CHEMICAL HERITAGE FOUNDATION

BERNARD N. FIELDS

Transcript of an interview
Conducted by

Sondra Schlesinger

on

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Chemical Heritage Foundation
Oral History Program
315 Chestnut Street
Philadelphia, Pennsylvania 19106

BERNARD N. FIELDS

1938	Born in Brooklyn, New York, on March 24
1995	Died in West Newtown, Massachusetts, on January 31

Education

1958	A.B., biology, Brandeis University
1962	M.D., New York University School of Medicine

Professional Experience

National Communicable Disease Center, Atlanta, Georgia

1965-1966	Medical Virologist, Virology Section
1966-1967	Assistant Chief, Arbovirus Infectious Unit

Albert Einstein College of Medicine

1967-1968	Postdoctoral Fellow, Department of Cell Biology
1968-1969	Associate, Departments of Medicine and Cell Biology
1969-1971	Assistant Professor, Departments of Medicine and Cell Biology
1971-1975	Associate Professor, Departments of Medicine and Cell Biology

Harvard Medical School

1975-1994	Professor of Microbiology and Molecular Genetics
1981-1994	Professor of Medicine
1982-1994	Chairman, Department of Microbiology and Molecular Genetics
1984-1994	Adele H. Lehman Professor of Microbiology and Molecular Genetics
1976-1994	Associate Editor, *Journal of Infectious Diseases*
1977	Visiting Professor, Washington University

Honors

1962	Founders' Day Award, New York University School of Medicine
1974-1979	Irma T. Hirschl Scholar Award
1974	12th Annual Redway Medal (with Cedric Raine)
1974-1975	Career Scientist, Health Research Council of New York

1982	Solomon A. Berson Alumni Achievement Award, New York University School of Medicine
1982	Wellcome Lecturer, American Society of Microbiology
1983	Lippard Lecturer, Columbia University
1984	Thayer Lecturer, The Johns Hopkins University School of Medicine
1987	Dyer Lecturer, National Institutes of Health
1987-1995	Merit Award, National Institute of Allergy and Infectious Diseases
1989	Niels Dungal Memorial Lecturer, University of Iceland, Reykjavik
1991	Dudley Wright Lecturer, Arolla, Switzerland
1992	Alumni Achievement Award, Brandeis University

ABSTRACT

Bernard Fields begins the interview with a discussion of his early years, growing up in Brooklyn, New York. Fields was encouraged by his parents to excel in scholastic endeavors. After graduating high school at the age of sixteen, Fields enrolled at Brandeis University. After a mediocre start, he finished college at the top of his class, receiving an A.B. in biology in 1958. Fields loved biology and wanted to become an M.D. He attended New York University School of Medicine, earning his M.D. in 1962. While at NYU, Fields first became interested in neuroscience and how diseases affect the central nervous system. He then received an internship with Beth Israel Hospital in Boston, where he became involved in infectious diseases. After completing his doctoral training, Fields took a fellowship in infectious diseases with Mort Swartz at Massachusetts General Hospital. Infectious diseases fascinated Fields and he began to move toward a career in microbiology and virology. In 1967, after two years of military service in Atlanta, Georgia, with the Centers for Disease Control, Fields moved back to New York with his new wife and three stepchildren, accepting a research fellowship with Wolfgang K. Joklik at Albert Einstein College of Medicine. While at Einstein, Fields began research on Reovirus, which would become one of his life-long research projects. His research focused on the genetics of Reovirus and how the virus interacted with animal cells. In 1969, Fields became Associate Professor of Medicine and Cell Biology at Einstein, and held that position until 1975, when he joined the faculty at Harvard Medical School as Head of Infectious Diseases. With his research fellows, Fields studied different strains of Reovirus and how they mutated to cause different diseases. Fields became Chairman of the Microbiology and Molecular Genetics Department at Harvard in 1982, ending his extensive research in infectious diseases just as AIDS hit the world scene. Fields concludes the interview with a discussion of the future of biological research, developing working relationships with students, and his personal battle with pancreatic cancer.

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. 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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DATE: 8 December 1992

SCHLESINGER: Let's start at the beginning.

FIELDS: I was born March 24, 1938 in Brooklyn, New York. I have an older brother who is twelve years older than I am and was from my mother's first marriage, and I have a younger brother who is three years younger than I am.

SCHLESINGER: Anything interesting in your early school years that you can remember, any special events?

FIELDS: I guess in my early school years, I was not a particularly good student. However, I tested well in aptitude tests. In Brooklyn in the 1950s there was a special program for students who seemed to have high aptitude called "Special Progress." Students in the seventh, eighth, and ninth grades were placed in a special school where you took two years instead of three and, thus, skipped a grade. I participated in "Special Progress," and in retrospect, I think it was probably a mistake because I was very young. I graduated from high school when I had just turned sixteen and frankly, I think I would have been better off had I been a year or two older. My experience in high school was that I was too young to appreciate what I had.

SCHLESINGER: So there were no special events. For example, summer experiences?

FIELDS: I went to camp. My family was not what I would call a very intellectual family. It was a Jewish, middle-class family and the values, the history of the family, in this sense, were that of second-generation immigrants from Europe, from the central region of Poland and Russia. My parents were both born in Europe and came to the U.S. and ended up in Brooklyn as part of a mass immigration of the European Jewish population.

SCHLESINGER: Were you religious as a youngster?

FIELDS: No. I went to Hebrew School, but I was not religious. I hated Hebrew School. I couldn't wait to be "Bar mitzvahed" and then vanish from the face of having to be involved in organized religion.

SCHLESINGER: But the decision to go to college?

FIELDS: College was never an issue. You had to go college, and education was always very important, in the theoretical sense. The professions were very highly valued. My father was a lawyer. Education was very important, but the content of education (i.e., scholarship) was not a major part of my family background.

SCHLESINGER: So you don't have any special memories of high school, any special friends?

FIELDS: Oh, yes, I have friends who remain close friends to this day. My oldest friend is from junior high school and high school, and, parenthetically, will be at the Bristol Myers [Bristol-Myers Squibb Company] lunch on Thursday. Two of them are part of a very small group of friends that did everything together. One of them was a scholar in high school, who became a scholar as an adult, and the other one became a lawyer, a very successful, famous lawyer.

SCHLESINGER: Was there any indication at the time that you were in high school that you were going to go into medicine?

FIELDS: I was sort of interested in biology and when I went to college, majored in biology. At the time, I think my background didn't lead me to think that biology meant that you could get a Ph.D.—college led towards the professions. I never considered biology as a field.

SCHLESINGER: Was there any special reason you chose Brandeis for college?

FIELDS: Well, I was a middling student in high school, in the middle of my class. I was very, very young. I was interviewed for Brandeis by a very wonderful man. I had very high SATs, like 800 in math, which was disparate from my high school record. I had a very nice interview and the interviewer said, "You know, you remind me of myself. I was very, very young." And he said that I didn't have the record for Brandeis, but something felt right and, "we'll take a chance." That is how I went to Brandeis.

SCHLESINGER: Sounds almost like he was one of the first people who made an impression on you.

FIELDS: He did, and I have to tell you, just as an aside, I received a very nice Brandeis alumni award this year. Another person received it with me, a woman by the name of Letty Cotton Pogrebin, one of the founders of *Ms. Magazine*. During her comments at the ceremony, she mentioned that the same person had interviewed her and said, "I'll take a chance on you" and how important it was to her. I talked to her afterwards, and the two of us felt the faith that this person

gave to us. It was very nice and important to both of us.

SCHLESINGER: Now, in college, what were the special remembrances that you have?

FIELDS: Well, the first thing is that I entered college with a great deal of insecurity and a very middling academic record. My first exams in college were consistent with what I had done previously in high school. I was a little overwhelmed, I had Cs and Ds and was very nervous. Then something happened during the first year. I suddenly realized I couldn't just repeat everything that was given to me—it's too much information. So instead of trying to repeat, I started to think and not simply regurgitate. In fact, I think I ended up with three As and two Bs after the first formal grading session, and I was shocked. Everyone else was, too. And then I did it again, and it was as if I had suddenly learned how to learn. I began to trust myself and enjoy college. Brandeis was a wonderful experience for me from the socializing point of view and from the academics.

SCHLESINGER: Any special teachers you remember?

