular influence, but their considerations in working on polyomavirus in Renato's [Dulbecco] lab, which was what they were both doing. I resonated with their concerns, which, as I said, were a molecular biologist's concerns. I can't remember any of the issues that they were involved in. I think the circularity of the DNA genome.

SCHLESINGER: I know there were experiments that showed that you needed DNA synthesis to get transformation.

BALTIMORE: I just don't remember what they were concerned with. But I do remember, when I came back from that trip, that very striking sense of saying to people I knew that I found some people I felt particularly close to.

SCHLESINGER: How did people respond to this proposition? Was there uniform acceptance that there could be a new enzyme being made by RNA viruses?

BALTIMORE: I think so; I don't think that was a problem. The problem was more in finding and showing it was really there than that anybody expected it wouldn't be there. Because, as I said, the notion that there was RNA synthesis was pretty well accepted based on the drug experiments. You could see visually the factories set up in the cytoplasm for the synthesis. So something was there, but no one knew how to really pin it down. The first paper was actually published in *BBRC* [*Biochemical and Biophysical Research Communications*] (5).

SCHLESINGER: Was that where you published the first observations?

BALTIMORE: Yes, and I don't know what people were concerned about with other viruses and in many cases they were well behind. People were trying to keep the RNA molecules straight. You know that was a big issue: how big they were, how many there were. You were able to get a nice, clean peak in a sucrose gradient with polio. That was what Jim Darnell was

doing. That was what was so attractive about Jim's lab was that he was able to look at the molecules. I was able to look at the synthesis of molecules but I couldn't look at the molecules themselves. I didn't know how to run a sucrose gradient. As I said, we tried a little bit, Richard and I, to set it up but we didn't know. We didn't know the mechanics that had been worked out and Jim helped. So that's why I went to Jim's lab really. It was to link into that new very powerful technology, to be able to look at RNA molecules.

SCHLESINGER: So this was the summer of 1963?

BALTIMORE: Summer, 1963. So that's a measure of what people were concerned about. They were concerned about how many RNA molecules there were, what their form was. Reovirus had just then come along with double stranded RNAs.

SCHLESINGER: At that time had people already looked at RIs [replicative intermediates] and RFs [replicative forms] in bacteriophage?

BALTIMORE: I don't remember. As I remember, I was just actually saying this to someone, it was Luc Montagnier's experiments that showed the first double stranded RNA, but I can't remember.

SCHLESINGER: In which kind of infection?

BALTIMORE: That was in EMC [encephalomyocarditis] virus-infected cells. What I can't remember was how that relates to reovirus. I know that it happened the first year I was a postdoc.

BALTIMORE: Are you now at MIT?

BALTIMORE: At MIT in 1963. It happened roughly at the time I went to Jim's lab, because we settled in to repeat them. Yechiel Becker and I were in Jim's lab and we published a paper on polio double-stranded RNA (10). It was partly derivative. We found some new ways of working with it, particularly the solubility of the RNA in high salt, which was suggested to me by the solubility of double-stranded DNA in high salt and that provided a trivial purification method.

SCHLESINGER: Was there any concern in Jim's lab about working with polio? I say this because Bernard Roizman tells a story about how at Hopkins [The Johns Hopkins University] they wouldn't let him work with polio so he started to work with herpes simplex virus.

BALTIMORE: Oh, that's right. I remember that. No, we had no problem working with it. I knew there were some people who were concerned. Obviously polio was something to worry about, but since everybody was vaccinated in those days we felt pretty well immune to whatever the virus might try to do to us. I think the only thing we were worried about was when people came from abroad and might not be vaccinated. We checked them. But all the time I worked with polio that was never a concern. I was very surprised when Bernard told me that story.

SCHLESINGER: By this time, polio was becoming an interesting research tool for several laboratories. Were there already reports of recombination of polioviruses?

BALTIMORE: Yes.

SCHLESINGER: How did those impinge on your thinking?

BALTIMORE: Oh, that was an oddity. I mean I knew about the recombination. I was interested in it, but it never went anywhere. They could never really make a map. If you look at it from a modern perspective, the map is what really gets you somewhere and they couldn't make a map. They couldn't get recombinational distances. So the phenomenon existed but it didn't have much of an effect.

SCHLESINGER: So from your perspective the issue at the time was really what was happening to the RNA molecules?

BALTIMORE: Yes. The issues were very much the mechanics of the RNA molecule, the mechanics of protein synthesis, some on how the particle came together.

SCHLESINGER: Did you try at all to look at the proteins at that time or was that before acrylamide gels?

BALTIMORE: No, we couldn't do much. I did some *in vitro* protein synthesis experiments. Some place I have a paper on that (11).

SCHLESINGER: But until recently, *in vitro* translation studies were a problem with polio anyhow.

BALTIMORE: No, polio was not so bad. Lydia [Villa] Komaroff did a thesis on polio protein synthesis (12). No, you needed polyacrylamide gels and until [Jacob V.] Maizel and [Donald F.] Summers came along with the gels and showed the polio peptides, it wasn't much of an issue. That was later, maybe in the middle of the 1960s. By that time I was out at Salk [Institute].

SCHLESINGER: So in Jim's lab what did you and Yechiel do?

BALTIMORE: Well we worked on double-strand RNA, we worked on the replicative intermediate to some extent. I can't remember exactly.

SCHLESINGER: Were you accepted back at MIT? Were people glad to have you back?

BALTIMORE: Oh, yes. There was no rancor about my leaving. I think again because Salva had been so good about it. He was just glad I was back and he, in fact, arranged to pay me. I think I was paid from a training grant while I was in Jim's lab. There was a lot of excitement. Sheldon Penman had just come up to Jim's lab from Alex Rich's lab. Sheldon had gotten out of physics and into biology through Alex's lab, but he didn't want to do structures, he wanted to get more into physiology. So he was running around the lab in a foolish fashion, but it was very exciting—pushing the sucrose-gradient technology. Somehow I think that was the year that polyribosomes were discovered, but maybe it was the year before. It was the year before, but actually John Warner and Paul Knopf had been in my class as graduate students at MIT. When I came back as a postdoc, it was only three years after I started as a graduate student. So most of the graduate students who had been with me were still there. I actually rekindled friendships with people I'd known for that period, like Ethan [Signer], but he had already left. Ethan was a little older. He had been in Cy's lab for some time. It was a very intense, very wonderful time because there were so much was happening.

SCHLESINGER: Was Jim's the only lab around MIT and Harvard [University] that was working on animal viruses at that time?

BALTIMORE: Jim's was certainly the only one at MIT and I don't remember what was going on at Harvard.

SCHLESINGER: So you didn't interact with people there?

BALTIMORE: No, I don't think we much cared what was going on at Harvard. Then Jim decided to leave. His wife wasn't happy in Boston (he was actually quite happy) and took a job at Einstein. So again, after the end of that year, I was going to have to leave and by that time I was feeling a real need to be more of a card-carrying biochemist. In Jim's lab you dealt with molecules very effectively and particles and things, but not biochemistry, which was what my first love had been, and which it has always remained. So I went to Jerry Hurwitz from Jim's.

SCHLESINGER: What were the experiments that you did at MIT? Do you remember you talked about the really breakthrough experiments you did as a graduate student. Was there anything comparable as a postdoc?

BALTIMORE: No, I don't think there were any real breakthrough experiments that I did that year with Jim. I was trying to think of them recently because I was going over this for a grant request. I even looked back at my CV and I can't find much that I did there. I started a bunch of things I think and was working a lot with Marc Girard who had just come that year. He was the first postdoc.

SCHLESINGER: Yechiel had been an animal virologist from Israel.

BALTIMORE: I guess so. I don't actually remember his background. Jim's lab was half involved with cellular RNA synthesis and half involved with viral RNA synthesis. I guess Klaus Scherer was there. The Scherer-Darnell experiments were roughly in 1962, I think, maybe before I came. So although I have the warmest remembrance of it and lots of excitement when I sit down and try to figure out what I really got done I don't think a whole lot came out.

SCHLESINGER: Well, let me ask the question a different way then. Can you recall how it might have influenced your thinking in terms of what was going on at the time, the direction that you might go?

BALTIMORE: I think that the whole issue of RNA molecules was the big deal, that you could purify them, that they have a defined size, and that they could be characterized. Jim's work was always very, quantitative in its orientation. Pulse-chase experiments, following things through. Those were all new to me.

SCHLESINGER: One of the first things that one learns as a biochemist is to balance numbers. Is that what you learned in Jim's lab?

BALTIMORE: Well, no you can't do that in a real physiological experiment. For instance, if you pulse and then chase uridine, the first thing that happens is that a bunch of it gets degraded and you can't balance the equation. In fact you had to fight with that issue continually—of not being able to do faithful mass balances.

SCHLESINGER: But you did need to know that of the counts that were being incorporated, you were examining most of them.

BALTIMORE: Right, you had to find out where most of them were. But my remembrance of that time, I must say, is pretty vague. I'm much clearer about when I went to Einstein.

SCHLESINGER: All right. Let's go to Einstein.

BALTIMORE: So Jim was going to Einstein and I arranged to go to Einstein. That enabled me to do what I wanted to do, which was to work with Hurwitz, but also to keep track of the polio stuff and a certain amount of stuff, particularly work that Marc Girard did. Jim was thinking of leaving viruses and moving towards cells. A lot of what Marc did I either directed or was involved in, I don't remember what all that was—to tell you the truth—but certainly it led Marc to come out with me to Salk where we did a lot of work on the replication of the virus. So I suspect that was most of what was going on. But I went into Jerry's lab and found an entirely different environment than I had ever imagined: an environment in which, what went on in the cell didn't matter, what went on in the test tube did. Everything I had done up until then, even when I had done *in vitro* biochemistry, had always been focused on questions that had come out of the cell not out of purified proteins. In fact, for all the biochemistry I had done I never had really worked with purified proteins at all except maybe for synthesizing AMP. So I learned about protein purification and I learned about the very great power that you got from working with purified proteins and I got a tremendous frustration from being unable to relate that to cells. I can remember actually trying to set up some sucrose gradients so we could do some cellular experiments. Jerry had never seen anything like this, didn't want anything to do with it.

SCHLESINGER: What were the enzymes you purified?

BALTIMORE: Well the first enzyme, the major enzyme I spent most of the time trying to purify was DNA polymerase, following a purification of Kornberg's.

SCHLESINGER: From bacteria?

BALTIMORE: From bacteria. It was all from bacteria. But the first successful experiment I worked on—I did things and I don't remember what they were—I do remember that one day I realized that the lab had everything it needed to study the initiation of RNA synthesis and that was something about which nothing was known, how you started the chain. So I collected all those things from the various people working—RNA polymerase from somebody who was purifying RNA polymerase, radioactive triphosphates, labeled triphosphates from somebody else. I showed triphosphate incorporation into an RNA polymerase product, which really demonstrated for the first time that polymerase products start with a triphosphate—start *de novo*. Then all hell broke loose because it was fundamentally an experiment somebody else should have done—almost anybody—[Abraham] Novogrodsky, [Umadas] Maitra should have done it. Somebody should have done it and they were pissed off at me because I'd done it. On the other hand it was very exciting because it worked so we came to some meeting of the minds and so we published the whole thing together (13). I think Maitra was the first author because he was the one who purified the polymerase. He probably did the most work.

SCHLESINGER: I can't help but ask you a question of whether this was the first time that you ran into this kind of problem?

BALTIMORE: Oh yes, it really was the first time because, well in Franklin's lab that kind of problem never existed and in Darnell's lab you didn't end up stepping on toes. But that was a bit of a shock to discover how passions could be released by having done such a simple experiment. Now I agreed to stay off of that so I decided to do the same thing for DNA polymerase and that I had to purify myself and so that was why I spent a lot of time purifying DNA polymerase. That was a hell of a purification—the Kornberg purification—because it involved an autolysis step in which you basically just let everything cook and degrade itself until the only thing that was left was polymerase—in principle—of course, since sometimes it was left and sometimes it wasn't left; a tough purification. But I got some enzyme and much to my credit was unable to show that it initiated. Of course, there I could prove a negative—that it is a totally primer dependent enzyme, and that of course is the truth. It is a totally primer dependent enzyme.

SCHLESINGER: At that time, is that what you thought or did you just not understand what was happening? Remember at that time the concept of a primer was not so well established.

BALTIMORE: No, it wasn't very current and I don't think we ever published it. But I think in our minds what we concluded was that if it initiates it was hard to show and I think you really

couldn't say that it was primer dependent but the notion of primers was certainly very current in my mind after that.

SCHLESINGER: At that time or after that, I'm trying to remember, what the first examples of primer dependency were.

BALTIMORE: Oh, sure it was polynucleotide phosphorylase, that's going way back.

SCHLESINGER: I didn't think that was primer dependent.

BALTIMORE: It was because you extended an existing chain. It was very hard to show *de novo* synthesis. That was the whole problem with polynucleotide phosphorylase, it didn't *de novo* initiate, and it doesn't; it just extends chains. So the notion of primers was much older than that and in all of [Gobind] Khorana's experiments all of those things were primer dependent but it allowed them to make chains of repeating nucleotides. No I don't think that was the case, remember that Kornberg had done a tremendous amount of work by that time and I think he was arguing that it [DNA synthesis] was primer dependent. I can't remember. But since we had figured out this triphosphate trick it would be possible to look at it and no one had done that. We were going to show it. In my own experience that was the first time I had been wrestling with such a question and it's interesting how much further wrestling I did with that thereafter with reverse transcriptase. So I had a successful experience in Jerry's lab but I wasn't happy. I wasn't happy because I was missing polio and because there was a lot going on.

SCHLESINGER: Were there other people working on polio?

BALTIMORE: Summers and Maizel were with Jim Darnell at Einstein.

SCHLESINGER: Your only real experience with polio had been with Jim?

BALTIMORE: I did a little work with Tamm. I worked on polio when I purified the polio polymerase or showed the existence of the polio polymerase, which was toward the end of my thesis. I don't even think that it appeared in my thesis but I did have that little bit of experience. It surely was not different, polio and mengo are extremely close, but in Darnell's lab they worked entirely on polio because he came from [Harry] Eagle' lab and Eagle picked up polio probably from [John F.] Enders.

SCHLESINGER: So is that where Jim came from in terms of his interest in polio?

BALTIMORE: Oh yes, he had been at the NIH [National Institutes of Health] with Eagle and then when Eagle went to Einstein that was part of the reason Jim went to Einstein.

SCHLESINGER: And Eagle came from Enders?

BALTIMORE: No, I don't remember exactly what got Eagle to work on polio. It may even be that Jim was the first one to work with it there. Leon Levintow was there.

SCHLESINGER: Most of Mike Bishop's work on polio was done at the NIH with Levintow.

BALTIMORE: That was later and that was the same lab. That's where Leon worked but by that time Eagle had left and had gone to Einstein. But Eagle was interested in growing cells, an interest he derived from working on malaria. I think probably the interest was fathered by Enders', [Thomas H.] Weller's, and [Frederick C.] Robbins' work on polio *in vitro* but again they worked with much more complex cellular systems. HeLa cells offered a very simple cellular system and that was Eagle's great contribution—to get HeLa cells to grow and, I think, to demonstrate how good the cells were. When they started to work on polio that was a utilization of the cellular system.

SCHLESINGER: When you were at Einstein did you have any contact with the virologists here at Rockefeller?

BALTIMORE: No, I think not, except I would see them but particularly since most of my work at Einstein wasn't virology and also the distance. I lived on the west side and drove up to Einstein from the west side of Manhattan, so I had no reason to be here.

SCHLESINGER: So you said you were missing polio?

BALTIMORE: Yes, right. I was missing polio and missing working physiologically rather than just biochemically. Renato Dulbecco came through and, I think if I remember correctly he was staying down here around Rockefeller, and called me and asked if I'd come talk with him. The exact details I don't remember, but what transpired was that he offered me a position to go to the Salk Institute.

SCHLESINGER: This must of been the beginning of Salk.

BALTIMORE: It was the beginning of Salk and Renato was still at Cal Tech, maybe he had already made the move. I don't remember, I think he had made the move. But it was very much on an edge whether the Salk Institute would or wouldn't happen or how it would look and so after he offered me the position there was then a couple of months in which he would say, "Don't make any commitments yet, there's a meeting tomorrow after that we'll know better." Then he would call me after that meeting and say, "Well we're still not sure what's going to happen or whether it's going to happen." This was all Jonas' [Salk] maneuvering and the maneuvering of the Polio Foundation—how much money they were going to put in and what was going to happen. It started in the fall of 1964 or sometime early spring of 1965. Renato said it was okay to come. So I virtually just packed up my bags.

SCHLESINGER: How long were you at Einstein?

BALTIMORE: I was at Einstein about eight months and then I said, "Jerry, I admire you. It's been wonderful, but this is obviously a mismatch." He said, "I agree with you entirely and we're still good friends."

SCHLESINGER: Now you are telling me about the problems of the Salk Institute. In the spring of 1965 things looked all right.

BALTIMORE: Right

SCHLESINGER: What kind of position were you going to?

BALTIMORE: I was going to an independent position within Renato's laboratory. Renato had a huge chunk of space that he was due to go into and he was willing to give me two rooms, as it turned out, in it. But the building wasn't up yet. So when I went out there we moved into a temporary, wooden building. Then I had a little bit if space but it worked out. I didn't have many people with me so I didn't need any space.

SCHLESINGER: Did you have anybody with you?

BALTIMORE: Well Marc Girard came out very soon thereafter. I think he must have finished up the year and come out in July, roughly, and I had a technician, later two technicians.

SCHLESINGER: Where were the funds coming from?

BALTIMORE: Renato's grants. Renato just applied for a supplement and they gave it to him. I never had to worry about money. I mean all through this time, I never got a grant of any kind. I was on a Rockefeller stipend here as a student, and then I was on the training grant at MIT, and I was on the training grant at Einstein, Harry Eagle's training grant. Harry said there was a slot here. There was much more money available in those days and people were a limiting factor. If they found somebody whom they wanted, they would bend over backwards to help. The money was there to help them. Then when I went to Salk, I didn't have to apply for a grant.

SCHLESINGER: But Salk didn't provide any research funds.

BALTIMORE: No, Salk was never a rich institution. It was always a very poor institution and, in fact, the building of the building had used up almost all the money that would have been an endowment. Jonas [Salk] simply sunk it into the building. The building is a great building and that was a good use of the funds. So no, the Salk had no funds.

SCHLESINGER: Were you the only person Renato was bringing in this type of position or were there other people?

BALTIMORE: No, I was the only one who Renato brought in that way. Other people later graduated into more independent positions like Walter Eckard. Walter was then very young and he was in Renato's lab. I don't know if there was anybody else.

SCHLESINGER: Do you think that Renato had some overall vision in bringing you to Salk?

BALTIMORE: Renato felt that the amount of space that he had was more than he could populate with the people who were dependent on him and he wanted to bring more diversity. I think Renato was one of the people who were always very concerned in giving young people a start and with keeping an institution young. He knew that the way they were going there, with these big labs that were controlled by senior people, there was going to be a problem with junior people. So it was an institution building to him and it was the way he thinks about things and it worked out well. Mel [Melvin] Cohn had some people who were pretty independent in his lab. They became my good friends, like Marty Weigert, but there was no place in the structure for

young people and that's what Renato was trying to make. I think he would have gotten somebody else. If I remember correctly, there was some thought about that, but basically he lets people grow into independence like Walter, rather that hiring independent people. I was going out there to work on polio.

SCHLESINGER: Did you actually come with any ideas that were written down or were you just hired?

BALTIMORE: I don't know, I knew what I wanted to do. I wanted to continue the line of work that I had been doing in Jim's lab and then Marc had sort of continued—which was to get at the replicating structures—replicative intermediates. What we then called replication complexes, which is still ill defined. I don't know when I got interested in proteins but that became very quickly a major focus. By that time the Maizel and Summers experiments had been done.

SCHLESINGER: Before we go to proteins, let's go back to replication I think that came before.

BALTIMORE: Yes.

SCHLESINGER: Can you recollect some of the questions at the time? It must have been interesting to try to understand how RNA replication was different from DNA.

BALTIMORE: The issues we were trying to get at were issues of initiation, of chain termination, but we didn't have good biochemistry to do that so we tried to characterize the structures that existed in cells. We fundamentally focused on the replicative intermediate because if you did a pulse-label you knew it was incorporated in that structure. It was a very heterogeneous structure. We ran lots of sucrose gradients to show its heterogeneity and, to tell you the truth, I don't exactly remember when that started.

SCHLESINGER: Wasn't an issue that the mechanism of replication was not like DNA?

BALTIMORE: I don't think we worried so much about semi-conservative replication because the RNA was single-stranded and we knew that there was a double strand. I guess the first issue was how did the double strand relate to the replication and I know that the final experiment that nailed that was Marc Girard's experiment showing that double strands just build up and that you couldn't pulse through them but you could pulse through the RI [replicative intermediate]. That was clearly the intermediate structure and the double strands were a dead end. It took a while to

sort that out. We originally assumed that the double strands would be the replicative intermediates. But once we saw that and realized that there were multiple growing chains then everything fell into place because it was a minus strand with multiple growing chains of plus strands on it.

SCHLESINGER: Do you know when the first evidence for a complementary minus strand came?

BALTIMORE: Well, the double strand; it was the one thing that the experiments said—that there was a minus strand—that was it. I mean, we could later purify it and get its base composition but we knew it was there before. You could displace one strand off and study the other strand. It was in the double strand and the issue of minus strand synthesis was in the back of our minds. We could never do anything with it; there wasn't enough minus strand being made and the techniques weren't good enough to pull it apart until hybridization came along. Eventually we cloned the molecule. You needed cloned molecules.

SCHLESINGER: But an awful lot of experiments with hybridization were done before.

BALTIMORE: But you couldn't get at the minus strand because there was just too much plus strand in the way. You could try to dilute it out, and we did things like that and I think at one point I did a base composition of minus strand, but it was very, very difficult; it was also very hard to keep RNA in those days. We were presumably plagued by small amounts of RNase and didn't know it until good inhibitors of RNase came along and new ways of making RNA like guanidine thiocyanate. It was always a battle to keep RNA intact. So that was one of the problems of the replicative intermediate being such a heterogeneous structure. You never knew degradation from true heterogeneity. But those issues, I don't think ever came into focus until I got back to MIT later. That's why I need to go back and have a look at my publications even to try to straighten that out because I don't have it very straight.

SCHLESINGER: What were the major new kinds of things that were happening?

BALTIMORE: I'd go to the proteins and that was in the hands of my first graduate student, Mike [Michael] Jacobson. He came from UCSD [University of California, San Diego] to my lab, did a rotation, enjoyed it, and stayed. There was a little bit of friction because they didn't want their students coming over. Mike always did things his own way and that was great because he was so good and that stuff moved along very well. As we began to realize in the pulse-chase experiments how big the molecules were, the notion came up that the whole genome was translated into one long protein. We started fighting that issue mostly using inhibitors. We ultimately showed that was true.

SCHLESINGER: Let's go back a little bit because what was known at the time in terms of protein synthesis was only the bacterial systems. I'm trying to get you to recollect what your thinking was. What led you to the idea that this is what was happening? How else could the data be interpreted? Did you have trouble proving it?

BALTIMORE: We had a lot of trouble proving it because although you could build up the intermediates, you had trouble chasing through them. We chased through some of the natural intermediates but we couldn't with the very big ones that built up. We had trouble chasing through because we had to use inhibitors to make them build up and then they were no longer sensitive to the proteolytic degradation pathways.

SCHLESINGER: Did you have methods for looking at peptides by then to show that the peptides in the large molecules were present in the small ones?

BALTIMORE: Well, no, that was all done because in virus-infected cells the only thing being made was viral protein, so you didn't have to worry about that. Everything was virus specific.

SCHLESINGER: How did you know that?

BALTIMORE: We did a lot of work on that going back to first work I did on my thesis. It was partly the work on mengo-infected cells. If you followed protein synthesis—and I did that as a part of my thesis—protein synthesis fell rapidly after infection then rose again and fell again. That rise was all virus-specific protein synthesis.

SCHLESINGER: How did you know this?

BALTIMORE: We knew it because for some reason L cells would stand up to forty-eight hours treatment with actinomycin, by which time protein synthesis was desperately low in the cells because they had run out of messenger RNAs. You could now infect those cells and now get a huge stimulation that had to be virus specific: it was actinomycin insensitive. There was no new synthesis of RNA going on except viral. Then you saw virus particles made. I just don't remember when we did the first gel to show that those all were the viral structural proteins—that's what I have to go back and figure out. But I never doubted it from experiments I did here.

SCHLESINGER: But you may have not doubted it but I suppose the rest of the scientific community might wonder what was going on in the sense that the first gels that one looked at had multiple bands and could be confusing. Maybe the best way to ask it is that there must have been times when you were challenged for some of your hypotheses and do you remember that?

BALTIMORE: You keep asking that question and I'm very vague about it because maybe of my sometimes unreasonable belief in myself.

SCHLESINGER: Well, because you would be convinced, who were the skeptics?

BALTIMORE: Well, you couldn't convince everybody. The problem was we were using what were the most advanced techniques to ask a question that required even more advanced techniques. It wasn't worth it because they didn't exist. I couldn't show that they were all virus-specific proteins by analyzing the bands until somebody figured out how to do that.

SCHLESINGER: So what you're saying is in the early experiments it was enough to say that all we can show is—

BALTIMORE: Right. That was way ahead of what you could say with almost any other virus. One of the extraordinary things about this virus, and the reason that it kind of led the field, was that its effects were so dramatic. So if you were dealing with small effects or a little blip on top of a big background or something then you worried, but when you are able to get a ten-fold stimulation of protein synthesis by knocking the background way down by virus infection and when we went to polio it was sensitive to guanidine. That's right we used guanidine a lot.

SCHLESINGER: Who was the person who discovered it?

BALTIMORE: Igor Tamm. Actually he didn't discover guanidine, he discovered HBB [α-hydroxybenzylbenzimidazole]. Somebody else found guanidine and guanidine was much cheaper to buy so we used it, but HBB was as good. He was working with benzimidazole derivatives with Merck and the one that they found that has come down to us is DRB, which is an RNA-polymerase inhibitor. I don't remember what DR stands for, but some derivative of benzimidazole. HBB was a curiosity because polio was very sensitive to it as it was to guanidine. You could get mutants that were resistant and mutants that were dependent on it. That's always been a terrific system from a genetic and physiological point of view but we always used guanidine as a control to show that any given effect was virus-specific and you could show that the rise in protein synthesis was guanidine sensitive and actinomycin resistant. I don't think there was a whole lot of debate about that all being viral protein synthesis. But as

soon as we could run gels then you could see all those bands. How did we know they were all virus-specific? I think from the same sorts of arguments—they were all guanidine sensitive—when the Maizel-Summer's papers were first published.

SCHLESINGER: That was before your work?

BALTIMORE: Yes, Maizel, Summers, and Darnell. I don't remember the gels being controversial. I mean you looked at them and just said there is the virus-specific protein because we knew that there had to be intracellular proteins. We knew the polymerase existed. There were lots of other effects on the cells and then to try to unravel which of these proteins did what. They pointed out that when you added up all the molecular weights there was too much mass for the size of the genome and so there must be precursor-product relationships and that got us going. My remembrance of all this history is a little vague, but a lot of that was Mike Jacobson's experiments, that and also on virion formation. He did beautiful experiments. He came with me back to MIT.

SCHLESINGER: One question I was going to ask you, at that time, were you involved at all in any interactions related to vaccines?

BALTIMORE: No, there was no discussion of vaccines that I was involved in, absolutely no relationships to medical things and it was many, many years later that for a first time I ever went to a vaccine meeting.

SCHLESINGER: So at that time there were no discussions about vaccines?

BALTIMORE: It was a settled issue. This was pure biology. In fact, I kept having to explain to people why I was working on polio.

SCHLESINGER: What did you say?

BALTIMORE: Because I was interested in it, because it was a paradigm of RNA dependent-RNA replication and of virology, and because it was a good system. You could make a lot of it [polio] and it had big effects on cells, but not because it had any particular medical relevance. At that point we didn't know of any picornavirus that caused serious disease. It was many, many years later when hepatitis A virus was discovered.

SCHLESINGER: So, let's continue at the Salk for a while. How long after you got there did Jacobson come?

BALTIMORE: Michael must have joined me maybe a year after I got there.

SCHLESINGER: Actually, how long were you at Salk?

BALTIMORE: Two and a half years.

SCHLESINGER: Not very long.

BALTIMORE: No, I wasn't there very long. A variety of things convinced me to leave to go to MIT. So I came there roughly in April of 1965 and I arrived at MIT Jan 2, 1968, but I actually spent three months in Paris in between, so it was two and a half years.

SCHLESINGER: So do you want to talk about the variety of reasons that made you leave Salk?

BALTIMORE: Oh sure, there were a couple. One was that I was getting too big in my own thinking, even the size of my laboratory, which had a student and a couple of technicians and then Alice [Huang] came and joined me as a postdoc. It was getting to be a significant fraction, a significant amount of laboratory space, and it wasn't clear whether that was the thing to be doing in Renato's lab. Secondly, the total lack of independence, not independence, the total lack of influence of junior faculty there got to me. I wanted more responsibility for my environment and other people felt the same way. It was really frustrating because there were these big shots and they just made policy and it all trickled down to us. It was all a matter of growing. I was growing and the place was constricting. The experience of being in California was one of the most enriching experiences of my life up to that time. I discovered the desert. I discovered the outdoors. It had a major effect on the rest of my life but I kind of missed the East Coast. I missed the cultural side of things. San Diego was a desert in more ways than one. Then there was a very particular incident but I think that just tipped the balance. I'll come back to that in a second.

So sometime late in 1967, I had, I guess, an inquiry from Harvard about whether I might be interested in going there and had gone and visited and that never worked out. But at the time I stopped by MIT. Salva said, "Look we always planned to get you back here, are you ready to come?" I said, "No, I don't think I'm ready to come but why don't we talk about it." So he said, "Look, we want you; we'll make you an offer. You just keep it in your desk." In fact,

Irwin Sizer, who was then Chairman of the Department put together an offer—I don't know what they had to do for that—and it was in my desk.

I don't remember when all this took place but somewhere around spring of 1967 there was an art show at the Salk Institute. The show was put together by my then wife and another artist in town. The other guy did things that were very sacrilegious and so when the art show went up—and they thought they were very much patrons of the arts when they were using the space at the Institute for an art show—people were horrified by the pictures and tried to take them down. I felt that was censorship. It became a major brouhaha and, fundamentally, I quit over that. But in fact I was getting to the point where I was probably going to leave anyway. So I picked up that offer and accepted it. I can't actually reconstruct the times of all that but my then marriage to Sandra disintegrated shortly thereafter—not really as a consequence of the art show. For all I remember the art show may have taken place after Sandra moved out. I'm not sure. So I then hung on for some time but I took off in the summer and went to Paris.

SCHLESINGER: By yourself?

BALTIMORE: By myself.

SCHLESINGER: Was Alice in the lab then?

BALTIMORE: Alice was in my lab. After Sandra moved out and when I was living alone, I did start seeing Alice and became very close to her but then I left. I had planned to do a sabbatical actually with Marc Girard in Paris and with Boris Ephrussi outside of Paris. I spent three months commuting either out to Gif where Boris was or into the Pasteur Institute. I was living near the Pasteur Institute. I was trying to work experiments back and forth. With Boris, I was learning about how to deal with cells and he was then doing a lot of work with cell hybridization. With Marc I was continuing to work with polio. I don't remember the exact experiments.

SCHLESINGER: At this time, were you still doing research full time in the lab?

BALTIMORE: Yes, I was doing experiments myself. I did experiments myself up to about 1975-1976.

SCHLESINGER: We'll come back to that.

BALTIMORE: I spent 80 percent of my time doing experiments, the rest running the lab. But the lab was small and I always worked very closely with a technician who could help me pick up things. If I did have to go off and do something, things would continue along.

SCHLESINGER: So did any of the work you did in Paris turn out to be special?

BALTIMORE: Actually we did some of the very first cell hybridization experiments at the same time as Mary Weiss did. I don't think we ever published them because her experiments were further along and actually we got some help from knowledge about her experiments. Boris was very close to her. I think they were drug-selection experiments. There wasn't enough time to have done anything in a major way. I was really playing around with the technology. I enjoyed being in Paris.

SCHLESINGER: Was there animosity at Salk if you actually quit? I don't mean with the scientists.

BALTIMORE: There was a lot of animosity from the President who hated my guts over this. Here he was trying to be a patron of the arts and he ended up having the whole thing be a scandal. It got a lot of notice; it was in the papers and stuff. San Diego is a deeply conservative community and I didn't care, but he cared. He tried to deal with this and he wasn't very good at it, either. So around the Institute I think people, in general, were pretty supportive. I mean they, the senior people, really wished that I wasn't leaving and that I hadn't made such a stink about that, and nobody was happy about that. But I think the junior people recognized that some of this was the frustration that I was expressing before about the powerlessness of junior people. This time I had just proved the powerlessness with the one time that we tried to do something, immediately they came down on our heads and said you have to do it our way. I just wasn't going to do that and this was a whole political aspect. I was very much involved in the antiwar movement. I spoke out a lot in San Diego and at rallies. So there was a big culture gap between me and people like Augustus Kinzel who was President of the Institute. The senior faculty were pretty liberal people. I'm sure they were supportive of an anti-Vietnam war stance but they didn't want to see the Institute involved in this kind of battle, particularly a battle that had a lot of implications for the community.

SCHLESINGER: Before we leave this subject, let's go over who was in your lab.

BALTIMORE: Right, in my lab there was a technician, a wonderful woman who smoked marijuana much of the day, a couple of technicians, and there was Alice who joined me the last year that I was in San Diego. She stayed in that lab. The lab continued to function the three months that I was away. Paul Berg came there, actually, that summer. So Paul was there.

SCHLESINGER: This is 1967

BALTIMORE: So when I came back, Paul was there and also Francoise Cuzin, who came with Paul. But in my lab there was Alice, Marc Girard, and Mike Jacobson. There was an occasional rotation student like David Gelfand from the UCSD but for the stable people in the lab, I think that was it.

SCHLESINGER: Was there a lot of interaction among all the scientists?

BALTIMORE: It was a wonderful world because everybody was new and therefore there were no hierarchies. People hadn't developed their social surround and were very open. So I would spend a lot of time with people much older than I was, which ordinarily you wouldn't be able to do—a guy like Leslie Orgel and I became quite friendly.

SCHLESINGER: At that time was he already interested in the origin of life?

BALTIMORE: Yes, he was involved in prebiotic synthesis—that went way back.

SCHLESINGER: I was trying to think of what were some of the major scientific issues at that time.

BALTIMORE: Well the major scientific issues that impressed me—Renato was interested in oncogenesis, but the major scientific issue that impressed me was immunology. [Ed] Lennox and Cohn, particularly Mel Cohn, had a very strong laboratory working in the area of immunology and I spent a lot of time talking with people but I didn't do anything about it.

SCHLESINGER: But at that time it was mostly antibodies.

BALTIMORE: It was all antibodies. T-cells were not an issue.

SCHLESINGER: I don't think they were known.