FIELDS: I do; they were not so much in the sciences. I entered college in 1954. This was the year when Herbert Marcuse taught me international communism and the history of the Chinese revolution. Irving Howe taught English. Max Lerner taught American Civilization. Brandeis was an extraordinarily interesting small school that was totally alive and spirited. In many ways, had I been more open to various options, I am not even sure I would have gone into science, because at the time—it was before Brandeis had really built science in a major way. During my third or fourth year at Brandeis, Nathan Kaplan was recruited and he built biochemistry, helping to make it strong in science. It was really more of a teacher school in the biological sciences. I do remember one teacher with particular fondness, an ecologist by the name of Carl Sinderman. We would take field trips to the coast of Maine, walk along the coast, and describe the ecosystem and real field biology, and I loved biology.

SCHLESINGER: When did you decide to think about medical school?

FIELDS: Well, I am not sure I ever thought about med school. I became a biology major and premedical concentrator and I still keep trying to figure out why I did that. I think I was powerfully influenced by my cultural growing-up. My parents had lived through the insecurities of the Depression; their families were still in Europe during World War II and were killed in the Holocaust. My mother's mother lived with us, and I kept hearing about different members of the family that she could no longer communicate with. I think there was tremendous insecurity in my childhood. The premedical and medical career track was a very secure career choice. Therefore, I majored in biology, loved it, and went to premed because it seemed to be what you did. In retrospect, I would love to go back to college because there are so many fields that are interesting. But I do like biology a lot; I love biology and it seemed to be the field to go into.

SCHLESINGER: Had you any exposure to research?

FIELDS: Minimal. I enjoyed lab work but I didn't do research really until later. Research wasn't part of the linear path that I think I was programmed into, and really it wasn't until later that I kept coming back to laboratory work and research and changed direction. But I loved the basic ideas in biology, I loved dissecting. The things we did in those days—you dissected a frog, and the field trips, and evolution. I loved biology.

SCHLESINGER: Before we leave college, can you remember any other special interests?

FIELDS: I am going to give you a few. One story involves someone whose name I won't mention, but a famous professor of English. When I first entered college, I was a very insecure student because I was not a good high school student. In addition, I did poorly in my first exams at Brandeis. During my first semester, I wrote an essay that presented some interesting thoughts. I gave it to this English professor who, after reading the essay, sent back the grades and commented in the report: "Did you write this?" I was really devastated because, first of all, he was asking me if I was honest because he thought that someone else may have written it for me since it was so different from my prior work. Secondly, I was very insecure and this famous, famous English professor said, in essence, "I don't believe you really could have done this quality work." Part of me is very stubborn; I responded by continuing to write "interesting" essays and becoming more comfortable with how to write and think. However, it could have been a shattering experience. That was my negative experience at Brandeis—the power of the professor could have caused harm, but he didn't. I have seen him periodically since that time, and I really wanted to confront him with what he did, but I didn't.

The other general experience that was important to me was that I was very young when I entered Brandeis and graduated at age twenty. I think that I always regretted being younger than my peers. I had good friends at Brandeis and good feelings about the school overall, but I feel that I was too young. There was no reason to rush ahead and be precocious academically and socially. The 1950s was a time when various experiments in education were done and I was sort of trapped in them because of my IQ test. In spite of these issues at Brandeis, I learned to love biology and learning. It was a very good school for me.

SCHLESINGER: Was applying to medical school a difficult experience?

FIELDS: No, not really. After my shaky start at Brandeis, I ended up a rather excellent student. Although medical school was difficult to get into in the 1950s, my record was good enough that I had no problem getting in.

SCHLESINGER: So what made you chose NYU [New York University]?

FIELDS: Well, it was in New York; I didn't get into Harvard; I didn't get into Yale. My roommate did. I got into NYU, Albert Einstein [College of Medicine], and a number of schools. NYU seemed like a good place. Why do you choose a school? You either felt good the day you went there or you liked the person who interviewed you. It felt like a good school and so that's why I went.

SCHLESINGER: Now, I'll ask you the same questions about med school.

FIELDS: Well, first of all, in med school, I obviously began to get interested in research because I would end up doing it every summer. I took physiology and had an idea about a problem in membrane biology and transport by membranes. Homer Smith, my first research advisor, was older and, actually, past his prime, but he was still an interesting professor of physiology. I worked for him one summer on a project using the toad bladder to try to extract different factors involved in renal transport. I did some interesting experiments—couldn't interpret them, probably still couldn't—adding lipid solvents to the difference sides of the toad bladder membrane and looking at the effect on transport. This was back in 1959. During school, I worked in another physiology lab, Bob Cook's lab, dealing with membrane transport. The approach was different than my prior work and I learned a great deal, but didn't get much done. One summer I spent in Brookhaven National Laboratory studying the effect of boron on brain tumors. The summer was too short to get much done.

While in medical school, I began to get interested in the brain. There was a professor who later went to MIT, Hans Lucas Tenber, who ran a journal club with a small number of interested students on aspects of neuroscience. I found it fascinating. I guess I have always been interested in the nervous system and how things injure it. I figured out why about ten years ago. My younger brother developed epilepsy when we were very young. I finally made a connection; part of my profound interest in the nervous system is related to my brother's epilepsy and how his injury occurred. Whenever I started to study viruses, one of the first experiments I carried out with viruses was to put them into the brain of young mice to see if mutants were altered in their capacity to injure the brain. I was also interested in understanding how viruses entered the CNS [central nervous system] to injure the brain. The connection seems obvious in retrospect. One day, I finally realized that I had always lived with the reality that my younger brother had epilepsy. I remembered episodes when he had seizures. He is fine now, and has been for many years, but his disease profoundly affected one of my main scientific directions. If your research relates to your own history, there is often a very powerful connection. Today, half of my lab remains totally dedicated to figuring out how viruses injure the nervous system. Clearly these memories influenced my being interested in the nervous system, even in med school, and in my summer research. With time, I began more and more to like laboratory work, I liked to try to define a problem. I had fun thinking of approaches to solve them. None of my summer or school experiences were ones where I actually solved a problem, but I clearly enjoyed research. Nonetheless, I had decided that I was going to be a doctor when I graduated from medical school.

In retrospect, NYU Medical School was an interesting place to go to school. It was a very exciting research place in the 1950s and remains research oriented. Immunology at NYU was well represented and, in addition, a good deal of basic science was being carried out. With the school's emphasis on research, and even though I did research in summers, I felt cheated. Here I was at

medical school and I really wanted a course, for example, in medical microbiology where I could learn about the diseases, and instead I kept hearing about bacteriophage. I and many of my classmates resented the research orientation of some of the courses. In retrospect, I certainly learned microbiology and I learned what I needed to. In a funny way, the research environment at NYU was probably very important as a model for how things can be done. It was a fun place to get an M.D.

SCHLESINGER: Did the faculty try to influence you?

FIELDS: No, it's just that if you were interested in research, the faculty was more interested in you. There was nothing explicit, but it was clear that the orientation of that school was heavy on research throughout all the levels. My first attending in medicine was Louis Thomas. The pathology department was run by Al Stetson, who was an immunologist. Baruj Benaceraff was on the faculty. NYU was filled with immunologists. In addition, there were excellent microbiologists and biochemists. You certainly knew what the value system of the school was. This orientation may have been an important reason that I chose the school. I probably would have denied that at the time, but I knew that it was a research-oriented place, no question about it. The faculty felt excited about the research, they felt excited about NYU as a school because all of this wonderful research going on. The complaints of students were that the faculty was not teaching enough clinical medicine, nonetheless the environment was very exciting. Thus my medical school experience was quite positive.

SCHLESINGER: Let's just talk a little bit about some of the highlights in medical school. Were you active in anything else besides research and taking courses?

FIELDS: Well, I did go to some things, like the neuroscience club. There was a microbiology journal club that Jerry Hurwitz ran, even though I wouldn't call him a microbiologist, but in the broader sense of biochemistry, he was. I was interested in the courses I was taking and carrying them all further than just course work. By this point, much of the insecurity that I felt when I entered Brandeis was no longer present because when I had gone through Brandeis, even though I started out as very insecure, I ended up with a very high achievement there. When it came to med school—it just seemed very easy at that point to do very well and I ended up coming very close to being first in the class.

SCHLESINGER: Where you actually first in the class?

FIELDS: I was first or second; it changed maybe in the clinical years. But I was in the top two or three, and I was president of the AOA [Alpha Omega Alpha] Honor Society as a junior and represented the school in graduation. So it was in that handful of two or three people who were flirting with the top numbers.

SCHLESINGER: What awards did you win?

FIELDS: There was some award that I won, but I have to be honest, I don't remember. I was asked to represent the school at the Founder's Day, meaning I carried the flag and I was the one who went up to get the degree for all the students. That was a very nice honor. I also have to tell you that a lot of my classmates were outstanding and a number of people in my class and the next class went into science. This includes such people as George Todaro and Bob Lehrer. But a lot of people ended up going into research in the fields of microbiology and immunology from that era. There was an exciting student body, which had a real sense of—almost mission in—research. Another point that occurs to me about NYU is that, while I was not in the program, they had a research honors program, which was unusual at the time. In the program, they actively recruited and helped pay for students who knew they were going into research. This program helped create within the student body itself a cadre of students who clearly were focused, perhaps more focused and more advanced than the traditional med students might have been. I think it was very good for the school. In many ways it was the forerunner of what became more formal M.D./Ph.D. programs. The NYU honors program brought in several students focused in research and very good faculty to speak to them and to the rest of the school. Although I was not part of the honors program, it was part of the atmosphere that I remember. At NYU that was quite special, particularly in retrospect.

SCHLESINGER: But during the time that you were in medical school, were you thinking about a career in research?

FIELDS: Absolutely not. I was aiming towards clinical medicine. Even though I had been taking several research rotations, that in retrospect indicated, "hey, you are not totally in a clinical track," I thought I was going to be a real doctor. I liked medicine a lot and I liked that clinical stuff. That's why I went to medical school. In fact, the only thing that I remember thinking, on more than one occasion, is that NYU is too heavily research oriented. In fact, I was considering that for my senior elective maybe I should take ophthalmology, ENT [ears, nose, and throat], and various subspecialties.

SCHLESINGER: Did you?

FIELDS: No, I think I ended up doing research electives. Part of me knew that I was not fully tracked in the clinical direction, but part of me kept telling me to get the clinical stuff and do it well. But I clearly had part of me, that I wasn't as aware of, saying "there is another track in you." But I really was not that aware of it at the time. Even though I did things that, in retrospect, made it obvious that I did have an interest.

SCHLESINGER: And your plans for after medical school?

FIELDS: Since I was going to be a doctor, I applied for and got an internship in Medicine at Beth

Israel Hospital [BI] in Boston, and did an assistant residency as well. The program was a very strong clinical one, which I wanted. It was at the Beth Israel Hospital that I began to get more interested in infectious disease and in molecular biology. The infectious diseases were interesting. There were a few people that influenced me. One in particular was Lou Weinstein, who used to come over and see difficult cases. He was not only a fascinating clinician, but a real showman. One dramatic case he saw was one of my co-interns, Steven Chaven, who subsequently became a hematologist. Steve developed a disease that looked like maybe it was a lymphoma, his lymph nodes enlarged and he developed a fever of unknown origin. He became very sick and very, very worried. The diagnosis wasn't clear and a lymphoma was seriously considered. Lou Weinstein came over as a consultant and spent about two minutes, at which point he said, "You have the 'typhoidal' presentation of infectious mononucleosis. In two days your tests will show it, you'll be fine. Don't worry, go back and rest." Two days later the tests showed mono; he slept better; we all slept better. He didn't have lymphoma, and it was quite an exciting, dramatic rethinking of the clinical problem. Lou had that effect. It was almost magic, because he had enormous clinical experience, was willing to go out on a limb, was usually right, (but not always), and he was really one of the people who got me interested in infectious diseases as a family of diseases. In fact, I spent two years at Beth Israel becoming a doctor, but I decided by that point, I would go into infectious diseases. After two years at Beth Israel, I took an infectious-diseases fellowship with Mort Swartz at the Massachusetts General Hospital [MGH]. What else do I remember about BI? I remember being extremely tired as an intern.

SCHLESINGER: How many years were you at Beth Israel?

FIELDS: Two years, the internship and assistant residency was my clinical training in medicine. I then had one year of infectious disease, and that was my clinical training.

SCHLESINGER: So a total of two years?

FIELDS: Yes. The internship is your licensing year, where you enter as student and you end up being able to handle medicine. I enjoyed it.

SCHLESINGER: Were there any special cases that you remember?

FIELDS: Yes. I remember one young woman who came in with an acute abdomen while I was an intern. I diagnosed her problem as a ruptured ectopic pregnancy. I stayed with her, rushed her off to the operating room, and helped save her life. It was a very powerful experience because she was at the door of death and everything had to be right since she had a real acute surgical medical emergency. I remember learning enough so that I began to be more and more comfortable with my understanding of the diseases and being able to diagnose them in a reasonable way. It is a very, very powerful apprenticeship. It's a license, you change and become a professional. So I enjoyed those two years, but I also realized that I didn't want to just be a general doctor or an internist, and that infectious diseases fascinated me. So I took a fellowship with Mort Swartz. Mort had set up an

infectious disease unit at Massachusetts General. He was an outstanding clinician and teacher. Part of his program was clinical presentation of cases seen at Mass. General Hospital and Tufts [University] (Dr. Weinstein's service) every Friday. One week at Tufts, and the next time at Mass. General. So I continued to get to know Lou Weinstein and we have been very close ever since. I developed clinical skills in the area of infectious diseases.

SCHLESINGER: At this point, were you still thinking about clinical medicine?

FIELDS: Yes, I was. However, I started to develop a serious research interest. Mort Swartz had trained in biochemistry, even though he was an absolutely outstanding clinician. He did some research at Massachusetts General, every seven years or so, would take a sabbatical working with Arthur Kornberg or others at Stanford. Mort gave the fellows a journal club on a new discipline that was beginning to appear called molecular biology. Mort was a very good teacher, very knowledgeable, and that absolutely fascinated me. Since I loved molecular biology, I spoke to Howard Hiatt, who had been my attending in medicine in Beth Israel and was now head of medicine at the Beth Israel, and to Mort Swartz, and they both told me that my next training should be a research-training experience. Howard Hiatt recommended that I should get advice from Salvador Luria, who knew molecular biology. I already felt that viruses were interesting and I went to MIT and I had a nice lunch with Salvador Luria.

SCHLESINGER: What year was this?

FIELDS: This must have been 1964. Salvador Luria heard what I was interested in, heard that I was training in medicine and liked infectious diseases, heard that I wanted to do molecular biology with animal viruses with some connection to infectious disease. He gave me four names to consider. Two of them were at Einstein, Bill [Wolfgang K.] Joklik and Jim Darnell. He also mentioned Maurice Green in St. Louis and Renato Dulbecco, who I think was still at Caltech at that time. I never did write to Dulbecco because I really didn't want to work on tumor viruses. I never did see Maurice Green because I wrote to Bill Joklik and Jim Darnell and visited Einstein. I met Harry Eagle, met the people at Einstein, and really liked the environment. I am skipping ahead because in between Mass General and Einstein, I went to the CDC [Centers for Disease Control], and it was during my first year at CDC when I met Salva Luria, visited Einstein, and Bill Joklik offered me a fellowship. Jim Darnell at the time didn't have space and I liked what Bill was saying, what he was doing, and I accepted a research fellowship.

The one gap in this story is what I had decided to do for my military service. I spent two years at CDC to continue my interest in infectious diseases and virology. The CDC at that time (1965-1967) was the Communicable Disease Center (now the Centers for Disease Control). I ended up at CDC because when I was at Harvard, Telford Work, Director of Virology at CDC in 1965, gave a talk in the Harvard Medical School microbiology course. He was an outside lecturer who came in and talked about arboviruses. He also showed a film and a presentation on his discovery of the epidemiology of Kyasanur Forest virus. He was a fascinating speaker. His studies involved epidemiology, collecting field specimens, isolating the causative virus and identifying it, and

connecting all the data to explain an epidemic disease. Part of the excitement that Tel generated was describing the working out of the field biology. I liked what he said and it sounded like a wonderful way to learn virology and to enjoy two years of the military. I was not really interested in going into the army or to the NIH [National Institutes of Health] at that time. I thought about NIH, but the field biology at CDC coupled with the laboratory work was very exciting to me. I was one of a few medical officers in the laboratory branch of CDC. I did not go into the EIS [Epidemic Intelligence Service], because the EIS did not stress laboratory work and I felt I wanted to do something in the lab. So here was an opportunity to do field epidemiology and play with the viruses myself in the lab. This approach obviously separated me from Alex Langmuir's shoe-leather epidemiology, where you don't touch a thing in the lab, you just do it in the field. I respected and enjoyed the idea of the epidemiology, but the laboratory was key at this point. It was already clear I was on a certain track.