BALTIMORE: I don't remember when the thymus was unraveled but antibody synthesis, particularly the lambda chain model that Marty Weigert worked on a lot, really was a paradigm for defining diversity. It really was a wonderful model—a lot of sequencing was involved. That had a big effect on me later because I was very aware of the immunological problems from the friendships I had. In some paper I wrote, I gave Marty credit for having been the person who got me started thinking about immunology. Oncogenesis was a big deal.

SCHLESINGER: At that time the issue must have been whether the viral genes remained in the cell.

BALTIMORE: Well, integration. I think we knew the viral genes were there but the issue of integration—what form the viral DNA was in—was a big issue and that was what ultimately won Renato the Nobel Prize. Much of that was [Joe] Sambrook's work. But I think Sambrook came very much at the end of the time I was there, if I remember correctly. There was a lot of work on messenger RNA, polyoma, early and late gene expression. [Robert] Holly was interested in cell-growth control. I heard a lot about that. Holly came on sabbatical with Renato and just stayed, he liked it so much. Salk had a lab, but that had very little effect on me. He was still doing work that came out of the vaccines and although I was working on polio, it was just two different worlds. Bronowski was there. He was thinking about the brain, which really was the beginning of the Salk program in neurobiology.

SCHLESINGER: At this point had you been involved in any kind of teaching?

BALTIMORE: No, not really because I'd never been in any teaching institution. You know I taught as a graduate student at MIT my requisite semester as a teaching assistant, a lab course with Jerry Letvin.

SCHLESINGER: I was thinking more in terms of developing broader ideas.

BALTIMORE: No, I was thinking very narrowly. I was very narrowly focused, really, until I went back to MIT and started working with VSV [vesicular stomatitis virus]. I had kept a very strict focus on nucleic acid replication and protein synthesis as it related to polio. I made a couple of forays into the cell and tried to characterize RNA molecules bound to proteins in the cell. I kept pretty close to the virus trying to understand the genetic organization and replication. Probably if I go back to my first grant application, which was only when I got to MIT years ago, it was to learn everything I could about polio. I remember that I felt I wanted to just know everything I could about one little organism.

[END OF INTERVIEW 1]

INTERVIEWEE: David Baltimore

INTERVIEWER: Sondra Schlesinger

DATE: 13 April 1995

LOCATION: Massachusetts Institute of Technology

SCHLESINGER: When did you come to MIT as a faculty member?

BALTIMORE: I came in 1968 arriving here on a cold day in January, the first of January.

SCHLESINGER: What were the arrangements that had been made for your coming here, what was the package that you were getting?

BALTIMORE: I never worried much about it. I had been at MIT before and I knew the people I was dealing with. They just said they would take care of me and I really didn't negotiate for anything. In fact, I remember kind of jokingly saying that the only thing I really cared about was that I got a decent parking space.

SCHLESINGER: Did you?

BALTIMORE: I did. Well, I mean, everybody did. But as a postdoc, I had parked out in some muddy lot over in what was supposed to be NASA's [National Aeronautic and Space Administration] space and I hated not having decent parking for younger people. So as a faculty member I wanted to make sure I got into a reasonable parking lot, which I did.

SCHLESINGER: Before you came were there arrangements made for applying for grants or for the teaching that you would do?

BALTIMORE: I had grants, because at Salk I had been quasi-independent. Renato took care of me but I think—actually I am fuzzy about this—I got a grant before I left there. In any case, I applied for grants and got them without any difficulty and I don't think there was an issue there. I don't know if we went over this, but I had accepted the offer to come to MIT in the spring of 1967 and then spent the summer in France. I came back to Salk in the fall, wound up things

there, drove across the country, and arrived here. But I don't remember writing a grant during any of that time. So either I had one or I did write one.

SCHLESINGER: You mentioned earlier that Alice Huang had come with you. Did anyone else come with you?

BALTIMORE: Yes, I had a student, Mike Jacobson. Mike drove across the country, had his notebooks stolen in New York and actually had to repeat a whole lot of experiments that had not been published. I can't remember, I think Mike got his degree at MIT—no, he didn't; he probably got his degree from the University of California, San Diego.

SCHLESINGER: Before we go into more detail about science, you mentioned Michael Jacobson. By the time you came to MIT in 1968, you must have been thinking of other things than basic research. I say that because of Michael Jacobson's leaving MIT to work for Ralph Nader, then his founding The Center for Science in the Public Interest in Washington, DC.

BALTIMORE: Yes, that's right. There was a whole culture of questioning of personal lifestyles as well as professional lifestyles and Michael's decision to leave basic research.

SCHLESINGER: Can we go into more detail about that? Was that kind of attitude something that was new here at MIT or was that something more common at the time?

BALTIMORE: I had encountered it already at Salk. In fact there was a very high degree of activism in the California community, much higher than in Boston. There was an alternative political party that was brewing in California. It never got very far; guys like Bob Sheer were involved. Bob Sheer was the editor of a radical magazine of the time that started out as *Hard Times* then changed to *Ramparts*. It had affected people's thinking also. Certainly there were a lot of people closer to immediate societal needs.

SCHLESINGER: We talked last time about what were the most exciting issues at Salk, and we talked a little bit about Immunology. Let's try to discuss this for MIT.

BALTIMORE: I really planned to simply continue along the lines that I developed. I came to MIT because of the richness of the scientific community, the students, and the general life of Boston, but not because I had any new scientific challenge that I was looking to pick up. In fact that is what I did, I just simply continued working on polio for the next eight years.

SCHLESINGER: Before we go into more detail on polio, you also began to work on VSV.

BALTIMORE: I came to work on polio and Alice came with me as a postdoc. We were already romantically involved. It was not long after I arrived, in fact, that I began, to think about VSV. I don't remember having committed myself to doing that beforehand. I came here in January of 1968 and by spring 1968 I had begun to think about whether it was a good idea to pick up VSV. Alice's work on the virus and its defective particles had influenced me. It was like polio in that it grew quickly to high titers. That was what I cared about from the experimental point of view more than anything else. It was different; it had a membrane. It had potential to offer. So we started looking at it. I am pretty sure we didn't start with the idea that it would be a negative strand virus.

SCHLESINGER: Let's go back over to remind ourselves of what was known about polio in 1968. You said Michael Jacobson had been working with you, so the concept of proteolytic processing must have been known.

BALTIMORE: The concept of the proteolytic processing was pretty well developed before we moved here. The replication had shown that there was a plus strand in the virion and a minus strand made in the cells, and double strands. Mark Girard had been involved in that. In 1968, when we came here, the paradigm of the genetic system was pretty well established—of a plus-strand virus—that was the coding strand. The other strand, the non-coding strand, I don't remember when the plus-minus designation came in.

SCHLESINGER: It came in when you described it in an article (14).

BALTIMORE: Was that the first time it was ever used?

SCHLESINGER: I think so; you get credit. [It is often referred to as the Baltimore scheme.]

BALTIMORE: Oh, that's nice. I never thought much about it. I think I was at least using it in the notes before then.

SCHLESINGER: It may be that the terms were used, but the concept of dividing viruses that way was what you are credited with doing.

BALTIMORE: Well, the concept of dividing viruses I certainly developed in that article for the first time (14). But the phrase plus and minus strands, no, I think it goes way back, I think even the phage people used that. Because remember there was all the work then through the 1960s on the RNA phages. And there was a whole issue about whether it had a minus strand or didn't have a minus strand. I think we used that terminology. So that was the background and we started on VSV, but I don't remember that we had any idea that was what we would find—that we would find a minus strand virus, which is what we did find.

SCHLESINGER: But there was evidence that it was different. You couldn't isolate the RNA [infectious RNA]. So what did you think?

BALTIMORE: It was not infectious.

SCHLESINGER: Right.

BALTIMORE: The RNA was not infectious but that could mean many things. I mean a negative result like that was not directly interpretable. It could have meant that, but it could have also meant that we just didn't know how to give the RNA to the cell, something trivial.

SCHLESINGER: In fact, my guess is that you thought it probably was not that.

BALTIMORE: I thought it was probably trivial, because you could get infectious RNA from most of the plant viruses that had been studied. There were certain outstanding mammalian viruses that had not worked, but it really wasn't clear why. Some had multiple RNAs as a genome.

SCHLESINGER: But even that idea wasn't so well known then.

BALTIMORE: No, it wasn't, more people were thinking about that. One of the reasons we picked it up [VSV] was that I had a new student coming who was starting as a graduate student in the fall. She came from Radcliffe [Institute for Advanced Study] and wanted to work for the summer—something we won't let students do anymore. But Martha [Stampfer] worked for the summer. I said, "Let's just pick up the VSV system and have a look at some of the molecular biology." Alice was curious about that because that had been what she worked on for a thesis, and I was curious as well.

SCHLESINGER: Eight years was how long you had been working on polio?

BALTIMORE: Right, it was not eight years at MIT. It was really from 1961 at Rockefeller and through all the years at Salk. So Alice and I kind of jointly sponsored Martha, and Martha got to work. Because Alice knew a lot about the virus, it was easy to get the virus growing. The problem of the T [truncated] particles was well enough recognized, so we knew that you had to use low-passage stocks. By the end of the summer we already knew that it was a minus strand virus. In fact there was a paper published just about that time from Fred [L.] Shaffer, if I remember, he never became particularly prominent but he really had the first evidence for it (15).

SCHLESINGER: What would be the kind of evidence he had?

BALTIMORE: Hybridization of the intracellular RNA to the virion RNA. I think it was a matter of taking polysomal RNA, that was a definition of plus strand or coding strand and that RNA hybridized to the virion RNA. Martha and Alice very quickly showed that there were multiple messages and that they all hybridized to the virion RNA. [This was published in 1970 with Alice Huang as senior author (16).]

SCHLESINGER: David, let's go back to polio now and what Mike Jacobson was doing after he came to MIT and what you were doing, because you obviously were working in the lab, too.

BALTIMORE: I was working in a lab until the early part of the 1970s. Mike had actually done a lot of the work on the cleavages of the polypeptides at Salk. It was the work at MIT that provided the definitive evidence. I did some of those experiments and he did some of those experiments.

SCHLESINGER: Do you remember some of the discussions—thinking about how the first cleavages took place?

BALTIMORE: That there would be cellular enzymes. We knew from the beginning that there were two possibilities: either a cellular enzyme or that there was some protease built into the polypeptide that could cleave itself. We couldn't find an experiment that would show which one was right. It took genetics to do that, finally. So we didn't spend a whole lot of time trying to think about that question because there wasn't much we could do but try to inhibit its cleavage. We inhibited its cleavage either by using inhibitors of proteolysis, such as di-isopropylfluoro-phosphate or TPCK, or by incorporating amino-acid analogs.

SCHLESINGER: Wasn't it the latter that you had to do to get the large precursor?

BALTIMORE: That's right, I think it was only when we got all of the analogs. I found all of the analogs I could that were incorporated. There were lots of analogs around that weren't incorporated, but there were a small number that would be incorporated and we put those in and it really took all of them to get the full-size polyprotein. I think that's true, that just inhibiting proteolysis wasn't good enough. Probably because proteolytic inhibitors don't get into the cell particularly well.

SCHLESINGER: Did this give you new ideas or introduce new concepts into your thinking?

BALTIMORE: Yes.

SCHLESINGER: What did it begin to make you think about?

BALTIMORE: One gene on a messenger RNA or one polypeptide on a messenger RNA. That was very much counter to what was then thought, based on bacterial messenger RNAs, which seem to encode a lot of different proteins in one operon that was transcribed into a single RNA and then translated into individual polypeptides. I spent a lot of time then looking through the literature on mammalian protein synthesis to see what it looked liked. First of all, those messages that we knew about —I guess there were very few—globin and a few others were all monocistronic. Then we looked at some very simple things like whether the small polysomes made large proteins or made small proteins, really if large polysomes made large proteins. If large polysomes made multiple proteins, then the size of the polypeptide wouldn't correlate with the size of polysome. In fact, there was a pretty good correlation between the size of the polysome and the size of the polypeptide.

SCHLESINGER: Was that done in uninfected cells?

BALTIMORE: In uninfected cells, yes, in HeLa cells. We did lots of crude experiments like that and they all led to the same picture, which was that it looked like most of the mammalian messengers, you certainly couldn't do them all, were monocistronic. That led us to think about whether there weren't some rules behind it that made things fundamentally different than bacteria, and that maybe the messenger RNA was at one end [of the RNA molecule] or something of that sort.

SCHLESINGER: To put this in the proper perspective, this was before people knew anything about the ends of messenger RNAs.

BALTIMORE: We didn't know there were capped ends. I don't think polyA had been discovered yet or had been recognized as important.

SCHLESINGER: Was this idea of monocistronic mRNAs accepted by people, or do you know whether it was?

BALTIMORE: You know I don't actually know how much resistance there was. Clearly, a lot of people had thought that I had gone too far. It all was in a discussion in a paper where I brought out these things, probably I had. But that is what it made me think about and many times in my scientific career something has caught my eye and then as soon as I say that to myself, I start thinking about what would that mean if what was remarkable was actually true. What was remarkable in this case was that polio had gone to these enormous lengths to make one polypeptide and I couldn't understand why, knowing what we knew about bacteria, there weren't multiple starts. It just didn't make any sense and it led me to believe that there was something intrinsic about mammalian cells that forced polio to do things differently than the RNA phage, for instance, which clearly had three different polypeptides encoded on its mRNA. I started thinking along those lines and everything fell into place—in my thinking anyway. It seemed worth putting that out.

SCHLESINGER: Did anybody else make these observations?

BALTIMORE: No, nobody had made the observation of a single polypeptide. The observation that there were cleavages was first made by Maizel, Summers, and Darnell, but those cleavages looked like they could all be involved in virion formation. It wasn't at all clear in any kind of pulse labeling that you did, because the polyproteins self cleaved. As soon as you make the protease it goes back and cleaves itself off and so you don't ever see the full-length protein in an infected cell or in any kind of very short labeling experiment. So there was no idea that this [a monocistronic genomic mRNA] could be true until we started putting in the protease inhibitors or putting in the altered amino acids. Then the more we put in the longer it got. One day I said to myself this looks like it is going all the way. Let's see if we can push it. So we really designed these experiments with pretty high amounts of analogs and inhibitors to see whether we could push it because if we could push it, that wasn't going to be an artifact. And we could.

SCHLESINGER: Well, wasn't there some argument that you created an artifact with amino acid analogs?

BALTIMORE: Well, you worry about that and it was very hard to prove otherwise until we sequenced the genome. You couldn't be absolutely sure there wasn't some artifact there. But it looked all right and as we got to know the inhibitors better we could use a couple of analogs. I can't remember which they were. As you began to look for the polyprotein coded by the complete coding sequence of the genome you saw more of it because small amounts of material made more sense.

SCHLESINGER: Were there other areas of polio that were leading you into new concepts? Or were your major efforts on this?

BALTIMORE: My major efforts were on that, although Alice was working during this time on protein-RNA binding, to get an idea what was bound to messenger RNA. I was beginning to think now more about cells and less about viruses, or a little about cells, still a lot about viruses. I found evidence of protein-RNA complexes and developed a very neat methodology for looking at them by filter binding. But it all turned out to be an artifact because you could take pure RNA and add it to an extract and it would just pick up proteins and bind them.

SCHLESINGER: Still true today.

BALTIMORE: Yes, that's right, it's a tough field.

SCHLESINGER: So Mike Jacobson and you were working on proteolytic cleavages. Let's go back to polio. At that time I think people began to do *in vitro* protein synthesis. Were you doing that too?

BALTIMORE: A little, and you couldn't do much. I couldn't get polio to really direct protein synthesis. In fact, when I was doing my thesis I tried some of that. I remember doing a little bit on *in vitro* protein synthesis. It was not terribly exciting and no, I didn't do it. It was somewhat later with a student, Lydia Villa-Komaroff, who really tried to program the system with polio RNA and we tried to force that issue somewhere but we never did as well as other people did. It turns out that mengo did a much better job as a messenger.

SCHLESINGER: I was thinking that *in vitro* protein synthesis must have been known to some extent because that is what Marshall Nirenberg used back in 1961 [in deciphering the code].

BALTIMORE: Yes, that's right. I am way off you are absolutely right.

SCHLESINGER: Were other picornaviruses being worked on besides polio?

BALTIMORE: You mean around the country, around the world?

SCHLESINGER: In general, I think.

BALTIMORE: Oh, there were a lot of viruses being worked on at various levels.

SCHLESINGER: Well, I mean at the level that you were working.

BALTIMORE: Strong molecular biology—there was the polio system and people were beginning to get into vaccinia.

SCHLESINGER: When did [Michael] Bishop do his work with polio?

BALTIMORE: It was the same time. He went to Germany for a while and when he came back he went to UCSF [University of California, San Francisco]. He picked up Rous in about 1968.

SCHLESINGER: I am trying to get back to your lab to see what was going on there. So first it was just you and Alice and then Martha was the first person that came there.

BALTIMORE: She came over that summer so I think probably it was only us and the technician. Let's see if I can remember who else.

SCHLESINGER: Well, Chuck [N. Cole] came.

BALTIMORE: Yes, I know the other students, but I am trying to remember if there was anybody else who came. I think David [M.] Rekosh was the second student who came and we had one paper already (17). I can't actually remember what it was about. Protein synthesis in *E. coli* extracts programmed by polio-virus RNA, I actually forgot that paper ever existed (17). It was done with Harvey [F.] Lodish.

SCHLESINGER: I think several people were trying to translate eucaryotic mRNAs if I remember correctly the TMV work was an artifact, I don't know what happened.

BALTIMORE: I don't know either. I would have to look back.

SCHLESINGER: Do you want to forget it?