Thus, after finishing my infectious disease fellowship with Mort, I went to the CDC. In July of 1965 I went to Atlanta and joined what was then the arbovirus unit of the CDC directed by Telford Work. I was second medical officer in that unit. Brian Henderson, who has recently become president of the Salk Institute, had preceded me by a year, and when I joined the unit there were two of us. The first thing you do when you get to CDC is you take the epidemiology course, whether you are laboratory or EIS. I then started doing field work, but mainly laboratory work in arboviruses. I had wonderful colleagues who were mainly veterinary virologists: Fred Murphy, Phil Coleman, and also Charley Calisher. It was a fun two years. I learned to feel very comfortable injecting the brains—and elsewhere—of mice, which I have done ever since. I was very comfortable with the broader biology—both in terms of field epidemiology and of biology issues of virology—of the virus in a host. You really become a field and laboratory biologist with this experience, not a molecular biologist. I ran some cesium gradients, but what you become comfortable with is looking at large numbers of mice, injecting them, harvesting them. I studied rabies virus and similar shaped viruses like VSV [vesicular stomatitis virus], as well as eastern equine encephalitis viruses, California encephalitis virus, et cetera. I gained a great deal of valuable experience in classic virology.

SCHLESINGER: Was there any connection with what was going on in Vietnam in terms of the viruses that you were studying?

FIELDS: The war would have already started, but the answer is: not very much. There was some going on at Fort Dietrick, and some in Utah. Our unit was mainly an extension of the Rockefeller Field Approach: find out what is going on with the viruses, isolate them, see what is around, see if they cause human disease, do epidemiology, bring it back to the lab.

SCHLESINGER: Did you do any of the epidemiology?

FIELDS: I did. I went to South Carolina to study meningitis and encephalitis outbreaks of a picornavirus. I studied western equine encephalitis in Wisconsin and Texas, St. Louis encephalitis in Dallas, Texas. The epidemic in Texas was an exciting investigation involving control of a St. Louis encephalitis epidemic. During my time at CDC I did very little international work. The

arbovirus unit, subsequently, when Tom Monath came in, studied such viruses as the hemorrhagic fever viruses and Marburg, but that was a few years later. I studied a case of Yellow Fever due to the Yellow Fever vaccine, but it was all within the context of the USA. Very little international. Brian Henderson, who had been there the year before me, seemed to do a great deal of international studies; he was a lot more interested. Not that I loved going to South Carolina more than I might have enjoyed going to Africa, but that was just my draw of the cards. However, I learned a great deal about classic virology and became extremely comfortable with virology. It also became absolutely clear to me—when I was offered a job to stay at CDC as assistant chief of the unit and to have a career in the CDC—that what I wanted to do next was to learn molecular biology and use it to study viruses. The people at CDC tried to convince me to stay on, they guaranteed all sorts of things, and they are nice people, thoughtful people, but at this point, I said, "I want to learn molecular biology."

SCHLESINGER: Before we go on to molecular biology, I think the years in the South also had some personal interest?

FIELDS: Well, I met my wife. She was a Southerner from North Carolina who migrated to Atlanta. She was in art school at the time with three young boys. She was recently divorced and I became attached, very quickly, both to my wife and to the three young children. We got married in Atlanta in 1966. It was a very important tour of duty for me, with a great deal of pleasure. Ruth is still an artist, we remain married, and it's been a very wonderful thing for me.

SCHLESINGER: So now we are at CDC in 1967, is that right?
FIELDS: Yes, finished in June of 1967 and then joined Bill Joklik's lab in July of that year.

SCHLESINGER: So now you moved back to New York?

FIELDS: Back to New York with wife, three kids, a dog, and three cats. That's when we moved into the Bronx right near Einstein in an apartment. The dog was a St. Bernard and that was an experience—walking the St. Bernard on the streets of the Bronx around Albert Einstein. And the dog—we had several acres in Atlanta—did not like the Bronx and I did not like having to come home for lunch because this dog was so huge that the kids couldn't handle her and I had to walk the dog for her daily rituals. We ended up sending the dog back to friends in the South. In other ways, the move to Einstein was a very interesting one. First of all, the environment at Einstein in virology and molecular biology was in many ways similar to what I described about the environment at NYU for immunology. The environment at Einstein for virology in 1967 was very exciting.

SCHLESINGER: This is the Department of Microbiology?

FIELDS: I joined the Department of Cell Biology, Harry Eagle's department, which is where Bill

Joklik was. I came to Einstein as a research fellow. A year later I joined the faculty. But I came to Einstein strictly because I wanted to get into a laboratory doing molecular biology in order to ultimately apply this discipline to studies of pathogenesis. Why did I choose Reo [Reovirus]? Simply, because Bill Joklik was working with Reo. He had worked on vaccinia and pox and when he started working on Reovirus, he pointed out the advantages of working with a virus that had genes in pieces. It seemed to me the more important thing at the moment was not necessarily which particular virus I was studying, but rather getting a system that I could learn what I wanted to learn. Reo seemed very well suited for that purpose. So my year with Bill was spent studying genetics of Reovirus. During the year, Bill accepted a job at Duke [University] and eventually left, but I certainly got to know him very well. I spent my time getting mutants, grouping the mutants, identifying where the lesions were, doing crosses to show that these viruses could reassort their RNA segments—really beginning to do very fundamental genetic work and at the same time do some biochemistry. I did some work on characterizing the mutants and began to be very comfortable with lab. It's 1967-1968, and all of a sudden I am in a lab full time. How did I get here? Remember, I wanted to learn molecular biology and it seemed that the only way I was going to learn molecular biology was to do it full time for a while. It wasn't that I had given up on medicine, it's just that molecular biology was the kind of approach that I felt could answer very fundamental questions. So I spent the year learning as much as I could.

The complications of my fellowship year—first of all, it was not easy living in the Bronx after living in the South. We ended up moving out to an area that had a little more space—to Larchmont. Bill Joklik's accepting the job at Duke left me in a little bit of a quandary. He asked me if I would go down with him. But we had just moved. Also Bill was moving right near Ruth's hometown and she wasn't really that interested in moving back home in 1967. In addition, we had just moved all the kids and it seemed very difficult to move again. At the same time, Irving London, who was Chairman of Medicine, and Harry Eagle, who was Chairman of Cell Biology, said, "Why don't you stay and join our departments?" They were very generous in terms of offering me a lab in the Department of Cell Biology and a position in medicine at the Bronx Municipal Hospital of the Einstein Med School. So I decided to accept, even though I hadn't spent much time in learning molecular biology. The environment at Einstein was very good. The opportunity to continue to learn molecular biology on my own existed, particularly with the help of a lot of colleagues who were very excellent, supportive people. So I decided, with some uncertainty, to stay at Einstein. The year was a good one. Scientifically, I felt I learned a lot; I isolated a lot of mutants. I did genetic studies that were the beginning of my studies on Reovirus genetics and were among the earliest animal viruses genetics studied.

SCHLESINGER: What kind of mutants did you isolate?

FIELDS: Temperature sensitive [*ts*] mutants. I did crosses between them and analyzed how they interacted and set up what we call recombination groups, which are reassortment based.

SCHLESINGER: Was that the first time that had been done?

FIELDS: Yes. Around the same time, George Hirst was working with flu and getting certain

similar features, but it was really—what we were discovering was that there were no simple precedents. Elmer Pfefferkorn was working with Boyce Birge on Sindbis mutants, which were totally different, since Sindbis contains a linear RNA. They were not getting the phenomena we were describing. It was thus interesting and challenging because there were no clear precedents, and it was an area that was fruitful for me for long-term studies. There were many issues about genetics of viruses, particularly RNA viruses, which were difficult, at the time, but were very interesting.

SCHLESINGER: What were the results that you were getting that were peculiar?

FIELDS: Well, the peculiar ones were that we couldn't find complementation. That is, when we did mixed infection with mutants at high temperature, we didn't get additive yields. We subsequently discovered this was because of the dominant interfering phenotypes. In contrast, every time we did mixed infections at 31 degrees, we could group the mutants extremely efficiently. We called this "recombination" or "reassortment" grouping and we thought the groups were most likely due to segregation of individual RNA segments. We were able to prove this interpretation in subsequent years. These were interesting experiments that were fun but had nothing to do with pathogenesis.

SCHLESINGER: Were you influenced by the work with polio?

FIELDS: Yes, Peter Cooper was working with polio and performing two- and three-factor crosses. I have to admit, I had a very hard time understanding his papers, but they were interesting experiments that subsequently turned out to be important and probably correct. The phenomenology we were seeing was really quite different. I was interested in all genetics because there weren't many of us doing serious genetics with animal viruses at that time. However, the polio experiments were not directly relevant to what we were finding. And the main thing we were finding was no complementation and high frequency of recombination. Peter Cooper was finding extremely low frequencies of recombination and trying to use three factor crosses to map a linear genome.

SCHLESINGER: But had it been established that the Reovirus genome was segmented?