BALTIMORE: I may want to forget it. Then Ken [F.] Manly joined me as a postdoc just around 1970. He was a student with Ethan Signer, and sort of moved down the hall. Cole probably joined me to work on polio around 1971.

SCHLESINGER: Well, Martha was working on VSV.

BALTIMORE: Yes, Martha was working on VSV but Rekosh and Chuck Cole were working on polio.

SCHLESINGER: A general question, then a specific question. I wanted to ask how Chuck got started on working on defectives [defective interfering RNAs of poliovirus].

BALTIMORE: You remember we published this paper, Alice and I, on defective particles and viral disease processes (18).

SCHLESINGER: Yes, let's go back to that.

BALTIMORE: Defective particles were such a dominant part of the infection cycle because they generated so easily that I started thinking about that. Alice and I began to just collect—she knew something about the literature and we found more—instances of the generation of defective particles and we began to realize that the harder you looked, you found them in every mammalian virus anyway that you could find. So we thought about this and decided that it could be a very general principle of virology that viruses tend to spawn particles, which would autoinhibit, inhibit themselves. A test of that was to look at polio for which there was no evidence and they clearly were not going to be easy to find with polio because otherwise they would have been found. We had some evidence that high-titer stocks tended to get lower titers after a while, after continual passage, which is the hallmark of defective particles. I suggested to Chuck when he started as a student that he pick this up and just look at it directly with polio

and that's what he did. I don't think there is any student whose work I ever directed more closely than Chuck's because the lifestyle considerations of the early 1970s hit him very hard. He was from Oberlin and he married while in Oberlin. They came to Boston, and they set up a kind of communal house with a bunch of other people. They cared a lot about their communal house, their animals, and each other. It was all very friendly, but Chuck tended to be a bit perfunctory as a student—very bright, very nice, and thoughtful but I think his head was to some extent elsewhere and so I had to do a lot of thinking behind that as well. I don't do that for students anymore. I've done that for very few other students and I never knew whether I had done Chuck a favor or not but I loved the material because it had a wonderful kind of mathematical side to it and actual problems and the whole issue of interference as well. You could separate the phenomenon into two different pieces—enrichment and interference—and look at them independently. You couldn't do real genetics so this was about as close to a genetic problem as I had. Alice left the lab around that time; I think she left in 1970. So I directed that. I never had anybody in the lab who was a kind of second-in-command.

SCHLESINGER: Why don't we just spend a little bit of time on MIT and how it works and how the program worked for graduates.

BALTIMORE: The program actually was not a whole lot different then it was when I started as a graduate student, and it's not a whole lot different right now. I mean you come in and spend a lot of time in classes for the first year or certainly the first semester.

SCHLESINGER: Were you teaching when you first came?

BALTIMORE: I started teaching a virology course just after I came, maybe in the fall after I came, something like that.

SCHLESINGER: Would this be to graduate students?

BALTIMORE: I was kind of asked to do it; people wanted to know more about animal virology. So I just developed a course and it was early in their second year [of grad school]. Because their first year was so busy with basic biochemistry and genetics and so on. Actually, it was sort of an elective or maybe it was literally an elective but it wasn't a core part of the curriculum by any means, you know there really weren't a whole lot of people thinking about animal viruses. I had to be the only person doing it. I may have had Alice give a couple of lectures on VSV, and I remember fighting through what turned out to be very important to me later, [Hidesaburo] Hanafusa's papers, and barely understanding them well enough to teach them to a group. To me, they were obscure papers.

SCHLESINGER: Actually, I remember that because I taught about the Bryan strain of Rous and it's almost impossible to figure out how they assayed for it.

BALTIMORE: Those papers were wild, but they were very important because they were taking apart the Bryan strain and taking apart Rous. They also made me aware of retrovirology and so when I came to the reverse transcriptase I had been thinking about RNA tumor viruses even if I had never done any experiments on them.

SCHLESINGER: When you and Alice developed the idea of defectives, did you ever think about trying to set up any kind of animal models?

BALTIMORE: She's been doing that ever since, but still has no smoking gun to say that they are important in disease processes and natural disease.

SCHLESINGER: Cytokines play an important role and that's why it's complicated.

BALTIMORE: It's really complicated. In a sense you have to do it genetically, you got to find a strain that doesn't generate DI particles and is infectious.

SCHLESINGER: You know there is a report on the literature about this for flaviviruses.

BALTIMORE: Actually, I lost interest in the more general issues of DI particles when the reverse transcriptase came along.

SCHLESINGER: I was going to wait until we get to reverse transcriptase. So, let's spend a little bit of time now maybe on just what it was like in the 1960s.

BALTIMORE: I'd been politically active in California, never a great leader, but I had spoken at rallies and I had felt very deeply—we were just talking about the [Robert S.] McNamara book (19). He says, as far as I understand it now, that we had the right answer. In fact there is a *Boston Globe* Mike Barnacle column, today, in which Barnacle says in the words I hate so much, "It didn't take a rocket scientist to find out that there was no reality to the arguments that were backing the Vietnam War." In the face of that kind of irrationality, taking to the streets, seemed like the only thing to do right then. I didn't have to because I was by that time well

beyond the age where people bothered with me for the draft. But on the whole, that had all affected me very deeply, very personally, as it had just about everybody I knew. I did rallies.

SCHLESINGER: These were at Salk?

BALTIMORE: No, these were actually in San Diego. No, Salk itself is too small a place to matter a whole lot.

SCHLESINGER: But it was safer.

BALTIMORE: It was safer, is a lot safer and UCSD was still a very new institution, although there was some organizing around UCSD. There were some wonderful old leftists in San Diego, basically "Trotskyites" who had maintained their political style from the 1930s and these people became the bulwark of the organization in San Diego. San Diego is a very conservative community. In fact, we were really pariahs, politically, given the general worry that we were going to face more than we were prepared to face, which we never did. I mean, we never had really hard times. Having this very small cadre, there were—I don't know ten or twenty people who tried to organize where we were to get a microphone, and who knew how to make posters, and they were just pros and they were terrific. Of course, their underlying politics was something that we probably wouldn't agree with.

SCHLESINGER: What group did you join?

BALTIMORE: Here, I don't remember joining any group except the "Peace and Freedom Party", but I mean there were activist groups around.

[END OF TAPE, SIDE 1]

SCHLESINGER: Well you described San Diego. What was going on when you came to MIT, how political, what kind of political activities did you do?

BALTIMORE: I didn't, really. I wasn't involved in any organized political activity. I was more really responsive to the events, national events, and I got involved with the "March 4th Movement."

SCHLESINGER: What was the March 4th Movement?

BALTIMORE: The March 4th movement was a kind of spontaneous student-motivated strike at MIT, which involved a day of activities and George Wald's great speech. There was something called SACC [Student Action Coordinating Committee], which may have been put together for March 4th or became March 4th.

SCHLESINGER: Was the political activity mostly within MIT or did it have any national implications?

BALTIMORE: There were marches on Washington.

SCHLESINGER: Did you go to any of those?

BALTIMORE: Oh, yes. You know, but very much as a follower. I was so conflicted about how much time I wanted to spend in science and how much time in politics and I wasn't sure that I was really particularly effective in politics. I wasn't a great speaker, I wasn't a great theorist and anyway it all seemed pretty obvious. So I was acting more out of my own sense that I had to do something and that these issues were just too important for anybody to deny, but not because I wanted to commit myself to a life in politics. I became involved in the fight against biological warfare research particularly through the American Society for Microbiology [ASM] where Alice and I sort of led an organization with Richard Novak. We set up tables and had sessions during the annual meeting of ASM.

SCHLESINGER: Did the administration of the ASM allow you to do this?

BALTIMORE: No, they didn't like it at all, partly because many of them were close to or even came from Fort Detrick or close to the people at Fort Detrick and saw this as a direct attack on members of the ASM, which it was. It was quite conscious and we felt that it was inappropriate for the ASM to be a respectable outlet for these people who were doing secret work anyway. You never knew what they were doing and they were, in a sense, perverting science. No, we were pretty much on our high horses as so many people who felt they knew what was right in those days were. I think we were right, and I don't have any problem with that. I guess it is important that the remnants of the biological warfare establishments, which were left after, in fact, [President Richard M.] Nixon closed it all down and said we are not going to any more secret work. The remnants of that are the best defense that we have today against emerging viruses because it is one of the few places where people have keep an interest in viruses that are

terribly lethal like hantaviruses or some kind of flavivirus or LCM [lymphocytic choriomeningitis virus].

SCHLESINGER: Let's go back to science for a bit, and as I remember you won an award around that time, in 1970 wasn't it?

BALTIMORE: Yes, I won the Gustave Stern Award. It was given at what was called "the birdseed meeting." It was called the birdseed meeting because it was put together by or paid for by the Hartz Mountain birdseed company. The reason for that was that they had turned to a man named Pollack, who was then working on psittacosis virus, when the canaries they imported turned up with psittacosis and they were being threatened with being closed down. In fact, he had developed an antigen test or something that allowed them to quickly rid their flock of psittacosis. So they felt a tremendous debt of gratitude to him and they liked him personally. He was a very nice man. He is the father of the man who was ultimately incarcerated for having been a spy for Israel. He [the father] worked on germ-free animals and did other sort of things, but he ran these meetings and they were the only really decent professional meetings that focused on animal virology. There was no society for animal virology certainly and the American Society for Microbiology meetings were enormous meetings in which virology had a role, but it was a small role, and they were mostly focused on bacteriology and industrial microbiology. So, those were important meetings. They were held in New York in hotels, in the Essex House mostly.

SCHLESINGER: Were you surprised when you won the award?

BALTIMORE: I guess I was surprised. I was certainly very gratified because I was pretty proud of having, at that point, that is in 1970, been nine years as a biochemical animal virologist. When I had started out there were virtually no such people and I had kind of been self-made. Probably it had been very important, because the award was given for work that I had done on polio but I had already started working on VSV and, now it is a little vague in my mind, but I think I got it right. When we were going down to the award ceremony, I was sitting next to Salva Luria, who was, I think, the one who actually gave me the award and probably nominated me for the award. He was asking me what I was doing, and I was telling him about how we got started in VSV and the strange nature of VSV in that it carried the minus strand in its genome instead of like polio, which had the plus strand in its genome. I think it was in that conversation that I decided to look for a polymerase in the virion of VSV. I decided it because it had been up to, then, one of three or four thoughts in my mind about what to do next. Then I had a variety of thoughts about what the negative strands might mean and one of them had been that there might be a virion polymerase, but I hadn't taken that seriously. Somehow the logic of it, when I said it to Salva, was so compelling that I committed myself as soon as I went home to do these experiments. Which I did, and they worked.

SCHLESINGER: So do you remember more details of doing the experiments? First of all, did you do them or did Alice do them? How did you work that out?

BALTIMORE: I did them. In fact, if I remember correctly, I am the senior author on that paper (20). Let me check before I start claiming something that I am entitled to. Yes, I had the idea and just came back and physically did the experiments. I think Alice made the virus so I asked her for some stocks that she had.

SCHLESINGER: Was she still in the lab then?

BALTIMORE: She was still in the lab, yes, this was 1969. The paper was published in 1970, but I think it must have been in 1969. She was still in the lab and she had the best stocks of VSV in the world, very high-titer stocks. There was a lot of physical material there. Suddenly, you are changing from seeing a virus as something that you use for plaque assays or that you use to cause cells to incorporate radioactivity or something, to using the physical virus as a reagent, a biochemical reagent so you don't know how much you need. You have no idea. That plagued my thinking about reverse transcriptase. So I said, "Give me your highest-titer stock and we'll have a look," and I certainly knew how to assay polymerases, since I had been doing it ever since I started in science.

SCHLESINGER: Did you add detergent right away?

BALTIMORE: Did I add detergent? I would have to go back and look at my notebooks. But I suspect I did because that is pretty obvious that it had to be inside the particle. I had been using detergents for years to dissolve membranes. So probably that was a simple thing to do. It was all pretty simple. Once you have the idea, the experiments are not hard at all. There was a precedent. I mean there were two precedents already, vaccinia virus had a polymerase and reovirus had a polymerase.

SCHLESINGER: Had the reovirus polymerase been discovered?

BALTIMORE: Yes, that had been discovered before. Now they had a different logic behind them for the vaccinia polymerase. The logic was that it was a cytoplasmic virus and therefore had to bring in its polymerase because the only place where there was an [DNA-dependent] RNA polymerase was in the nucleus. For reovirus, it was a double-stranded RNA and so in order to make a messenger RNA you needed a new polymerase, which is maybe not that dissimilar to a negative-strand virus, in fact. So the logic wasn't new, but the idea that an

enveloped virus might have a polymerase in it had no precedent. As I say, it really wasn't that new, it was just that you had to commit yourself to do the experiment and find the material to do it, and then it was easy.

SCHLESINGER: So you were lucky that you choose VSV. If I remember correctly, some of the other negative-strand viruses were harder.

BALTIMORE: We also tested NDV [Newcastle Disease virus] and there was less of it, but it was pretty easily detected (21). But flu turned out to be of course very difficult because of this cap-snatching trick that flu does. So it wasn't a simple matter of assaying the polymerase. I spent quite a while trying to show polymerase in flu but couldn't, and didn't know why.

SCHLESINGER: So that must have been an exciting moment when you discovered the polymerase in VSV.

BALTIMORE: Oh, that was wonderful, I mean, since it didn't kind of creep up on me, it just happened. It was really good, super. In modern terms, a very robust kind of experiment, lots of counts, and easily manipulated. There were paradigms on how you did the experiment with polymerase that I could draw on.

SCHLESINGER: So that must have changed your thinking about what to do.

BALTIMORE: That happened in early 1970 and then I started thinking about what extensions to do. First of all, I wanted to now concentrate on VSV more and we did on the molecular biology of it. Secondly, I wanted to see if there were other viruses like this. I might as well kind of skim off the surface in a sense, so we did the experiments with NDV with Mike A. Bratt because he had the virus. The ones that obviously became the most important were the RNA tumor viruses. They were not then called retroviruses because the notion of retro didn't exist. There's a long story. Do you want the long story now or do you want to get a bite to eat and then have a long story?

SCHLESINGER: I'm happy to stay.

BALTIMORE: All right, let's just stay. Well the long story is that I had known Howard Temin from high school. I don't know if we have talked about this one, I think we have already. I was very aware of his work, and very aware that it was not widely accepted and I read some of it and it was not, experimentally, particularly compelling. Therefore the notions behind it were not

compelling and I hadn't really thought about cancer at all to that point. I think it is really important that what drove Howard to thinking about it was the stability of cancer cells, particularly Rous-transformed cells and perhaps most important of all, the stability of cells—the morphological stability of cells transformed by different virus strains. The different strains gave different morphologies, which strongly argued that morphology of the cell was determined by viral genes. That notion absolutely required that the [viral] gene[s] be there in the cell somewhere, and so to him it was obvious. I remember his never wanting to argue with people about this because he knew it was true—the same kind of thinking as the polyprotein in our earlier discussion of poliovirus. He was faced with this anomaly—the stability of the transformed state and so there had to be DNA there and if it were an RNA virus then it had to make DNA and that was all there was to it. But he couldn't convince anybody else and there just wasn't a good way to do it experimentally.

When I had taught, remember I had said I taught retrovirology, it was not then called retrovirology, but RNA tumor virology. I can't remember whether I even taught Howard's papers. I think maybe I did, I am not positive. What I do know is that I taught a paper by Vogt and Duesberg in which they had developed a somewhat obscure argument; not obscure, an indirect argument for a DNA intermediate. This was before we discovered reverse transcriptase and was one of the only other papers in the literature that supported Howard. It had come out very recently in *PNAS* and I have forgotten the details of it, but I think it started me thinking that maybe Howard was barking up the right tree. So I had all those thoughts in my head and I was even teaching in the spring, I think. As all this was going on, I called up George Todaro, who was an old friend from Swarthmore days and worked on RNA tumor viruses, and said, "George where would I get some virus?" I literally didn't know a single person who worked on those viruses. There was nobody in the Boston area who worked on them and I didn't even know what a preparation looked like. I also called Peter Vogt, because I knew Peter was trying to make significant amounts of virus. I didn't know that—what I knew was he worked on it. Why Peter Vogt? I think because he came from the same tradition of having been with Rubin and having been at Colorado at the same time that Richard Franklin was there. I had met him. I guess it is just because he was one of the few people I knew. I certainly didn't know Hanafusa. I don't know why I didn't call Howard, maybe because I didn't think that he would know what physical amounts of viruses were about. He probably wouldn't have. So Peter said that he had a little virus and he would send it to me and he did. Meanwhile I got in touch with Todaro. Todaro said, "There is a program at the National Cancer Institute [NCI] to make virus." He gave me the name of the guy, and I called this guy and he said, "You want virus? How much?" I said, "I don't know how much. How do you quantitate it?" Well, you quantitate it in ml. He said, "How many ml do you want?" I said, "What is in the ml?" He had no idea what was in the ml. There was some criterion—a contract of making this stuff and the criterion was: ml of virus-infected supernatants. So they had all these mls around. It was very expensive stuff. We finally agreed on an amount and he said, "How should we send it?" I said, "I don't know; put it on dry ice and send it up." He said, "Maybe we should send it with a courier." I said, "Why do you want to send it with a courier?" He said, "Well this is very expensive." I said, "How much is it worth?" He said, "I don't know, tens of thousands of dollars." Later, I was told that it may have been worth a lot more than that, actually, because this contract had been going a long time,

making a tremendous amount of virus. It may be that I am the only person who asked for it. So this was a big moment for Holdenreid.

SCHLESINGER: Was that his name?

BALTIMORE: Yes. So we finally agreed that he could just send it by air freight, and he sent it. It came with glass sealed vials and I had to use a file to get it open. The Vogt stuff came first. So now I had to decide was I going to look for an RNA-dependent DNA polymerase, fundamentally test Howard's notion, or was I going to look for an RNA-dependent RNA polymerase, which is what I had been finding in vesicular stomatitis virus and NDV—put it all in the same bailiwick as what I had been doing. Well, I took the conservative approach—to look for an RNA-dependent RNA polymerase. I used up a significant amount of stuff that Peter Vogt sent me. It was a very small amount of stuff. Then again, I didn't know how much was in it; it was water. I couldn't find anything, luckily. Also at that time, you may remember that [Sol] Spiegelman was making big noises about how there had to be an RNA polymerase like with Qβ. So then the material came from NCI. I opened one of the vials and I just took a little and used it as a biochemical reagent and now assayed for a DNA polymerase. I wouldn't know what it was dependent on, but I looked for a DNA polymerase. I got a minuscule amount of radioactivity over background and Alice has never understood why I thought that was a positive result. I didn't know if it really was positive or not, but anyway, it was more encouraging than the opposite. So the next day, I just took a lot of it and spun it down in the centrifuge and got a big ugly pellet of stuff and resuspended that and used that as a biochemical reagent. Then I got a lot of counts and then it was easy to show that it was a polymerase. Then I had to go back and try to do it again.

SCHLESINGER: So whom did you tell first?

BALTIMORE: Alice.

SCHLESINGER: Or I should ask when did you realize how important it was?

BALTIMORE: I think right away. I mean it was pretty clear that that was going to revolutionize things and even if I didn't know a whole lot about cancer I knew that understanding cancer-inducing viruses was important. I didn't go running up and down the halls. I just don't do that. I just set to work, but the next day, and I have gone back to my notebooks and actually followed this through, you can follow it through day by day in the notebooks. I had about two days to work on it. I think the one experiment—I had run a glycerol gradient or a sucrose gradient to see if it banded at the right density. Just about the time I got the fractions of that collected, it was announced that Nixon had invaded Cambodia,

which produced the greatest explosion on American campuses that has ever been seen. I stopped everything that I was doing and joined everybody else out on the streets and didn't go back to the laboratory for a week. Came back to the lab and finished the experiment, assayed the sucrose gradient, and there it was, the right band.

SCHLESINGER: The sucrose gradient was the virus peak?

BALTIMORE: Yes, it was banded virus, and then did all the other controls, and had a paper in another week.

SCHLESINGER: Well, but you must have at some point called Howard?

BALTIMORE: It was about then when I called Howard, after I had done enough experiments that I was sure we had everything in place. When I was about to write a paper, I called Howard. He had discussed his work a couple of days, literally a day or so before that in Houston.

SCHLESINGER: Was it an agreement on your part to publish together?

BALTIMORE: Yes. Actually I held up publication because I had a full paper ready and he didn't. The paper was going off that day to *Nature* (22). What happened next? Well actually, before the paper appeared, the whole thing got announced at the Cold Spring Harbor Symposium. Because sort of the next week was—we are now getting toward the end of May and the Cambodian invasion was the beginning of May. At the end of May was the Cold Spring Harbor Annual Symposium. Although it was on something else, word of this had gotten around and Jim [James D.] Watson invited both me and Howard to come and talk—to make an announcement of this. You know, the press was not then as much on top of things as it is now. If anything like that happened today, it would be literally headline news at least in the *New York Times*. But it certainly wasn't then and I don't remember that there was any excitement about it beyond the scientific community. I don't think there was any realization of it, or the implications. I don't remember articles and I don't remember feeling that there was a lot of pressure on me. Alice had decided that she was going to teach that summer in Taiwan and she went off and taught in Taiwan. Then I met her and we spent some time together in Taiwan and then went around the world. So I took off, I don't know, six weeks; probably the longest time I have ever taken off in my life—the summer of 1970. I gave one talk in Japan on the reverse transcriptase. It was a different time, and we didn't patent it. Never occurred to any of us to patent it. I mean the issue just didn't come up. I mean it could have been one of the absolutely key patents of biotechnology.

SCHLESINGER: You would have put MIT in an incredible financial position.

BALTIMORE: No question. MIT would have had a patent as valuable as Stanford's because every gene that is isolated comes about using the reverse transcriptase. Then Inder [M.] Verma came.

SCHLESINGER: Was he the first postdoc to come and work on reverse transcriptase?

BALTIMORE: He actually came to work on VSV. Uri Litauer was his Professor in Israel. For one reason or other, Inder got his Ph.D. in Israel. Uri Litauer was here and heard the story and came back or it was published. I guess it was published and they read about it and Uri said to Inder, "You are not going to work on VSV." Inder came, and I said, "Inder, look this thing is really interesting and there are some fairly obvious experiments to do, why don't you spend six months working on this and then you can go work on VSV?"

First, I had no idea it was going to take over the laboratory the way it did. But there was so much to do and it was so exciting and now the public interest built when people like Spiegelman and later [Bob] Gallo started pronouncing on it. It was interesting. Here, I think, there is an interesting lesson in science. Because two of us had done it independently, coming at it from two different backgrounds in science, I don't think anybody doubted it. Because this announcement was its own confirmation. So it fit the paradigm of something that you believe in science. Anyway, although it was revolutionary in its implications, it was straightforward biochemistry. I mean, any high-school kid can assay reverse transcriptase. The guy who nailed the whole thing shut did it overnight. Because after we gave the talk, Sol Spiegelman, who had heard Howard's presentation in Texas had come back and said to his lab something, I don't know, I have never actually talked to anybody in the lab about it. Something like, "You know, maybe we ought to look at this." But then he heard the presentations in Cold Spring Harbor and apparently he went right back to New York and he said, "Let me see if this thing is true." No, there was zero doubt about it. The scientific press was all over it and there were big articles in *Nature* about it, and also *Nature*, of course, published the original article and there were articles almost ever week about who was doing what, who was claiming what. Spiegelman, of course claimed he discovered viruses everywhere [reverse transcriptase activity]. There were philosophical implications. There was a Lamarkian implication to the reverse transcriptase that you can make genetic changes based on events in the soma.

SCHLESINGER: Did you yourself think about this or write about it?

BALTIMORE: Yes, I didn't write about it much, I thought about it. Howard wrote a little more about it. He almost got sucked in a little to thinking about the Lamarkian implications. I found that so unlikely, although I was perfectly aware of it, and I didn't want to find myself in bed

with some really strange people. Letters from a lot of strange people, who saw those implications and wanted to ride the bandwagon. But they were all there and they are real and it turns out there is a hell of a lot of reverse transcription around.

SCHLESINGER: Actually more than one would have expected, because I think it took a long time before people could find viruses.

BALTIMORE: It was very slow to develop the generality of it and also the extent of the mouse genome, the human genome too, better known than the mouse genome, that comes from reverse transcription which is something between one and 10 percent of the genome comes about by reverse transcription. All these pseudogenes as well as the retrotransposons and that is an enormous amount. It's a very wide spread process but it is still doesn't really allow for fixation in the germ line of events that have occurred.

[END OF TAPE, SIDE 2]

SCHLESINGER: David we are in 1971, you had made the discovery of reverse transcriptase.

BALTIMORE: I spent a certain amount of time thinking about new directions because I realized that having walked into the cancer problem through a strange but very open door that it was a very interesting problem, and that the interaction of viruses in cancer was something that I wanted to devote some serious time to. By that time I was feeling sort of expansive in my science, partly because of the success of reverse transcriptase, but partly just getting to that age. It was something that started with a movement to VSV and then picked up steam with the discovery of reverse transcriptase. I looked for a system where I could work biologically. I decided two things. One was that I had to work with good viruses, and remember, I had to get this virus from the NCI as some unknown mixture of stuff that a contractor had produced and that wasn't my idea of virology, it was a fine stop gap. I didn't want to work with chickens and most of the manipulable systems were in chickens. I did want to work with mice. I had been in high school at the Jackson lab [Maine] and I always understood the power of working with mice. I thought about all those parameters and decided first of all I had to find a good virus so I looked around and it was clear that Moloney Leukemia virus was the fastest growing virus around.

SCHLESINGER: Was that the one that was provided to you by the contractor?

BALTIMORE: No, it was actually Rauscher. Rauscher is a bad mixture of things that had helper viruses in it. Moloney is a helper-free, I mean was an intrinsic virus; it didn't have any

complicated history, defective particles or that sort of thing. It didn't look like it did. So I got a stock of the best Moloney virus around and tried to endpoint—you couldn't really plaque it because there was no decent assay but you could endpoint dilute it and try to get a good high titer stock. That way, I would get rid of defective particles if there were any. Actually, it turns out that retroviruses really don't generate defective interfering particles they generate defectives but they don't interfere much. They were genetically, at least, relatively pure, not as pure as if I plaqued it, but relatively pure. I think Hung Fan may have made the first virus like that. He joined me as a postdoc and he had done his degree with Sheldon Penman. He took off on the biochemistry. Ultimately, Inder was the one who showed you could reverse transcribe messenger RNA and really demonstrated the biotech use of reverse transcriptase. That's what we really should have patented but didn't. Phil Leder did it about the same time.

SCHLESINGER: He didn't patent it either.

BALTIMORE: He didn't patent it either, no. Verma's work involved a nice collaboration. It involved some people at Children's Hospital who knew about globin. They had purified globin messenger RNA and then got excited about looking at specific defects. There was an explosion of molecular analysis of globin messenger RNA. Inder took off in that direction, that was the obvious thing to do and we did a lot of that, and that I knew how to do. It was good biochemistry and molecular biology but I had learned a lot from having biologically well-characterized materials, like polio or VSV. We made this stock of Moloney, which got used for many years. With that we could begin to characterize a life cycle of the virus and to get some *in vitro* parameters, but that wasn't cancer and Moloney causes a very long latency indirect tumor since it doesn't have an oncogene. We really didn't know that at the time, but we knew it was a long latency disease and I wanted to find a mouse equivalent of Rous sarcoma virus. Something that causes a short latency disease was potent and worked *in vitro*. The best thing would be to cause leukemia *in vitro* because leukemia is in some ways the hallmark of virus-induced cancer.

SCHLESINGER: How would you measure leukemia *in vitro*?

BALTIMORE: We did, and we found the Abelson leukemia virus, which transforms bone-marrow cells into continuous culture *in vitro* and those cells then cause leukemia if you put them in an animal.

SCHLESINGER: When you say you found it, what does that mean?

BALTIMORE: That's what I was going to tell you because its a good kind of MIT story. So I discovered the reverse transcriptase. People around knew about it in the department and one day in late 1970 or early 1971, something like that, a postdoc stops me in the hall and says,

"You know when I was at NIH I did something interesting you might like to know about." I said, "Come tell me about it." His name was Herbert Abelson, and he told me that he had done some experiments at NIH in which he took Moloney virus and injected it into thymectomized mice. Moloney disease is a thymus-dependent disease, so most of the mice didn't get anything. But he wanted to see if there was any secondary disease that might come up. In fact, in only one animal out of a hundred-and-something did any secondary disease appear, and that was a very virulent leukemia, which he could then transfer with a spleen extract—a virus preparation from spleen—to other mice and they would now get the same disease. So that was Abelson disease and it was called Abelson virus. I had never heard of it, although it had been published but I really didn't know much of the biological literature.

I got all excited because the disease it was causing could have been a B-cell leukemia, it turned out to be a pre-B-cell leukemia, and it didn't seem to be a thymus-dependent disease. So it was in a new area, and I had always had a vague interest in immunology, so this sounded like something I might care about. The speed with which it occurred suggested it might work *in vitro*. I said, "Let me have a look at it." Actually there was another guy who had gotten interested in it, Chuck Scher at Harvard. He had started working with a man named Siegler and they very soon thereafter, maybe, I think, showed and published that you could transform fibroblasts, 3T3 cells, with this virus. At that time, I got a postdoc who thought it was very exciting to work on this problem. I didn't have any room for her because, well we'll come back to that. Trying to expand my laboratory within the confines of where we were, particularly doing very biological kinds of experiments, was difficult and there was just no space for it, but we had already committed ourselves to going to the Cancer Center. So she went over to Scher's lab at Harvard and worked out, there, bone marrow transformation by Abelson virus and we all published it together (23). She came back to the lab once we moved to the Cancer Center and that was the system that we then focused on because it had all the properties that I wanted.

SCHLESINGER: Was that Naomi Rosenberg?

BALTIMORE: Naomi Rosenberg, right. She was from Vermont, went to the University of Vermont, came from a very unlikely background, but was interested in the biology of leukemia viruses. To me that was just exactly right. So those were the aims that I took, we did biochemistry, we looked at *in vitro* virus replication.

SCHLESINGER: This is a major change for you, in a sense, because now you are also out of the lab.

BALTIMORE: I was not totally out of the lab, but I was certainly moving in that direction, that's right. Donna [F.] Smoler [a technician] and I worked together at the bench for a number of years and worked out a lot of the biochemistry of reverse transcriptase with my doing some of the experiments, she doing some of the experiments. I was certainly getting more and more

involved outside of the University, as well as inside the University, as well as with these various different directions in the lab. So I couldn't spend concentrated time at the bench. There comes a time when, if you can't spend some absolute minimum amount of time, it's not worth being there at all. The time issue didn't really come up until around 1973-1974, somewhere in there. I went on sabbatical in 1975 to work in the lab, and did work in Jim Darnell's lab, actually got a limited amount done for reasons that I will come to—I got the Nobel Prize. That was the last time I really tried. Well, there was one other time I tried to work in the lab, which we will come to when we get to how I got into immunology.

SCHLESINGER: Let's go back over what the lab was like at this time—early 1970s.

BALTIMORE: Well, I had a couple of groups. I had a group working on polio: Chuck Cole, David Rekosh, Bob Taber, the others. I'd have to go through all my publications to figure out if there is anybody else there. Then I had the VSV group, which was really Martha Stampfer. By that time Alice had left and Martha stayed with me. I guess after that no one else picked up VSV, so it pretty well stopped when Martha left. But I had a VSV group, I had a polio group, and then I had people working on in vitro growth of Moloney virus and some problems that later became the problems of N- and B-tropic viruses. Ken Manly was involved in that. Bob Weinberg joined me for a while and then became independent. Nancy Hopkins joined me for a while, then became independent.

SCHLESINGER: But now you're going over a longer period.

BALTIMORE: This is all between 1970 and 1972 or 1973. Because it was all before we moved to the Cancer Center. We moved to the Cancer Center if I remember correctly in 1974 and then Bob and Nancy were independent. They both had their own labs and so they both had been through the lab. I remember well, and this is what generated the Cancer Center in a sense—two things happened. One was that a lot of people in the department got nervous because no one had ever worked near a cancer virus before. Maury Fox particularly was very nervous about these kinds of things. In order to make sure I wasn't about to kill all my students, never mind the Faculty and everybody else in the building, it was a problem that I saw building. If we wanted to do more and more of this, we were going to have more and more problems. The second thing was space. I had this very nice laboratory that I had inherited from Boris [N.] Magasanik. I shared it first with a guy named Yankofsky who was here when I came but he left very soon after I came. Then Harvey Lodish moved into that space and I shared the laboratory with Harvey. Shared meaning that we each had our own space but there was a certain amount of interdigitation of space. We had two offices next to each other with an outside secretarial office and our people were very close to each other. It was a very nice situation. But there was only so much space there and Harvey is an expansionist type. So no matter what I was doing, we were stuck. The teaching labs were down at the other end of the hall and there was no way to move down there. So I was sort of boxed-in and people recognized that what I was doing

was both good for MIT, quite unique in its directions, and was going very well. I had a certain amount of national prominence. Luria came up with the answer, which was the Cancer Center.

What had happened was that the National Cancer Institute had established a program of development of cancer centers around the country and within that there was the possibility of a basic cancer center, although they were looking more for integrated cancer centers that included a clinical and outreach and all sort of things. That money was there and Luria realized that we could put together a very credible application for that and use the money to renovate a building, get more space. It would be good for me. He was always watching out for me, and it would be good for MIT. He convinced Jerry Weisner, who was President, that this was a good idea. Weisner gave him carte blanche. He wrote an application, the application was accepted, we built the Cancer Center. We hired Herman Eisen from Washington University to be Head of Immunology, who has been one of the most important members of our Faculty ever since. As young professors, we hired Bob Weinberg, Nancy Hopkins, and David Housman, who had been Harvey Lodish's student, actually. He had worked in this joint laboratory we had and we all respected him very much. He wanted to move in directions of leukemia and the control of blood cell growth. He spent some time in Toronto learning from the real masters. Very few people recognized, but David knew full well that these were the guys that you learn from [Till, McCullough, Bernstein, the Siminovitch axis].

We are going to get ahead of the story for a second and I'll go back—but that was the fifth floor of the Cancer Center with those young people. Anyway, let me go back to how I started this. So we made that commitment, it must have been around 1972, maybe even earlier. I had already "schnored" a piece of space from Salva, because Salva was sort of closing down his laboratory, or at least shrinking his laboratory a little bit. Again, as always, he tried to be nice, so he had given me one room, the one nearest to my end of the hall and. I had this little pod over on the other side, then when we committed ourselves to the Cancer Center, I really squeezed as many people as I could in there. I got another little pod of space over on the other side of the hall, and I squeezed Nancy Hopkins and Bob Weinberg in there. Then when we got to the Cancer Center there was this sense of liberation from this jerry-rigged operation that had held together—barely. But we did all of the cloning of the virus in that circumstance. We did everything except Naomi's work, which was done over at Harvard. We did all the biochemistry and Inder was probably the major leader of that work. Meanwhile I kept the polio and VSV stuff going so it was a very exciting time and I was spending a lot of time on logistics. You know, thank God, Salva did most of the designing of the building, and Salva knew how to design a building. One of Salva's great prides was he knew how high you had to put a goose neck pipe to get a one liter cylinder under it, a five-liter cylinder or something.