FIELDS: Biochemistry showed the segmentation, so our first interpretation was that our genetic results were most likely the genetic counterpart of the genes in pieces. However, the history of *E. coli* and phage genetics said that non-linked markers didn't mean separate chromosomes. The results could mean distance in the genetic map. In fact, the phage geneticists like Alan Campbell said to me, "This sounds like the early history of *E. coli*—I don't believe the genome is separated." When Bill Joklik left Einstein, my first grant had to do with the genetics and Reovirus.

SCHLESINGER: Who else was in the lab at that time?

FIELDS: At that time, Dick Bellamy and John Holoczieck, who was a very helpful postdoc who has subsequently died. He worked on pox virus. Claudio Basilico was there on sabbatical. I think it was the four of us. We really were the core, and the technician and a student, but it was a nice lab size and it was a very good, high-quality group.

SCHLESINGER: You hadn't learned any molecular biology before that. How were you learning it?

FIELDS: Well, I was learning it by doing it, by reading protocols, by asking how to do these damn extractions, RNA extractions, phenol extractions, and running gradients. Jake Maizel was down the corner, so I took a hammer and crashed the glass around the gel to pull out the gel at that time and then cut it into little pieces. I read a protocol, tried it and asked for help and then when it came to interpretation, would discuss it with Bill or others if it was the technology. Don Summers was around and Jim Darnell, Phil Marcus, and Mary Jane Osborn were still there. There were a lot of people there—Jerry Hurwitz, Lucy Shapiro, and Tom August. There were many people who you could talk to. What you had to do was just do the experiments and talk. And that is one of the reasons I saw, early, that I could learn it. The other thing you learn, and I guess this comes to eventually being confident enough, is you can do it yourself. You don't need to have someone to tell you exactly what to do. It helps if you do go through it, but it's not critical. To me the more important issue is: what's the question? You can learn the methods from people who know it best on your own as long as you know what question to ask.

SCHLESINGER: Were you also practicing medicine?

FIELDS: Not during the fellowship. It was a full, American Cancer Society-supported, 100 percent, research fellowship and I did not want to do any medicine that year. In fact, my goal was to get comfortable enough to have a lab and write my first grant, which I did.

SCHLESINGER: This was 1968?

FIELDS: This grant was written in 1968, the winter of 1967 and spring of 1968 and was funded with the title "the genetics of Reovirus." Reading my grant now, I'd say the reviewers were very generous. However, in 1968, genetics of animal viruses was not a large field and it looked like a promising one. I got a grant from the NIH. I set up my own lab, and also started doing infectious disease consulting one or two months a year and attending in internal medicine for one month.

SCHLESINGER: You had actually been away from medicine for three years, is that right?

FIELDS: Yes, that's right. But I became part of the adult infectious disease unit at Einstein, which included Ruy Soeiro, Steve [G.] Baum, and myself. We supported each other and each of us had a very strong research program. By working together, the three of us helped each other and we could be protected for research when we weren't on service. I never felt that I could survive as a researcher if I had to be the ultimate person who got called when a clinical problem appeared. And the organization of a department of medicine either allows you to do research or it doesn't. If it doesn't respect the need for true protected time, it is very difficult to do both. It is difficult enough even if they protect you.

SCHLESINGER: Do you remember what kinds of infectious diseases you were seeing at that time?

FIELDS: Well, Bronx Municipal Hospital was a pretty busy city hospital. We saw endocarditis, drug addict endocarditis, staphlococcal, meningitis, pneumonia, exotic diseases, and some tropical diseases (i.e., malaria).

SCHLESINGER: But not a lot of sexually transmitted diseases [STDs]?

FIELDS: Well, a lot of STDs would be seen in specialty clinics. However, I saw some syphilis. As a consultant we didn't see the primary STDs (i.e., gonorrhea) that were seen in a clinic of dermatology. I saw some TB [tuberculosis]. AIDS [Acquired Immune Deficiency Syndrome] didn't exist at that time, or at least we didn't recognize it. We saw fevers of unknown origin. You really saw a spectrum of diseases. And the diseases were quite fascinating, I enjoyed consulting in infectious diseases. Even though I hadn't done that much infectious disease before, I had gotten pretty good at it and was very comfortable as a consultant, enjoying the rounds and the teaching. The months I was on service, I would often be home late. It was becoming a burden trying to keep the lab going while on service.

SCHLESINGER: Who was in the lab?

FIELDS: Well, my first postdoc was Harriet Zuckerbraun. She got married during her first year and her husband was not very supportive of her continuing. Rise [K.] Cross was my first student. She started as a technician and was very motivated, and I supported her to become a student. She did some really classic work on Reovirus genetics. There were two other students who I shared with Ruy Soeiro: Ted [G.] Krontiris and Mike [M.] Sveda, who is now in a company. I had a small lab and I did a lot myself back then. We got a lot done in a reasonably short time. I have to say that around 1968 and 1969 my interest in the nervous system reappeared. I had isolated a number of *ts* mutants and I thought it would be interesting to see if they were altered in pathogenesis. One of the motivations for this idea was that the disease SSPE [subacute sclerosing panencephalitis], which had been discovered to be caused by measles virus, looked like it might be due to mutants. Since I had mutants of a virus that caused acute CNS disease in mice, I was interested in the generic

question of whether a Reovirus mutant might alter the disease. It would thus be possible to consider that SSPE disease relates to measles viral mutants. I initially collaborated with Henry Wisneioski, but he was too busy. Henry and I did some experiments but he recommended Cedric [S.] Raine. Cedric and I collaborated for the next four or five years studying the mutants of Reovirus, their interaction with the nervous system, their attenuation. The major finding was that single step mutants were altered dramatically in their ability to produce acute CNS disease. In addition, there were long-term, delayed effects and different outcomes following infection from different mutants.

SCHLESINGER: Did you know what genes the mutants were altered in?

FIELDS: At the time, we didn't, although we knew they were in different mutant groups. We didn't know for sure which mutant genes they were, although our idea was to try to relate specific viral genes to specific steps in pathogenesis. Ultimately, it was a very instructive approach, but limiting. The fundamental problem you face with *ts* mutants is that they don't grow well at higher temperatures, including the temperature of the body. That being the case, it is often difficult to distinguish phenotypes caused by changes in different genes with phenotypes related to high temperature. And that was a problem that really wasn't solved until much later, when we started to use reassortants that grew normally at body temperature. Since the body temperature is partially non permissive for *ts* mutants, you will always have the issue of whether you are studying the gene you think you are or whether the effect is due to the non-permissiveness at high temperature. But the more important issue was that it provided us with an approach that allowed us to say that you could use genetics to study pathogenesis of a viral disease. I remember when I gave a seminar in medicine at Beth Israel, they asked for a manuscript about this approach. That was really the point—to show that mutants are altered in pathogenesis and that this fact might be relevant to other diseases that involve viruses where mutation in individual genes can alter them. Of course, we now know that mutation is important in a wide variety of viruses. Ultimately we couldn't really pinpoint the genes using *ts* mutants.

There were a few other experiments in the Einstein years that I remember as really exciting. One of them was an experiment that Rise did for a certain purpose. We had identified an aberrantly migrating protein and thought it might give us some interesting clues to use as part of the genetics, maybe as a third marker. And Rise did a cross that showed, right in the gel that she first analyzed, independent segregation of that marker from the mutant we were studying, showing that it was not the gene in that mutant. We had thought previously that it was that gene, but it wasn't. However, the result showed that the third factor marker would allow us to map the location of our mutants because if we could find markers for each gene, then we would be able to see, for all our mutants, which ones segregated and which ones didn't. The gel, which was the basis of this result, was in the very nice paper by Rise in *Virology* on the first three-factor crosses showing independent segregation (1). Nonlinkage proved, genetically, that we were studying reassortment and showed that we would be able to map genes. It also allowed us to suggest, for example, that the *ts* A mutants were in the M2 gene. These mapping results subsequently were confirmed using serotype markers and allowed us eventually to map all the mutants.

SCHLESINGER: I am just curious whether you were still smashing gels at that time?

FIELDS: No. By the late 1960s, although we didn't have Laemmli gels, we did use strains to determine mobility. The identification of mobility markers was one of those experiments where you suddenly see that you can now solve the genetic mapping. When I moved to Harvard we determined which mutation was located on which gene segment. The genetic mapping was the basis for all the subsequent studies on pathogenesis. The other very interesting experiments were the ones where we were inoculating virus into mice and showing that different mutants were altered and attenuated in what they did.

SCHLESINGER: But what about the problems you just mentioned with temperature sensitivity?