SCHLESINGER: I remember him telling us about that.

BALTIMORE: Right, he loved that. So, I was able to make a significant intellectual input into designing the Cancer Center. Finally we got Frank Solomon and we had a wonderful place. It opened, I would say, in 1974. I might be slightly off.

SCHLESINGER: We can check that.

BALTIMORE: Actually I am just looking through now to remind myself of whom else. There were a few other people in the lab as I look through. Actually, there are two things I should tell you about. One is Ron [P.] McCaffrey. David Nathan, who is just now retiring as Physician-in-chief at Children's Hospital, was head of Hematology at Children's for a long time, but as a young guy coming up at Children's had taken a sabbatical and come to MIT for a year, knowing that MIT was doing things that could be relevant to medicine. David had very little background in molecular biology, in anything but clinical medicine, but had a very good feel for what was going to happen in the world. He was in Paul Gross's laboratory; Paul Gross is a developmental biologist who was here [at MIT] then. David Nathan didn't get much done but enjoyed himself. He wandered down to the laboratory that Harvey and I had one day, and discovered what Harvey was doing. Harvey was working on erythropoesis and that's what David really cared about. Harvey was working on it in a way David never imagined and jumped out of his skin. David's a guy with great enthusiasm, still is. When he saw what I was doing with reverse transcriptase—and the opportunity! He kind of encouraged that whole globin reverse transcription project. He just thought this was the greatest thing in the world. When he went back to Children's, he went back with a commitment to sending as many of his fellows to MIT as he possibly could, and he did that thereafter. All of the great hematologists of the world had their time at MIT—Y. W. Kan and Bernie Forget—either in my lab, in Harvey's lab or in somebody's lab. So David calls me one day and says, "I have this boy you got to take. He's been over in Egypt working and he's coming back and he is just the right person." Well, the boy walked in, the boy is about 6 feet 4 inches, dirty-talking Irishman, wonderful, wonderful man—Ron McCaffrey. McCaffrey doesn't know anything. He does not know a DNA molecule from a protein molecule.

SCHLESINGER: He's an MD?

BALTIMORE: He's an MD and he had done a little research in NMRU [Naval Medical Research Unit] in Egypt. He was very haemalogic but very much involved with some interesting people in leukemia research, particularly a man named Bill Mahoney who, I think, was working on experimental leukemia at St. Elizabeth's Hospital. So Ron came from a very different background from anybody I knew and the first thing I did was kind of give him a book and say learn a little biochemistry. But Ron had great enthusiasm and great desire to learn and to succeed. He, because of his interest, actually had come here with this notion in mind. I said, "Why don't you try to find a good assay for using reverse transcriptase to look for human tumor viruses and we'll go into leukemias and we'll screen leukemias and see if we can't do it?" At this point I had actually, more or less with my own hands, shown that small oligonucleotide-type primers on homopolymer RNA templates provided the most sensitive assay for reverse transcription. A lot of people had picked that up and used it, but I felt that nobody was giving,

exploiting the potential for selectivity, specificity that you could get from appropriate mixtures. So I put Ron on to finding out which combination would be most diagnostic. Then using column chromatography to look, to separate out enzymes as individual peaks and screening various things to look for reverse transcriptase. We showed, for instance, that in infected cells you can demonstrate the enzyme that way with good controls because they were realistic assessments of the potential of the assay. Spiegelman and Todaro were doing assays and [Ed] Scolnik and [Stuart] Aaronson were doing assays; there were lots of people trying various things. But I just felt I knew the situation better than they did.

Ron got the assay going and it was real a struggle for him because he was basically learning what each word meant as he was doing the experiment. But he stuck with it and finally he got to assaying tumor cells. He called me up one Saturday at home—with a peak off the column that responded to the diagnostic template primer. "I found it." I guess my reaction to amazing events is very negative and cool. Maybe it's the same because you are asking me what my reaction to reverse transcriptase and it was basically, "What do you do next? What's the next experiment? How could I be wrong?" So my reaction to Ron was, "Sounds terrific," because I had to support him—he was almost like a child. "But why don't we do a few controls, leave out the template, leave out the primer." He had just done one tube effectively or maybe a couple of replicates of it but I guess it was a peak off a column so it was clearly there. But he hadn't tested whether any of the things that were in the assay were required. That's the first thing you do.

So I am teaching over the phone and telling him to assay for the peak fraction, for whether it needed template, needed primer. Sunday morning I got a call from the most dejected man on earth. It didn't need the template. It wasn't reverse transcriptase because it wasn't copying anything. Well, here's where my years of kind of random understanding of what was going on in the world helped, because I knew what enzyme that was. That was terminal transferase. No one had ever seen it before outside of the thymus and I knew instantly that we had a diagnosis for thymic leukemia. I had to bring Ron back from the depths of depression to realizing that he was doing something important that may not have been the thing he set out to do. Now he has made a whole career on the investigation of terminal transferase in leukemias and its use as diagnostics. He's developed a whole therapeutic notion now, which hasn't yet caught on, but I think it's interesting.

SCHLESINGER: Where is he?

BALTIMORE: He's at Boston University. So we published a paper in 1973 on terminal transferase in a case of childhood leukemia (24) and later actually did a whole clinical study and published a paper in the *New England Journal* [*of Medicine*] (25) that established terminal transferase as a marker for leukemia.

SCHLESINGER: What was it?

BALTIMORE: It was a template-independent DNA polymerase and there really was only one that had been described by Fred Bollum, of course it's used now in all sorts of technological things. But it's fundamentally a marker of early lymphoid origins of cells. We had to find out that it was in preB-cells as well as *prêt-cells*. Actually, there are a number of directions that this took us. It was my first, probably most-successful foray into clinical medicine. But also I got to thinking about why was terminal transferase in human leukemia cells. Thinking about that was one of the things that drove me into immunology, finally. I published a little theoretical paper on what terminal transferase might do, suggesting that it was involved in the generation of immunologic diversity (26). At that point we didn't know much about immunologic diversity and it turned out that the way I was thinking about it was wrong—that it might go in and change base pairs in the DNA by cutting out the DNA that was there and polymerizing random nucleotides in. But it turned out to be right in the sense that terminal transferase makes the so called N-nucleotide grouping at the joints of the immunogloblin genes. It is a somatic mutator but it isn't the only somatic mutator. The one that does the generalized somatic mutations still hasn't been found; I am still looking for it.

SCHLESINGER: Let's talk about the ASM Eli Lilly award.

BALTIMORE: Actually if I remember correctly, I probably got that in 1970, but the paper is dated 1971 (14). I think it takes that long to come out and it was relatively soon after I discovered the reverse transcriptase. In fact, I may have won the award just before I discovered the reverse transcriptase, but by the time I gave the talk I had. I am not positive, in any case.

SCHLESINGER: I'm sure you're right about that, because I remember that meeting and I didn't remember the date of it but the meeting must have been in the spring.

BALTIMORE: Well, if it was in the spring, it would have to be the next year, had to be 1971. So maybe I had already discovered reverse transcriptase. Anyway I got the paper that came out of that meeting, the *Bacteriological Reviews* paper was in 1971 (14). That was when the award was. So the award was probably announced in the early spring of 1971, then I got it. By then I had discovered negative-strand viruses, discovered reverse transcriptase, and had been working on polio previously. So I was thinking about how all these related to each other and developed a little scheme that relates various classes of viruses to one another, which everybody still uses for teaching purposes, which I gave in that talk, then published in *Bacteriological Reviews*.

SCHLESINGER: There was only a little stir at that meeting not a big one only because of the 1970 meeting.

BALTIMORE: Yes, Jonathan Beckwith had won the prize in 1970 and gave his money to the Black Panthers.

SCHLESINGER: Didn't you give the money to Michael [Jacobson and the group is the Center for Science in the Public Interest]?

BALTIMORE: I gave some to Michael Jacobson and some to somebody else, I can't remember.

SCHLESINGER: So you don't remember that?

BALTIMORE: Actually I don't remember what I did, but I do remember creating some stir.

SCHLESINGER: Was there a problem, I mean did anybody write you nasty letters?

BALTIMORE: Well the Eli Lilly people were particularly pissed, because they were pretty straight-line guys and weren't interested in seeing politics mixed up in their little public-relations prize. They did invite me to visit them in Indianapolis. I went there and had an interesting time. No, Jonathan Beckwith had a much more dramatic effect.

SCHLESINGER: So was that a milestone when you got the award? This was the second award you won.

BALTIMORE: Well, I've got to be honest. Awards have never been milestones in my life.

SCHLESINGER: Even the Nobel? Well, I am going to ask you about that.

BALTIMORE: Even the Nobel Prize. I mean the Nobel Prize was so clearly an enormous perturbation in my life, but I guess I have never felt that that was what I needed as a justification for what I was doing, or as recognition of what I was doing. Partly because I have been lucky enough to make a variety of discoveries whose impact is easily measured by just looking at the literature as it evolves. That means more to me than the prizes do, quite honestly.

SCHLESINGER: Around 1973 or so, tell me what's happening in the polio work? VSV is being closed down.

BALTIMORE: Yes, VSV closed down.

SCHLESINGER: Were you having, not difficulty, but did you feel very schizophrenic?

BALTIMORE: No, not at all. In fact, I kept polio going until a couple years ago without ever having any problem. It's a small field, easy to be fairly on top of the literature without having to spend as much time as you have to do in immunology or as fast moving as those. It was a wonderful tool for teaching, because you are working with the whole organism not just some enzyme. Polio impinges on everything else in the cell.

[END OF TAPE, SIDE 3]

BALTIMORE: I think that somewhere in 1972 or 1973, three people joined my laboratory all from Gobind Khorana's lab—all postdocs. They had all come with him from Madison, [Wisconsin] and all of them were involved in the gene synthesis experiments, basically gene technology. The three guys came down from there all with the same request: "Can I get into something more biological? My training is as a chemist but I am interested in what's happening." Particularly they saw the reverse transcriptase, because it was an enzyme, as a tool for moving them into something more biologically relevant, instead of just using enzymes the way they always had as tools. I think the first person who came was Peter Besmer. He made a wholesale change. He left behind enzymology. He left behind everything and started working on very biological questions. Published a number of papers and spent something like five years with me working on xenotropic viruses and working on B-tropic viruses. He got a job at Sloan-Kettering. After something of an eclipse, he discovered the kit oncogene, which turned out to be the W locus and was a very important moment in hematology. The second was Amos Panet. Amos stuck more with enzymology, but did it in the context of retroviruses and has later played some role in the study of HIV [human immunodeficiency virus]. He is an important virologist in Israel today. Ian Molineaux, who didn't spend very long with me, went over to Malcolm Gefter's lab and did some work on immunology. It is pretty interesting that just at that time we were kind of infecting people with thinking about new avenues of biology that they could link into their own particular training in Gobind's lab. Actually I had spent a little while in Gobind's lab, maybe that helped.

SCHLESINGER: What did you do there?

BALTIMORE: I am trying to remember what I did there. I remember being up there for something about the reverse transcriptase experiments. I was making DNA or—I can't remember—something that they did very well. They said, "Come on up, and you know we will help you out," so I got to know them.

SCHLESINGER: So when these people came into your lab, how much interaction did you have with them?

BALTIMORE: I sort of see people daily, just around. I've always interacted with my laboratory for many, many years through a full meeting once a week, where everybody talks about everything they have been doing, so that we are all up to date on each other. Then it depends on the individuals. Some individuals I didn't bother for long periods of time. Peter Besmer, I knew I didn't have to bother for ages because Peter knew what he was doing. He wasn't actually particularly communicative, so it was easy for him to just go on and do what he did. Other people I got to know very well. Actually, it's interesting, I got to know them well enough that—now that we are talking about things that happened twenty years ago—we remain friends for over those twenty years, and I see them all if they are in town, or wherever they are.

[END OF TAPE, SIDE 4]

[END OF INTERVIEW 2]

INTERVIEWEE: David Baltimore

INTERVIEWER: Sondra Schlesinger

DATE: 29 April 1995

LOCATION: David Baltimore's home, Boston, MA

BALTIMORE: Alice, when did we decide to go on sabbatical in New York?

HUANG: We went 1975 or 1976.

BALTIMORE: I know but when did we decide to go and why?

HUANG: When and why? You were due for a sabbatical and I had a RCDA [Research Career Development Award] for my 4th year.

BALTIMORE: Anyway, so that's what I remember, we just kind of decided to take a sabbatical.

SCHLESINGER: All right. You had mentioned that you were getting interested in immunology.

HUANG: You were looking around because you were thinking of going into immunology.

BALTIMORE: Right, I remember. Fundamentally, the original impetus to take a sabbatical came from the idea of becoming more involved in immunology. Also it was convenient for Alice, so we committed ourselves. Then I started looking for a place, presumably in the winter of 1974-1975, in there. I talked to people in Australia and in Basel. I could have done either one, but I guess we finally decided it was just too far away—we had a small baby and we weren't sure whether we wanted to take her out of the country. I had a big lab and lots going on and I didn't know how far away I wanted to be. So it all became a very convenient sort-of compromise to go to New York. Alice had a good place to work in New York with Purnell Choppin. Jim Darnell and I had remained close from the time that I had been in his lab at MIT, and then I was sort of with him at Einstein. So I decided to do something that had no real learning component to it, but was just a change of venue. I figured I could also learn some

things. In the end, I did learn some things from working with Warren Jellinek, whom I ended up doing some experiments with. He was a young assistant professor in Jim's unit and was extremely, technically very knowledgeable and interested in interesting things.

SCHLESINGER: So, in fact, you changed the idea. There was no longer any focus on immunology.

BALTIMORE: There was no longer a focus on immunology. I figured that I could kind of absorb that if I needed to and that New York was as good a place as any, although there wasn't anybody there with whom I could learn. Of course the Nobel Prize came that fall just after I arrived in New York. That pretty well undermined a lot of the time that I had on the sabbatical.

SCHLESINGER: So why don't you describe a little bit about what that day was like.

BALTIMORE: Well, this was a remarkable kind of situation. I came back from the Soviet Union. I had gone with a group from the National Academy of Sciences on a trip to the Soviet Union. We had gone to Moscow and to Tashkent. Actually, the meeting was held in Kiev and then we went off to Tashkent, to Bukara and came back. It was an incredible experience as it was for anybody in those days who went to the Soviet Union—to discover how backward it was, how poor it was, how difficult it was to do science. How paranoid everybody was about the secret police, but how wonderful the people were all as individuals; extremely well educated, thoughtful. The man I developed the strongest admiration for was Vadim Agol, whom we know is a great scientist and who had devoted his life to doing science in the Soviet Union. Had he been able to work and travel outside the Soviet Union, he would be one of the world's great scientists today. As it is, he is highly admired in the virology community but really not known by anybody else. I got to know some of his friends and late at night in Kiev as we were drinking more and more vodka, a lot of these guys would open up, some of them terribly irresponsibly, but they felt that the place that we were living, which was a student hostel in Kiev, was a safe place to talk. So it had been a very intense, very exciting, very politically demoralizing experience because if this is what the Left meant then, a lot of people have been kidding themselves for a long time about directions of politics. So it was complicated.

I came back and moved immediately to New York, or maybe we had moved already. I can't remember. I came back to New York and we got settled, I think we just moved down right away and we got settled in the apartment at Rockefeller and then spent a little time getting settled in the lab. We brought a housekeeper with us and were getting organized in New York. Right in the beginning of October, Alice went to a meeting in Denmark. It was a meeting on comparative leukemia and she had done some work on VSV pseudotypes that was relevant to that. It was kind of amusing because it was a meeting that I, in principle, should have been at. Although, I had decided not to go. We couldn't both go away at that point anyway, and I knew I was traveling plenty; I didn't need that meeting. Howard Temin might have been there but

wasn't. So the meeting took place and I was living in New York. What happened was that the session Alice was talking in was presumably on a Monday morning, whenever it is the Nobel Prize is announced. George Klein was the organizer of the session and at the end of the session, George got up and said, "I want to summarize this session," and went on, as Alice said, endlessly, summarizing unnecessarily this whole session. He finally said, "Look the Nobel Prize is going to be announced in a half an hour, but I can't keep talking for a half an hour. I've got to tell you who is going to win the Nobel Prize." He announced that Howard and I were going to win the Nobel Prize that year. So Alice ran to the phone and called me and woke me at 6:30 in the morning or something in New York. It was about noon in Denmark. So I'm probably the only person in history who learned that they won the Nobel Prize from his wife. She woke me out of a sound sleep and told me this. I laid back after the conversation -

SCHLESINGER: That was the first inkling that you had?

BALTIMORE: Yes. Well actually, as we thought back, we'd been given a sort of signal by another friend of ours the summer before that there was some likelihood, but hadn't interpreted it. He said something about Stockholm in the winter. But I hadn't really been thinking about the Nobel Prize at all. I mean a lot of people had said that the discovery of the reverse transcriptase was going to be honored with the Nobel Prize. I had no perspective on the issue. I hadn't really thought about Nobel Prizes or even a whole lot about relative value of experiments. I was enjoying myself, just doing what we were doing. So, I didn't know the Nobel Prize was going to be announced that day—had no idea. I really paid no attention to it, luckily. It was never an issue, so it came as a total surprise—literally out of the blue.

SCHLESINGER: I think I had told you that Milton [Schlesinger] that year had received a letter asking for nominations and he had nominated you.

BALTIMORE: Well, who knows what was important. I don't.

SCHLESINGER: So who was the next person that called?

BALTIMORE: Well, that's even a little story of a moment. So I hung up the phone, kind of rolled over in bed. Meanwhile, Teak, my daughter, was up and the nanny [Nora] was up taking care of her. Teak was age one then—maybe she had been awakened by the phone call, I don't know. So I lay in bed and nothing was happening, you would expect bells to be going off or something. It was just quiet, silent. I finally got up out of bed and I went to Nora, and I said, "Nora did you hear the phone ring before?" Because I didn't actually believe it was a dream but there was no aftermath. You have the feeling that there should be inundation, but of course Alice knew before it was officially announced. So it was about half an hour before anybody

called. It was a newspaper reporter, then all hell broke loose. But I had this moment of wondering whether it had been a dream. The *New York Times* came over, actually and took a picture of me carrying Teak. So Teak was the first child I have ever seen on the front page of the *New York Times*, because of the *New York Times* sort of policy, I guess, of not putting children's pictures on the front page. It was just the back of her head, it wasn't the front, but it was a picture she treasures. Other reporters called and, you know, the usual stuff. There were the calls that you get—everybody wanting to know what you are going to do with the money and you don't even know how much money is involved and the last thing you thought about is money and all of that. But then I got a call from MIT. I had at that point been on the MIT faculty for seven years. I was an American Cancer Society Professor, and I guess the President called to congratulate me. You know, I had never had anything to do with the President at MIT. You can imagine, even the relatively senior-academic staff is largely focused on the department and may see a Dean occasionally—the excuse to see the President is very rare. So although Jerry Weisner was a guy I admired, at a distance, extremely, and I sort of knew a lot about him, I didn't really know him very well. I hardly knew Walter Rosenbluth at all, who was the Provost. But I had a great loyalty to MIT because, as we have discussed, really my whole career revolved around MIT in one way or another. So I right then decided—I guess they called and they asked where I planned to hold a press conference. I think I called them back. I may have thought about it for a minute or something. But in any case, I decided the right thing to do was to go back to MIT. So I packed up and took the ten-o'clock shuttle or something back once we got through the preliminaries of life. I was met at the airport by Weisner, I think, or Weisner or Rosenbluth, maybe both, which really touched me. Now having been the president of an institution, I know that there is no question that I would do that—absolutely no question. But at the time it really, it was signal to me, as it was meant to be, of how much they cared. So I went back and there was champagne and the usual kind of press conference and stuff. Then there were little parties and then kind of everything died down. I stayed at Maury Fox's that night and flew back down in the morning.

SCHLESINGER: Tell me a little bit about your parents in this.

BALTIMORE: Oh, actually that is a story. I forgot that. That fall, my father had a heart attack. Actually, once they went into it, he had prostate cancer and probably the heart attack was secondary to that. It was an embolism or something, but he was pretty sick and had been getting better and I of course had seen him. He was at Mt. Sinai Hospital. I had seen him every day. He was in a private room and the private phones don't go on until 8 o'clock in the morning. So there was no way to call him and tell him. My mother was at home. She, of course, I called right away. They lived across town from me, but we couldn't tell Dad. He heard it first on the television and of course got very excited, so excited they put him back in intensive care. I went and visited him there on the way to the airport. Actually, I had the cab stop. I knew I just had to see him for a minute. They were, of course, ecstatic. They both came to Stockholm, but my father was still very weak and very ill and never fully recovered. He died a couple of years later, largely of chemotherapy in an attempt to try to control the cancer. But man, they couldn't believe it! They had both been, I don't know if we talked about this, but they were both born in

New York City. My father was from a very poor family; my mother, from what then might be considered a sort of Jewish, middle-class, immigrant family. Her father was a tailor and they had a little money and had had a real business. My mother had gone to college; actually my mother would have been a terrific scholar. But my father had never gone to college. So for them to see me reach so high in the academic world in such a short time was extraordinary. I was thirty-seven then.

SCHLESINGER: David, before we go to Stockholm, let's talk a little bit about what happened between October and November. You went back to New York?

BALTIMORE: I went back to New York the next day and we were living in New York. Alice came back from Denmark. She had had a big party that night [in Denmark]. Actually I've heard about that party from any number of people.

SCHLESINGER: To celebrate?

BALTIMORE: It was kind of a celebration.

SCHLESINGER: Sad that you weren't together.

BALTIMORE: I know, it was terrible. That's one of the reasons that she did that. But then she came back, I don't know, a day or two later. I mean it's all the same thing that anybody can tell you, I mean a fantastic number of letters, phone calls, telegrams, and all of that.

SCHLESINGER: Anything special that you remember in terms of people who you hadn't heard from?

BALTIMORE: Oh, all sorts of people I hadn't heard from, you know, from high school and people who I had known very slightly and some people I had known very well. There was one guy who sent me a letter and signed it "Brother something-or-other." I think I told you about this—I had gone to grade school with him.

SCHLESINGER: Grade-school teachers or old friends?

BALTIMORE: There were old girlfriends, there were—I mean, you know, just name it—not grade school, I think a high-school teacher, not many, a couple. But I think the impact of that on Great Neck High School was very strong. Because I have heard about it ever since.

SCHLESINGER: Did you ever go back to Great Neck High School to talk after that?

BALTIMORE: I don't think so. That was all wonderful and finally, there was so many of them, that I printed up a little card of thanks and sent them to a lot of people and just wrote a little handwritten note on it, because I had to, you know, focus on the Nobel Lecture. The Nobel Lecture is not what people think it is, it's really a scientific lecture given to your colleagues at the Karolinska Institute and the benefit of it is for the scientific community of Sweden. There really is no public Nobel Lecture and there is no public statement in fact by the Nobel Laureates at all except for about a one-minute comment that is made at the Nobel Dinner by one representative of each group and Howard represented us and talked about smoking—a sort of famous moment.

SCHLESINGER: Tragic, I guess, or was it famous?

BALTIMORE: Oh, it was famous because instead of the usual thing, which is to kind of thank everybody or to make some comment about the importance of science or whatever, he said something that represented me perfectly well because it's a feeling that I had for a long time and that is: that here we were being honored for a Nobel Prize in cancer research and yet we knew full well—he said that the major thing anybody could do for the cancer problem as it exists, particularly in the Western World, is to get people to stop smoking, and that was more important than discovering the reverse transcriptase or anything else in terms of actually living bodies. I had been involved in that politically, I have been involved in that in the American Cancer Society. Howard has been the spokesman for that for a long time. I must say, independently. We never sat down and said let's do this because it was dead obvious that that's what was needed, but he did make this little speech. Alice noticed that the Queen, who was there, was smoking and that the King's uncle ostentatiously lit up a cigarette in support of her at that time. So it was actually kind of slightly embarrassing. The Queen who was there was not actually the wife of the King. The King had no wife but I think she was some vague relative who was the Queen of Denmark who came over and was very regal.

SCHLESINGER: Did you feel that once you won the Nobel Prize from that time in October that you had to be more careful about your statements?

BALTIMORE: I didn't have to be careful at all before because who would think to ask me about nonsense? But now people could ask you about almost anything and I think it is

important to be honest and to answer things that you felt you could answer and not answer other things. You don't have to be so much careful as honest.

SCHLESINGER: Was there anything that you remember in the first few months where people wanted you to do something that you either turned down or that you agreed to do?

BALTIMORE: Well, actually I think people would be a little embarrassed to call in the first month or two, actually before the prize is given, to start trying to get you for lectures and things. But the drumbeats of that sort certainly started out early and continue to this day. Suddenly you are asked to be a figurehead at a whole lot of events and actually its sort of independent of whether you are any good at anything or not. Just being a Nobel Laureate had a scientific meaning at a public event or at a fund raising activity or whatever you wish. It adds a certain amount of luster and so you get an enormous number of requests from people.

SCHLESINGER: From your CV, David, I noticed that even before this you were beginning to serve on national committees. Perhaps you could talk a little bit about how you began to see yourself as a spokesman for science and what your impressions were about beginning to serve on committees.

BALTIMORE: Actually the first advisory panel I sat on was the advisory panel for Genetic Biology of the National Science Foundation and that was in 1969. I was asked to do that before any of this. That was solely on the basis that I was, I guess, known as a significant, young contributor in the general field of animal virology and perhaps cell biology. But I got a wonderful award just after the reverse transcriptase from the head of that panel, Herman Lewis.

SCHLESINGER: I remember him.

BALTIMORE: He was a terrific man; he used to be a professor at MIT.

SCHLESINGER: Yes.

BALTIMORE: He had this terrific panel. I just looked forward to each of those meetings because the group was so wonderful and the discussions were wonderful. It was enriching because it was more genetics than I ordinarily heard, drosophila genetics and things like that. But the award I got was for the best discovery made by a member of the review panel—basically the best discovery ever because, you know, you usually take people who by the time they get to that they are past the peak of their scientific career. So he was very impressed when

I discovered the reverse transcriptase at the same time that I was reading all those grants in areas I didn't understand. Then I was asked, I guess right after discovering the reverse transcriptase, to sit on the Cancer Center Review Committee, which became the Program Project Review Committee of the National Cancer Institute. It sort of oversaw a lot of the developments in the Cancer Center's new program projects.

SCHLESINGER: Were you one of the younger people on the committee?

BALTIMORE: I was definitely one of the younger people and one of the few people who had a basic science orientation. I worked hard for that committee and the follow up committee for four years doing site visits, and, really, for the first time learning about the whole cancer establishment in the United States—what the Centers were doing, the heritage of cancer research, which was so awful. I mean, so unrigorous and unfocused on any molecular issues at Sloan-Kettering, at Roswell Park [Cancer Institute], and at M. D. Anderson [Cancer Center], which were historically the three great cancer centers in the United Sates. It was illuminating and interesting and I think I was able to make a significant contribution to the scientific rigor of some of that. That went on until 1975, I guess. I am just looking at when I got involved in the American Cancer Society Public Issues Committee. That was a committee that I encouraged very strongly to set up because the American Cancer Society had been notable for its lack of involvement in public issues. I think the reason is because many of those public issues, like for instance the tobacco industry subsidies, the advertising of the tobacco industry, and all the issues around smoking, are highly politically charged and the American Cancer Society had kind of hidden behind its tax-free status to say, "Well we can't be a lobbying agent." Well, the truth of the matter is you can be a lobbying agent up to a certain amount. I thinks it's up to 10 percent of your total funds, which for the American Cancer Society is a huge amount of money that they could be using to involve themselves in public issues in the interests of lowering cancer rates. So I ended up on that committee.

SCHLESINGER: Did you get much opposition from other people on the committee?

BALTIMORE: Well, the committee had a number of people who represented a kind of hierarchy in the American Cancer Society who were definitely trying to keep things under control so there were some, you know, there was a lot of discussion especially about how far do we go and what can we do. But I tried to be a force for more action rather than less. Actually, I began to realize it was also limited how far they could go, both in terms of undercutting their financial base, which I certainly didn't want to do because the American Cancer Society had been historically and to this day a major source of funds in basic science because their policies, in terms in what they want to support, have been so enlightened.

SCHLESINGER: Do you have any idea what gave them this enlightenment?

BALTIMORE: No, I don't know the answer. It goes back to the early part of the post-war era.

SCHLESINGER: There wasn't anybody in particular that was running the Cancer Society?

BALTIMORE: Well, I guess there probably were people and I don't know who they were.

SCHLESINGER: I was just curious to know, and it sounds like you just carried on a tradition

BALTIMORE: I think that's right. They carried on and they have continually carried on this tradition and have been very clear in their understanding that all of the activities of modern cell biology, genetic biology, biochemistry, molecular biology are relevant to understanding the cancer problem and that therefore it's appropriate for them to fund those things more or less independently of whether there is a direct cancer focus to a particular grant. It's solely on the basis on merit. But I don't know where that tradition comes from.

SCHLESINGER: So you were involved in all this even before you won the Nobel Prize. Were you involved in any of this before reverse transcriptase?

BALTIMORE: Well, not cancer.

SCHLESINGER: But you became an American Cancer Society Professor

BALTIMORE: In 1973. We are now talking about 1978 and on, but I had sort of earlier been focusing on American Cancer Society's activities partly because I was an ACS Professor. So the question you had was about becoming a national spokesman, and I guess it was a slow learning process about issues that I cared about. I mean it went back as we talked about some time ago to biological warfare, which is an issue I had become interested in the late 1960s and that was the first foray into a public policy forum. I more and more felt that I had to remain focused on the areas that I cared about and cancer and smoking was one of those areas. I was on a committee on cancer and smoking at one point, but I don't remember exactly what it was. I think it was the National Academy.

SCHLESINGER: Around the time of the Nobel Prize did you write any articles that were for nonscientists? I don't remember seeing anything in your CV.

BALTIMORE: Coming out of the interest in biological warfare, I had been interested in the hazards in just ordinary scientific work and I had been in a sense forced to think about that because as I think I mentioned when I first discovered the reverse transcriptase that involved me in working on cancer-inducing viruses and there were a lot of people around MIT who were concerned.

[END OF TAPE, SIDE 1]

BALTIMORE: So I got interested in issues of biological hazards in general, and that was because, I mean, among other reasons after I discovered the reverse transcriptase and started working on tumor-inducing viruses, there were a lot of faculty around MIT who were worried that we were going to adventitiously cause cancer in people working in the laboratory and that we had to be careful about what we now call biohazard problems. I thought a lot about that and decided that, at least from what I could tell, that really wasn't a problem because there had been people working with these viruses under much less-stringent conditions than I did for many, many years and there was really no evidence, and still is no evidence, that anybody has ever gotten cancer from them. But it was sensitizing to think about it and it became sort of a national issue for reasons that I have now forgotten in the early 1970s. I remember there were a number of meetings in which we talked about that—particularly a guy whose name I can't remember, and people from Salk. It was a concern, and so we had the meeting at Asilomar [California] about this, which was the first Asilomar meeting, in 1973—not the famous meeting. A book on biohazards in biological research was published as a consequence of that.

That really was the predecessor for the recombinant DNA debates. So that when there was a Gordon [Research] Conference and the first reports came out of about recombinant DNA and people got concerned that there might be biohazard issues there, Paul Berg turned to me as one of the people to become interested, to become involved in this issue and we held the first meeting. That meeting really decided on the quote "moratorium" on certain kinds of research activities at MIT in our little conference room with Paul Berg, Dan Nathans, Jim Watson, and a few other people from which we designed the letter that announced the moratorium and got other people to sign onto it and projected the Asilomar meeting, which was then held, if I remember correctly, in 1974. I may be off a year somewhere in there. Then we organized it. I was one of the organizers of the Asilomar meeting and we had this really extraordinary meeting trying to understand what kinds of biohazards there might be, to evaluate them and to provide a base for some kind of regulation of recombinant-DNA work. It was very clear to us that we were reenacting some of the activities of the physicists around the bomb. It was clear to us that we were raising issues that a large part of the scientific community wished we wouldn't raise, but we felt that being responsible before the fact, because nothing had ever happened, was better than being held responsible after the fact. I think we served the scientific community extremely well in that although that is a continual debate about whether it was a good thing or a bad thing. But in any case, that was just twenty years ago. It was a very powerful time and then the RAC

[Recombinant DNA Advisory Committee] was set up, which I later joined. I wasn't on the initial RAC. Now out of all that, and the debates in Cambridge that occurred, I mean that's an endless story, some of which I remember and some of which I don't.

SCHLESINGER: Apparently, Charlie [Weiner] has a lot of that on tape.

BALTIMORE: That tape probably remembers more than I remember right now. But out of that came a very strong feeling on my part that you can't limit scientific progress by selecting one region of science and saying we are not going to do that but we are going to do other things. Because science progresses in just totally unexpected ways, nobody expected recombinant DNA capabilities to come along and even if you did expect it and said it was a bad thing—I don't. I think it was a great thing. But if for one reason or another you thought it was a bad thing to try to find the precursors before they are there, and block them so that the technology doesn't come up, it is impossible. It came out of nowhere, I mean it came out of an agglomeration of the activities of many people in many disciplines, in virology, bacteriology, and whatever else. In 1978 I wrote an article about that in *Daedalus* (27). *Daedalus* is the publication of the American Academy of Arts and Sciences and they had a whole issue on limiting science. I presented that perspective and I think that article has had a fair amount of currency.

SCHLESINGER: Now that you bring up the fact that recombinant DNA was beginning in the middle 1970s lets go back to science and how that sort of impinged on your thinking. We're now back in 1974-1975. Recombinant DNA really wasn't known at that point. I think no one was thinking about it.

BALTIMORE: Well, that's an interesting point because of all this happening at the same time. I can't really take it apart but I made a major contribution to that in the discovery of the reverse transcriptase. But the kind of work that started up in the mid 1970s, which involved the utilization of enzymes as tools in the manipulation of DNA, was pretty foreign to me. So I didn't sort of jump in on that, although I recognized the importance of it without any question at all. What I wanted to do was to apply it to animal virology. Of course, the first thing we did was to put a moratorium on any research in animal virology because that was one of the areas that we focused on as potentially very hazardous and the Recombinant DNA Advisory Committee put much of that work with any kind of pathogenic virus in class 4, where you couldn't do it. In fact, the only experiments that ever got done were some experiments by George Van de Woude in the isolation facility at NIH, which existed there because of earlier concerns about cancer viruses.

SCHLESINGER: Well, didn't Mal Martin also do something?

BALTIMORE: I think Mal Martin also did at that time. I was just thinking that, but it was very limited. It was limited what you could get done, and clearly in the circumstance at MIT, we weren't going to do anything. Now when we built the Cancer Center we put all the rooms under negative pressure so it was pretty easy to build a P3 facility into the Cancer Center. We did do that by that time I was in the Cancer Center and—I can't remember, I think it wasn't in the original plans because they were built in 1972 or so—very soon after we put up the building, we found a room and we made it a P3.

SCHLESINGER: We talked last time about reverse transcriptase and that Inder had done some experiments. Was he the first one to sort of begin to think about using the enzyme to transcribe messengers?