FIELDS: We proposed that certain genes, like the M2, might play a particular role, but built into it was the internal limitation of using *ts* mutants mentioned above. What was clear was the fact that you could do genetics on these mice and could attenuate and alter the disease. What was not so clear is what genes were involved in each step of the process. We had reached the limit of the *ts* mutant approach, which is why we stopped it once we identified the genetic markers. Thus we could map and determine the physical basis of each of the genes—what protein and RNA each gene had encoded and we showed that we could study the genetics of pathogenesis in mice and that the answers would be somewhat unpredictable but potentially very interesting. These two directions were the peaks of the first seven years.

SCHLESINGER: How long were you at Einstein?

FIELDS: I was at Einstein as a fellow from 1967 to 1968 and then on the faculty until 1975, and they were very good years. Einstein was and is a wonderful place. A lot of people in the same boat, smart, young, interested, and insecure. Einstein was a place that was very supportive. It also was insecure; it was not well endowed, everything was out in the open. Faculty meetings were fun because people argued openly, yet everyone worked together and there was a great deal of support. There were many people who had set the right atmosphere for doing science: Harry Eagle, Matty Scharff, Irving London. There was an extraordinarily high-quality group of people who were doing many good things. This "critical mass" attracted a cadre of outstanding people who went on to do research in animal viruses, molecular biology and immunology as well as other areas. I think the most singular force in building Einstein was Harry Eagle. He moved the NIH laboratory of molecular biology from the NIH to Einstein. Eagle always felt that it was important for people to interact. He didn't want people to close the doors, lock up and do their thing in isolation. His view of a scientific environment was that it should be supportive and interactive, then you recruit smart young people to support and let them do what they are going to do. He was a remarkable man—absolutely remarkable—and his tradition has certainly been followed by others, like Matty Scharff, who has stayed there all these years. And other key individuals include Barry Bloom, Jerry Hurwitz, Lucy Shapiro and Tom August—it was quite an exciting place.

So why did I leave? I still had two identities. I related to the infectious disease service,

which I enjoyed, and I did science. In 1974, I received an offer from Gene Braunwald and Ed Linn to come to Harvard Medical School to be the head of the program of infectious diseases at the Brigham [Brigham and Women's Hospital] on the same kind of part-time basis that I had at Einstein, with my labs based in the microbiology building on the research quadrangle where I could have students. You have to remember that I trained here, I taught in the microbiology course at Harvard at the time I was a fellow at MGH—I was a fellow here and I knew the clinical people at Harvard extremely well, particularly Mort Swartz, Arnie Weinberg, and Lou Weinstein. I also knew many of the faculty and I had tremendous respect for them. Harvard was not the center of virology, but it was an excellent center for science and there were a lot of good people. Ultimately, choices of this type are decided in ways that are unclear. I was actually very conflicted because Einstein had been very good to me and I was an associate professor. The promotion to professor would have gone through. It wasn't issues of support or tenure; Einstein said they would match money offers, but it's not like a sports bargain. You decide if you are going to move. I just felt that I had done three years of training here and the infectious disease community was outstanding and it seemed to me to be time to make a move.

SCHLESINGER: Were you concerned about becoming head of infectious diseases?

FIELDS: I was head at Einstein, too. And what that means is you just have to make sure you share things properly and everyone works together. People warned me about being head of infectious diseases, but we were able to recruit Lou Weinstein, who was retiring from Tufts, to come to the Brigham. We were able to recruit very good junior faculty and it was not really a problem. One of the reasons you come to Harvard is the quality of the students and the ability to recruit very good postdocs.

SCHLESINGER: Who moved with you?

FIELDS: Well, I moved with Frank Ramig, who was a postdoc at that time. Steve [L.] Wechsler and Usha Ray, who, unfortunately, subsequently died from a brain tumor. Both Steve and Frank have continued in research careers.

SCHLESINGER: Was everyone working on Reo?

FIELDS: At the time, Steve Wechsler was working on measles. I had briefly been convinced by the Multiple Sclerosis Society that since I had a mutant model of SSPE using Reovirus, I should prove it with measles virus. It sounded simple and straightforward but, of course, I was going from a naked double-stranded, double-capsid virus to an enveloped virus of a totally different type. If you are going to do molecular biology, you have to start from scratch. And I spent a few years studying measles with a student, Katie [C.] Stallcup, and with Steve Wechsler. This diversion convinced me that you need to learn one virus well. I had one other little diversion—Ruy Soeiro and I worked with Friend leukemia virus together. Ted Krontiris and Mike Sveda in New York both worked on Friend leukemia. That experience also convinced me not to keep going from virus

to virus. So I briefly studied Friend leukemia and I published a few papers (2). I briefly studied measles, published a few papers (3), and realized in both cases that I would pursue Reovirus for my career. After Steve left, I urged him to take the measles project and told Katie if she wanted to continue she should, but I didn't want to continue studying measles. The first major experiment we did at Harvard was to finish the mapping of the Reovirus genes and determine the relationship between the genes, the mRNAs they encode and their protein products and how they related to the *ts* mutants.

SCHLESINGER: So now you started to look at RNA?

FIELDS: Both RNA and proteins, which we did even before we came here, but finished when we came here. At the same time, now we had our system to answer questions about viral genes in pathogenesis. Howard [L.] Weiner came as a postdoc shortly after I got to Harvard and used the reassortants that we had been generating and mapping to do the first tropism experiments in 1976. It was the next exciting experiment. It was fun finishing the mapping, but it was exciting running down the hall betting which genes were going to be involved in different properties. I'll never forget when we took the reassortant viruses that we have—now knowing which gene was which—and none of them were mutants. So they were all wild-type viruses with segregated genes that we had already studied extensively in New York. We knew that Type 1 Reoviruses all produced ependymitis and Type 3, encephalitis.

SCHLESINGER: That is what I was going to ask you: when did you switch from looking at temperature sensitive mutants?

FIELDS: We knew the basic genetics in 1975. As soon as we came to Harvard, we started the pilots. In fact, we had done the pilot experiments with serotypes in New York but it was only descriptive until you had a genetic way to segregate genes. It was the reassortants that allowed us to start to link viral genes with pathogenesis.

SCHLESINGER: But you must have known that the different types gave you different phenotypes?

FIELDS: From the first experiments with Cedric Raine in New York we knew that all Type 3s caused encephalitis. The literature had told us and we confirmed in Boston that Type 1 caused ependimytis. Thus we had done some of that background in New York. Cedric and I published some papers on the tropism of Type 3 (4). But Kilham and Margolis had done some very nice experiments showing the differences between serotypes. And using individual strains we expanded the collection of Reoviruses, confirmed differences in disease and tropism, and clarified that these differences were not isolated differences, they were serotype specific differences. We then did the genetics when the strains became available and from the very first genetic experiments with tropism, the genetics said S1 caused tropism. And that opened a whole new area.

SCHLESINGER: Was that one that you had guessed?

FIELDS: No. I had guessed it was M2. The nice thing is you can be wrong and it is more interesting. At the time, we didn't know anything about S1 or the attachment protein or hemagglutinin. We then studied various properties that told us that the S1 was the attachment protein. I guess we published it sometime in the late 1970s. That paper was one that was very exciting because that was the result that opened up the fact that we could now use the genetics to study pathogenesis (5). We continued to do genetics because we had to understand these strains and mutants and we still do. But this now was a major directional change because it gave us the handle to study something that, at that time, wasn't being studied, and would allow us an opportunity to really open up an area—which was correlating genes with pathogenesis—to build an understanding of what Burnet had tried to do in the 1950s with flu. He tried to map virulence genes of flu and he gave up. And it is easy to see why it was not easy. It's still not easy, but there are many reasons and you have to adjust for high-mutation rates. There are a number of technical things that we've learned and others to be careful with. But it works and you can do it, you can confirm it and then it makes sense in terms of structure and function. So that was really the most exciting experiment we did on coming to Harvard. We began to look at structural motifs. Rhonda Bassel-Duby and I flew to Jake Maizel at the NIH in 1985. Rhonda had finished cloning the S1 gene and we saw a motif that looked like myosin. We came back to Boston and started to look at where the myosin motifs were and I remember that Max Nibert was in the lab. Max studied the computer and said the myosin motif looks like a coiled-coil. This was our first success in beginning to relate the structure of a viral protein (sigma one) to function.

SCHLESINGER: We're jumping ahead now. When you first came, of course, recombinant DNA was something people didn't even imagine.

FIELDS: Right, this was already now the mid-1980s. Jumping from the 1970s, that's ten years ahead. Well, the 1970s, in many ways for us, was the completion of the genetics and the first and extensive use of a variety of biologic phenotypes. Why does the virus get into the environment? What genes are involved? Why does it target in a certain way in the host? How does it spread in the host? How does it injure cells? What is the basis of hemagglutination? What gene is doing it and why?

SCHLESINGER: These are all questions that make a lot of sense now. I would like you to try to go back and think of whether these were actually questions that you had thought about before you had any idea of the answers.

FIELDS: First, I was always interested in the steps of the interaction of the virus with a host. Remember it goes back to experiments I had done with Cedric Raine. It goes back to injury of the nervous system—how does the virus get into the brain and injure it? I had always used the Burnet-Fenner steps of pathogenesis as a model. Read the [Frank Macfarlane] Burnet textbook (6)

preceding the [Frank] Fenner textbook (7), preceding the [Cedric A.] Mims textbook (8). What are the steps of pathogenesis? What are the issues? How do you explain it? In fact, when people came into the lab in the 1970s, I'd give them Burnet's book. I had it right here, and would say, "Read this chapter because he defined the questions that were the classic questions that were forgotten when viruses became more molecular biologic." Thus the steps were right there. And once tropism mapped to S1, you could suddenly and immediately see the gold mine. Don Rubin came in to do the first M2, I remember Rafi [Ahmed] was doing S4. It was the whole series of looking at phenotypes that map to one or another of these properties. In essence, we realized that the biology of Reovirus was now available for us to relate to genes. Look for the polymorphism and see what gene or genes it is. And that approach dominated the lab for the next several years. It was as if you see gold lying all over and the issue is what to look at next. I want to know about virus spread in the environment—all right, put it into the mouse, collect the stool, look at its transmissibility to litter mates, and ask what genes.

SCHLESINGER: That is an interesting point I want to bring up because many of the experiments are done by injecting the virus into the brain. Did that bother you?

FIELDS: Sure it did, but at the time it was fine and later we started to try to mimic natural routes and do oral infections by inoculating the virus. Don Rubin, back in 1981, was the first one to start putting virus directly into the stomach of a newborn mouse using a little catheter—into the gut. And once we knew how to study peroral inoculation, we started to use that route exclusively, for the last several years the peroral route is the only route we use.

Eventually, the diverse experiments began to make sense. We began to see that the product of the S1 gene was the attachment protein, that products of M2 and S4 were complexed. S4 stabilized the virus while M2 went through processing leading the virus to the cell membrane. It made sense in terms of ultimately the different particle forms and what their functions were and what they did. So that really, the 1980s, in a sense, was more and more information about viral structures and relating them to function in cells.

SCHLESINGER: When did you begin to use recombinant DNA?

FIELDS: In the early 1980s. I recruited Rhonda Bassel-Duby, who was the first one in my lab to sequence and clone successfully. In the 1980s we knew what genes we wanted to sequence. S1 was obviously high on our list. M2, S4 were also of interest. We based our sequencing on the genes that we knew functionally. We were not the only ones sequencing—Bill Joklik's lab, Patrick Lee's lab, Aaron Shatkin, and others. But our focus was to let the virus tell us what to be interested in and then to do whatever seemed to be the critical next approach, and to go with it.

SCHLESINGER: Let's go back a little bit. You were head of infectious disease at Brigham. How much of your time had been devoted to clinical medicine?

FIELDS: Two or three months a year. But even during that time, it was half a day because there was a whole staff of people. People like Lou Weinstein, Jamie McQuire, Tom O'Brien, and others at Brigham were doing infectious diseases for a living. Also, they were visible, they were around the hospital and I wasn't. I was very involved in the training programs. But I didn't need to be. My identity was not linked to being the person who ultimately answered the tough infectious disease questions. If it was, I wouldn't have been able to do what I did. I was very comfortable when they called someone else. In fact, that's what I wanted. Sometimes they called me, and I had to go, something that was not my first choice. Now when did it all change? It changed really in 1981 or so. I had been asked to consider the chairmanship of the Microbiology Department before, but I really didn't want it. I liked what I was doing. However, I finally decided that I could do it well. Also, I was increasingly finding that I was working too hard by going and doing infectious diseases while running a lab. Clearly, the lab was my primary interest, it always has been. But my primary mission during clinical times was service, and I just found that it was increasingly difficult to go on service. Because the literature I read, the meetings I went to, what I thought about all the time was more basic research. The fellows began to know more than I did about the next generation of antibiotics. It isn't that I didn't have a good time attending and did not have a lot to teach fellows, but, you know, you run out of energy to go to the clinical literature and spend so much time. Linked to my decision to accept the Microbiology Chair was the opportunity to give up my position as Head of Infectious Diseases [ID], and remain associated with the division, but give up medicine.

SCHLESINGER: Was that a difficult decision?

FIELDS: Extremely. In fact, my wife points out that when people used to ask me what I did for a living, once I gave up being head of ID, I had a hard time answering. Because, you know, I'd gone to med school, I had completed an internship and residency, I had been in infectious disease all the time and I had done research in infectious disease. Now all of a sudden I was really living full time in research and I wasn't going to be doing infectious disease. It was an identity crisis for me. From the time I went to med school, being a doctor was my identity. It never really was, in the sense, what I did most of the time. I never practiced medicine primarily. It was always compartmental. But it was very difficult. But it finally just made sense. I enjoyed infectious disease but it became too much of a burden.

SCHLESINGER: You actually stopped doing infectious disease just as AIDS came in to the picture.

FIELDS: Yes, that's right, the timing was right there. I've seen patients with AIDS, but not as a primary physician.

SCHLESINGER: So you still see patients?

FIELDS: No. I've seen them and someone pointed things out to me because I have been interested

in AIDS as a problem.

SCHLESINGER: So has AIDS influenced the way you think about research?

FIELDS: No, the only way that it influences me in a major way is that I think the solution to problems like AIDS will come through a broader base of research then by just doing research on AIDS. And I'm concerned that people may think that sounds self-serving.

SCHLESINGER: We were just talking about AIDS, which is an epidemic, or a pandemic that no one would have expected. And what I want to do is shift a little bit to ask you about what you see as the future and the direction of biological research, particularly in the areas that you are most familiar with.

FIELDS: Well, actually AIDS is a good starting point for that because we really are coming out of the era, and still in part are in the era, where molecular biology has been the dominant science. Molecular biology is basically a reductionist science. You get a gene, you get the messenger, you get a protein, you go powerfully into that gene, and by studying it you understand an enormous amount—it's extremely powerful. Of course, when you come to a problem, illustrated by AIDS, you realize that a micro-organism or a virus or a host is not reductionist. It has multiple components and you start moving into the complexities of biology. There are many problems in trying to translate the general reductionist approaches of molecular biology into the solution of a problem like AIDS. One is: if the funding agencies are filled up with people who primarily look at the world through the molecular biology approach, there will be key gaps in our understanding that involve more complex multiple system involvement, such as many biologic issues. These would not fare as well in the very review process by which the government funds science. In fact, by overemphasis on molecular biology without an appreciation of the gaps in understanding, more biologic issues that sound like lower tech, but are in fact very important, can in the long run hurt and slow down the solution of important problems. Thus, since the process of judging is largely made by people who usually come out of the tradition of molecular biology, it can, in subtle ways, lead to discrimination against the very science that is much of the future. Complex problems involve taking simpler reductionist systems and putting them into the framework of more and more complex biologic systems—such as the interaction of a virus with its host.

If I were to emphasize where the future is, I would say much of the future is using the fantastic power and insights of molecular biology into more and more biologic systems, and making sure as we approach problems in more complex systems, we don't give more complex systems short shrift. A judgment of this type has very important policy implications for government. It has great meaning in terms of the future of how the government chooses to spend its money. Let me illustrate specifically. If you wanted to solve a problem, say AIDS—a complex problem—do you assume that we know most of what we need and try to engineer the problem by using the methodology of recombinant DNA and modern immunology, or do you instead support research at a broader base on the assumption that there are still very important scientific gaps in this complex biological system? Obviously, if you make the wrong choice and feel the problem is ready for Manhattan-type

engineering projects, then you can spend an enormous amount of money, and, in my view, not get a solution. On the other hand, if you put resources into a broader scientific base, you may speed up a solution. These are difficult issues, but I am concerned that at the moment, issues of this type are not directly addressed often enough in policy areas. I think issues of this type are going to be true for many other problems in complex systems. Think of the issues of breast cancer or heart disease.

SCHLESINGER: How would you address them?

FIELDS: I would first look at the problem, put multi-disciplinary people together, respect different viewpoints and try to define where are the gaps in knowledge. What do we not know? Gaps could involve immunity, host genetics, or the fact that we don't have the basic descriptive pathology adequately worked out. There is no such thing as high-tech or low-tech in the gaps. If we are missing a basic pathologic observation, all the molecular biology in the world isn't going to solve the problem. Therefore I believe multiple viewpoints have to be examined—and it is critical to have people who are broadly based. One of the central issues is training. We need people to deal with broadly based science or we will train people more narrowly because of the power of some of the more narrow approaches, which are extraordinary but limited.