BALTIMORE: He was one of the first. Phil Leder's lab at the same time did similar experiments.

SCHLESINGER: But this was still before recombinant DNA.

BALTIMORE: That was before recombinant DNA and so we could make DNA representations of genes but we couldn't stitch them together. The power of restriction enzymes was only then becoming available. You could map things with restriction enzymes but you couldn't put things back together again.

SCHLESINGER: When did you become aware that this was going to be something that was actually feasible?

BALTIMORE: Oh, the moment I heard about it. I mean the moment that Paul Berg called me and told me about that. I don't remember the year exactly but it's probably that Gordon Conference—probably held in the summer of 1973, I'm guessing. They wrote this letter, which was going to appear in *Science*, but even before then Paul had called me. He hadn't been at the Gordon Conference, Maxine Singer had. She got in touch with him, and he told me about the experiments that had been done at Stanford, and actually, which Paul had, more or less, set the base for himself in his own work, although the experiments were done by [Stanley] Cohen and [Herbert] Boyer. As soon as I heard about it, it was clear that a new era was open because I mean, I knew that the blockade to working with mammalian cells in the way you could work with viruses or bacteria was the ability to manipulate DNA. There it was, falling away. Then as we thought about the hazards, we also thought about the opportunities. You know there I was kind of salivating to be able to do those experiments and in fact, in the end, we were the first ones to clone and sequence the polio-virus genome with Eckard Wimmer also at roughly the same time. We were the first ones to show the infectivity of polio DNA so there was no

question I was committed to that and we also were very early on involved in tumor virus work but we had to wait for the recombinant DNA guidelines to come down.

SCHLESINGER: But did you start in your lab just learning the methodologies? Because a lot of the methodologies could be done in other systems.

BALTIMORE: Truth of the matter is we started that in immunology. Now that you reminded me, what I really believe is that—you asked me why I had gone on sabbatical—I must have decided in 1974 that I wanted to apply recombinant DNA methods to immunology, but I didn't know enough about immunology to know how to get into it. Then [Susumu] Tonegawa did his experiment just around that time, again I don't know what the dates are exactly.

SCHLESINGER: Why don't just mention what Tonegawa's experiments were.

BALTIMORE: That there was DNA rearrangement at the heart of the issue of immunologic diversity. He showed that by nonrecombinant DNA methods, by Southern hybridizations methods. They used restriction enzymes to cut DNA and could define bands [on a gel] and what they showed was the restriction patterns were different. But the way they did it was by cutting the DNA and then running huge gels and eluting each fraction, and hybridizing it. It was very complicated.

SCHLESINGER: When did you hear about that? From the literature?

BALTIMORE: Well, no I heard about it before, certainly before it was published. It was everywhere.

SCHLESINGER: All right, let's finish recombinant DNA and then start on this.

BALTIMORE: Well, I mean I think it's relevant because you asked how I got started in recombinant DNA methods. It was just after I came back from sabbatical, that I decided we really had to get into the applications of recombinant DNA in immunology because if we were to be involved in immunology, this was the moment to do it. It was Tonegawa's's experiment that convinced me of that. Actually, on sabbatical I had spent a little time doing more kind of DNA-molecule manipulations than I had previously done, but not a lot. It wasn't even DNA it was mostly RNA. I had some very good people in the lab and we had been talking about this back and forth and I said, "Well I am just going to get started." So these are almost the last

experiments I ever did in my life with my own hands. I set up PBR322, the plasmid, growing in what was the safe bacteria.

SCHLESINGER: Was this 1976?

BALTIMORE: It was the Roy Curtis strain. Right, that was the only thing you could use to grow plasmids in those days, so I was growing them up. I grew them up over night, and they grew up slowly. Then I grew them up for another night and they grew up very fast and I knew that I had contaminated it. Meanwhile I had in the lab Al Bothwell and Al was trying to work on problems related to adenovirus because, actually, Lennart Philipson was on sabbatical in the lab and Lennart had enticed Al into thinking about adenovirus and Al had previously worked on adenovirus, so that was all right. He wasn't getting anywhere, and he wasn't really doing what I wanted him to do and I always thought that I did this consciously but I am not positive. It was kind of to show him how bad I was at doing this and Al said to let him do it. That got him involved in immunology, which at that point was what I really wanted. Then Fred Alt came to the lab, and Enzo Enea came to the lab and he joined him and they together really set the whole basis of immunology that we carried forward over the many, many years thereafter because they were willing—and this something I felt was absolutely necessary—they were willing to use subtractive hybridization methods to get at clones for the various types of immunoglobulins; lambda chains, kappa chains, heavy chains, various heavy-chain types, variable regions, constant regions, all of that sort of thing. Tonegawa had much of that stuff already, but nobody could get it.

SCHLESINGER: Where was he?

BALTIMORE: He was in Basel. There weren't many other people who had it, and people were not being very generous as they often aren't in the early stages of development. So I said, "First of all, let's do it, and second of all let's give it to everybody, because there is too much going on here we've got to open this up." We did that, we made them available to everybody once we got probes. I started talking with Klaus Rajewsky and he taught me a lot of immunology.

SCHLESINGER: Where was he?

BALTIMORE: He was in Cologne, Germany, but we would meet at meetings and as I became interested in immunology, one of the things I did was to go to a lot of immunology meetings, just sit and listen to people. The Cold Spring Harbor meeting, I remember. I was at quite a number of meetings. I got to know Klaus. Klaus was, at that point, a very good friend of Wally Gilbert. Wally was also thinking about immunology and I think Wally actually spent some time at Klaus's lab and he got involved in whether T cells could smell or not—that's another story.

Through Klaus, I decided the thing we really ought to focus on was to prove the molecular basis of an idiotype—an idiotype being an immunologic specificity carried by antibodies to a specific determinant from multiple animals of the same inbred strain, indicating that something was going on over and over again in a reproducible manner. The likelihood was that it was a variable region, but how many variable regions would show the same idiotype? Was there one gene involved or many genes involved? A whole lot of questions like that I thought we could answer. So we sort of focused on getting to that, in fact co-published the first papers on that with Klaus because he provided a lot of the reagents that helped us and the hybridomas from which we got the genes and things (28). Along the way we did quite a number of other experiments in immunology but that was sort of the one we that we focused on getting everything together to do and on that basis set up the whole program in immunology and then we carried forward and then I finally became, as time went on, I became aware of more and more interesting questions that we wanted to investigate. So did Fred Alt, who was in the lab there who was such a brilliant scientist.

SCHLESINGER: When he came to the lab he hadn't had any immunology?

BALTIMORE: No, he didn't, he worked with [Robert] Schimke on gene amplification, actually developed facility with subtractive hybridization that carried us forward. I mean it was really the basis of our being able to isolate all those probes because Fred was terrific at that. Al Bothwell developed recombinant methodologies and he was terrific at that. I worked with both of them very closely. Then more people came into the orbit of all of that. I have to look back.

So the first paper that I see looking through my CV on molecular immunology actually came from an ICN, UCLA symposium in 1979 and that sounds about right. That was Alt, Enea, Bothwell and I, entitled "Probes for specific messenger RNAs" because that was the first thing we did was get those probes together (29). But I am reminded by looking at the CV that actually the first important paper that was published in immunology came from an entirely different route and it was the demonstration of immunoglobin synthesis by lymphoid cells transformed by Abelson virus (30). It was the paper that showed that the Abelson transformants are in fact preB cells and that preB cells make only heavy chain and not a light chain, which had been really missed by everybody else.

SCHLESINGER: Why is that, is it because they didn't have the right probes?

BALTIMORE: Because they didn't have the cell lines and because they were working with cells from animals and also the reagents weren't particularly good for looking at that and the reagents worked much better in a cell-culture system. So that was Ed Siden who did that, and Naomi Rosenberg, of course, was central to that. She was, I think, just about at that time leaving the lab and setting up her own lab in Tufts [University] where she has been very successful.

SCHLESINGER: Can you put your work in some perspective for immunology? We talked about this once, of what was known about cellular immunology. But to go back to the 1970s, which is where we are now and you mentioned Tonegawa's work, but maybe you could say a few words about what people were thinking about in immunology because it wasn't such a molecular field at that time.

BALTIMORE: No, it wasn't a molecular field until recombinant-DNA methods really settled in, really until the 1980s.

SCHLESINGER: But maybe some of the big issues that you would have become aware of.

BALTIMORE: Well, I became aware of the issues in immunology when I was at the Salk Institute and largely through discussion with Marty Weigert and with Mel Cohn.

SCHLESINGER: Those issues were antibody issues at the time.

BALTIMORE: They were entirely antibody issues although they knew about the cellular issues and discussed the cellular issues. They were a little too complicated in the language to define—for me to really dig into those—so I focused my attention, and to this day really still focus my attention, on B cells and on antibody. Antibody presented a classic, clean sort of problem, which was the enormous diversity of structure that had been shown starting with [Gerald] Edelman in the face of a region of constancy. So there was the whole business of how you put together variable, and constant regions. I was aware of that problem from the time I was at Salk and was thinking about it thereafter. That's what led me to publish this short theoretical paper on terminal transferase as a potential generator of diversity because I was aware of those problems and had been thinking about them over that period of time.

There was a great paper that was the predecessor of that from Sidney Brenner and others, which suggested that there might be some kind of a diversity generator and I suggest in there that it might be terminal transferase. So I was thinking about those things all through my scientific career. Those are the issues I wanted to get at. Basically the generation of diversity was the thing that interested me. What Tonegawa showed was that one part of that was the rearrangement of the genes but that was only the beginning and we knew it was only the beginning because—well for a whole lot of reasons—but I guess in a sense what I was trying to do was to put in context the role of genetic diversity and the role of somatic diversification. That's what I did, as it turns out. So those were the scientific issues I was getting at, and those are the people who really made a difference in my thinking about it. But it was a classic molecular biologist problem, I think. I can't image any molecular biologist growing up without

an awareness of the apparent paradoxes of diversity and constancy and how those would be solved. I can remember, before Tonegawa's experiment, talking with lots of people, going back to the Salk Institute days about whether that recombination was occurring at the RNA level or the DNA level.

SCHLESINGER: Or the protein level, if you remember.

BALTIMORE: Or the protein level, that's right, and where it fit into the developmental pathways of the cell. Once Tonegawa showed that it was at the DNA level—and I bought that pretty quickly, although it wasn't a perfect experiment but then—once he started using recombinant DNA methods, the experiments got very convincing. There was no issue and he led that field forward personally for a very long time. But he was not much of an immunologist in the sense of understanding some of the classic immunologic questions that were behind there. I wasn't either. But I think through Rajewsky I was really helped to understand what those problems were and to see how we could use our technology to begin to design the right technology to get at those questions, and that's what we did.

So there were two lines of work. One was this question of diversity and the other was development because I had started to become interested in developmental questions, really terminal differentiation questions. That is, you can divide developmental biology into people who are interested in the establishment of early patterns and the process of committing cells down certain kinds of developmental pathways, and people who are interested in looking at the events that occurred during the terminal stages of differentiation like the formation of red-blood cells, or the formation of antibody-producing cells. So I got interested in the formation of antibody-producing cells, which led me to think about whether the Abelson lines might help us to understand that, which led us do those experiments that I was just talking about. So those experiments were more focused on developmental issues, but they would of course link up because now we could try to put in developmental context the events of DNA recombination, class switching, and all those things. That's fundamentally what Fred Alt and I then set out to do once we had the probes. Everything was, on the one hand to try to probe the issues of diversity generation, but on the other hand to try to put the issues of diversity generation within a developmental context in the B lymphocyte.

SCHLESINGER: Is there a paradigm or some remembrance you have of how you and Fred worked on deciding what experiment to do?

BALTIMORE: We would just talk and talk until we found an experiment to do. We knew what materials we had, we knew what materials we could get, we kept track of the literature, and it was a tremendous collaboration. I think to this day, during those discussions, we set the basis of thinking about the developmental issues, the linkage of developmental and diversity issues.

SCHLESINGER: But were there any kind of plans?

BALTIMORE: Much of it turned out to be right! No, we didn't sit down and say let's do this. It just happened that way. I mean at one point, as they say, I sat down and said, "I am going to get into immunology," and that just meant doing this PBR322 growth experiment. I didn't know where it was going to take us. I had no idea. I am very bad at master plans, but I knew what intrigued me. I hoped that by just getting started we would find a way to link the methodology that was developing to the biological questions that intrigued me previously. As it turned out, we were able to do that.

I mean, all this time the work was continuing on tumor viruses. The paper that we published in 1979 on a model of reverse transcription was, really, a kind of culmination of everything we did following the discovery of the reverse transcriptase (31). So there was a whole decade of work on tumor viruses that we're not discussing a whole lot.

SCHLESINGER: And polio.

BALTIMORE: Yes, polio and actually even some other viruses. We picked up other viruses. We picked up Uukuniemi virus for awhile, largely because of Ralf Pettersson.

SCHLESINGER: Well, actually, David, there was a point in your lab where the groups really got divided and that you began to have different meetings.

BALTIMORE: Separate group meetings. That was after immunology got to be a big deal. I think up until, I would guess—I can't tell you exactly—maybe the early 1980s, we always met together every week and I tried to keep everybody in the lab. I mean, I thought that it was good for them because it meant that everybody in the lab was thinking about all of the problems or at least being exposed to all the problems, I don't know what they were thinking about. I know that a lot of them turned off. You know, the virologists never really fully understood the immunologists and vice versa. But I thought that was part of my educational function and anyway it was a technical back and forth that was important, even if the conceptual areas didn't get understood completely. For instance, Vince Racaniello, who came into the lab and who cloned polio and showed its infectivity on everything, was a master at technical things and he may not have involved himself in any of the immunology but was an important contributor to the technical ability to do certain kinds of experiments.

[END OF TAPE, SIDE 2]

BALTIMORE: Yes, I believe that I encouraged Vinney [Racaniello] to do the key experiment. He had cloned polio and sequenced it, and I said, "Look why don't you just take the clone that has the whole thing [genome] in it and throw it on the cells and see if it makes polio viruses." I don't know why that should work, I couldn't imagine why it should work, I still don't know why it works. But it seemed like it was just so simple. He did it and it worked. Then, the moment we saw the first plaques, the first thought was "vaccine," because the vaccine was at that point very effective but nobody knew why it worked because nobody knew where the mutations were in it, how many mutations there were, and what made it effective. We knew that there was a certain amount of breakthrough [virulent virus] from it, so it seemed that we could make a better vaccine. What we had not taken into account was that you virtually couldn't test a better vaccine to find out whether it was better or not. Therefore there has been no change in the vaccines that are used, in spite all of the molecular progress. Of course, lots of other vaccines are trying to be made using molecular methods.

SCHLESINGER: I think you actually have a patent on using polio with heterologous sequences (32).

BALTIMORE: We have a number of patents. With heterologous sequences, we put in a patent application on that and that's been actually licensed. They are working on it at Lederle, in principle. I don't know what they are doing.

SCHLESINGER: Was it a new concept for you to think about patenting when you patented the polio vaccine?

BALTIMORE: Well, that's true, but the patent I'm talking about is more recent. We patented the infectivity for infectious polio and that certainly was a new concept, in fact, I guess that was the first patent that I ever made (32). Oh, I know there was one other patent we applied for. Alice and I applied for a patent on DI [defective interfering] particles, which we never got, in 1972 or something. In fact, I thought at one point that DI particles might turn out to be more important than reverse transcriptase. I was wrong. But we really were convinced that the DI particles were a very important basis of disease and one could make vaccines through DI particles. So we applied for that patent but I guess it was abandoned. [Turning to Alice Huang, David asked:] Was the DI patent abandoned finally?

HUANG: No we got a patent; it just ran out.

BALTIMORE: We got the DI patent?

HUANG: Yes.

BALTIMORE: I don't have it on my CV as a patent.

HUANG: Really, I have it on mine.

BALTIMORE: Oh, would you give it to me please?

SCHLESINGER: You don't even have the polio patent on your CV.

BALTIMORE: Yes I do. It is the first one, "the production of complementary DNA representing RNA viral sequences by recombinant DNA methods and uses thereof." It is in fact that. Then we also got a patent on the use of VP1 because we were able to show that the VP1 had the appropriate neutralizing determinants, but that hasn't gotten us anywhere either (33).

SCHLESINGER: Was it your idea to patent polio or was it MIT's idea?

BALTIMORE: I think by then I was aware of it. What I don't remember is how we decided to patent the DI particles. Alice might.

SCHLESINGER: I'll ask when I interview her. Because we only have a few minutes left, I wanted to ask about polio, how that was impinging on everything else, and how you handled the work on polio.

BALTIMORE: It had its own lab and there was a wonderful spirit among the people who were in that lab over the time: Victor Ambros, Burt Flanigan, Ralf Pettersson, and quite a number of people—Margaret Baron—a very good group of people. They knew that they were a separate group and that, in a sense, the excitement of the laboratory had moved over to the other side. But they were all committed to it. I was too. I never lost my involvement with it or caring about it. I mean, everything that happened through that period I was involved in, cared about.

SCHLESINGER: You mentioned the work on the heterologous sequences, but did that begin in your lab—the introduction of heterologous sequences into polio—or is that just something you're part of because of your interactions with Vinney?

BALTIMORE: No, the new patent was the work of Mark Feinberg and Raul Andino (34). What they showed was that you could put another gene into polio by inserting it right at the beginning of VP4, right at the beginning of the polyprotein, and putting a cleavage site in there. That it is cleaved off by the protease, and works better than any other method of putting genes into polio. Actually that was their idea. I am not on that patent, come to think of it, because they really had thought of it, done it, and carried it through.

[END OF TAPE, SIDE 3]

[END OF INTERVIEW 3]

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