SCHLESINGER: One of the problems of being broad based is that, one then says, you become superficial. So how do you feel?

FIELDS: Well, I think it depends on how deep you dig. I think if you think of, for example, a problem in pathogenesis, the problem must involve multiple levels. That is, if you don't know the descriptive aspects, you can't solve the descriptive problem. The pathology may appear to be superficial, but in fact, it is critical. If you don't know that a virus is targeted to a particular cell type or know what that cell type really is, then what good is it knowing that it has got ten genes or fifteen genes? That's one level. The second level of physiology and function is critical. In addition, studies on genetics and molecular biology are also critical. All levels are very important. I think it is possible to be superficial, but I think it is also possible to be very deep but too narrow. It is in balancing the broader biologic insights of breadth with some depth that provides a powerful approach. The solutions of complex problems need a system that allows multiple inputs and smart administrators who recognize the need for diverse viewpoints and can identify synthesizers who can pull together diverse information into policy decisions. But it speaks to the need for the scientific base to be broad. This is going to be an increasing problem in an era where we tend to train people who often have a very powerful approach to a narrower window, and we can't ignore the reality of the need for breadth.

SCHLESINGER: How would you set up a training program for the young scientists?

FIELDS: I would set it up by mixing people with different backgrounds together trying to solve the same problem. In other words, if you were to try to solve an infectious disease problem, recruit

clinicians who are interested and smart to work with Ph.D. molecular biologists next to an M.D./Ph.D. who knows the immune system, next to students who are working on anatomy. They should all have the same focus on what they want to solve and make sure they talk to each other. This type of multi-disciplinary approach where communication is wide open—that's how I would approach a policy direction.

SCHLESINGER: But I don't think you are advocating very large laboratories?

FIELDS: No, I am not. The main point is that the laboratories that are involved encourage cross collaboration, cross talk. I would not set up huge empires where one individual then tends to control the direction rather than allow multiple voices to speak. It's critical to maintain individual investigator-initiated research. This approach has been the driving force of the U.S. system. But in addition, encourage and reward interdisciplinary and collaborative research. How that's done can't simply be answered in a sentence because it is necessary to balance the available resources and funds to maintain the support of the individual investigator while at the same time, supporting some large, programmatic grants. The most critical point is to encourage collaborative research endeavors, make it attractive, and set up systems that encourage collaborations, without destroying the multiplicity of research efforts that come out of individual investigator-initiated grants.

SCHLESINGER: And how influential do you think the government should be in this?

FIELDS: Well, I think there is no choice. The government has to play a central role. Industry, in my view, will never provide the kind of resources for the individual investigator-initiated type of research programs because the bottom line in industry is that there is a bottom line. Companies have to be responsible to those who paid to get them going. They have to make a reasonable profit. Ultimately, the profit motive is incompatible with investigator initiated research programs where individuals get an idea with no immediate payoff that they want to pursue. If the new idea is really an interesting but not applied one, it's unlikely to be of enough interest to obtain private industrial support. The NIH has a major responsibility to keep new ideals in biomedical science the high-priority area. In this era where budgets are tight and funds are tight, basic research may be one of the most threatened areas of all. The ability to allow individuals to follow their own intuitive directions and be supported for it is the key. This has been one of the strengths of the U.S. system. Unfortunately, it is currently under attack from multiple sources. In my view, by not allowing more broadly ranging research, we are narrowing the base, and are slowing down the solution of the very problems that, by funding in non-targeted areas, we are trying to solve. I think that these are fundamental policy issues.

SCHLESINGER: And what role do you think the scientists should have now in trying to affect this?

FIELDS: I think scientists have to keep talking, advising, and communicating with the public.

When scientists isolate themselves, they are not giving critical input. We scientists need to participate in the process. It means that we must go on advisory committees, or councils, or whatever is necessary to give advice and input in order to help influence the future direction of biomedical research. I think it's called "citizenship." Many of us don't want to spend too much time performing "citizenship," but it's critical to spend a certain amount of time or we will all pay the price.

SCHLESINGER: Do you want to talk about some of the committees you served on, not just to mention them, but any that you felt had been particularly valuable?

FIELDS: I think one that I particularly enjoyed was the Task Force of Microbiology of the NIAID [National Institute of Allergy and Infectious Diseases]. The task force was an attempt to define areas that might be important in the next decade.

SCHLESINGER: When was that?

FIELDS: Maybe two or three years ago. I helped establish a retreat with about fifty scientists. It included scientists, people from the NIH, as well as academia and industry. It was multi-disciplinary and involved very basic scientists as well as clinicians. The meeting was fun because, for the most part, people listened to each other and came up with important recommendations. The task force was an attempt to define some opportunities that might be available to solve some important problems. I think the process of involving a multiplicity of viewpoints was the key to its success. Also, the participants had fun in talking to each other and in hammering out the definition of what are the important issues. I felt it was fun, useful and, hopefully, helpful to the NIH.

SCHLESINGER: But you don't know if the NIH will pay attention to you?

FIELDS: Well, they have highlighted the report, they circulated it to study sections, they discussed priorities established by the report among funding agencies. However, I don't really know the answer to that question.

SCHLESINGER: Did it make you think about different directions in your own research, or do you feel that your own research had been a reflection of this?

FIELDS: Since I was the overall chairman of the task force, it was in part a reflection of my own approach to science, which is multi-disciplinary and very much starts with the biologic problem and then trying to solve it. In that sense, it was a personal kind of statement.

SCHLESINGER: Were there people who disagreed with this point of view at the meeting?

FIELDS: They didn't say so, but maybe that means we didn't allow free expression. I don't think that is true. I think there are some people who feel that there is a certain approach to solve a problem, to define it precisely, while others are more fluid in problem solving. I do think it's fair to say there are different ways that people try to solve problems. But I think the dominant view at the meeting was very much the one that I'm expressing—of the value of a multi-disciplinary approach. I think that in this day and age, many scientists would agree with this approach. I think the recognition that fundamental science issues are increasingly trying to deal with more complex systems, some of which are very important human diseases, is a major way of thinking for many people in the scientific community right now. It may not have been true ten years ago. I believe that there has been a major evolutionary change involving the raising of priority of solving important human diseases.

SCHLESINGER: In that regard, then, how would you defend the research on worms and on zebra fish?

FIELDS: If you talk about degenerative disease of the brain or infections of the brain—and we do not know how neurons communicate with each other—or if we try to figure out how a virus moves around in the nervous system while causing encephalitis, we are one step behind knowing how to approach such problems. If we know how neural pathways develop and communicate, and neurons touch each other, and what their markers are—and just to take one example of the power of studies on the worm brain—we are provided with very important paradigms to thinking about systems that are more complicated. It may not be possible to dissect those factors in humans. To use our studies, we try to study how a Reovirus moves through neural pathways. The more we know about those pathways, the more we can learn how viruses can cause CNS disease as well as how the brain works. When we are dealing with areas that we have only very primitive knowledge of, then simpler systems such as the zebra fish, the worms, aplaysia, have unique principles to teach us about increasingly complex developmental problems. To me, model systems that are unique are extremely important.

SCHLESINGER: One of your roles has clearly been that of a teacher of students and postdocs, and I would like to ask you how you see your role when you are trying to develop your students into future scientists?

FIELDS: One of the first things that needs to be really emphasized is that students and postdocs have been absolutely central in the most exciting discoveries that I feel we've made. They are the people who have done the experiments. In many cases they understood, first, why they were doing the experiment, defined the questions, and did the experiments that are central and intimately part of the success of many labs. Thus the students and the postdocs are the heart of the lab. I have been extremely fortunate in having a large number of outstanding students and postdocs. What do I do with a student when they come to my lab? How do they pick a project? Here is where intuition is

not just scientific; it's got to be personal because people don't realize that running a laboratory is a very interpersonal process. People come in and one of the things I try to learn from the student is what are they like. Do they like to be told, really, very much what to do? How much freedom are they ready for? When are they ready for it? How can you encourage them to find their own internal scientific voice, because it seems to me that the students, who at any level often make the most profound discoveries, are talking from a very unique perspective—which is often their own metaphors, their own insights. What I like to do when I first meet a student is to tell them various things going on in the lab, what questions are being pursued, how people are pursing them, and ask them what sounds interesting to them, what excites them in the types of things we are doing. Once we talk for a while, they read recent publications. Students or postdocs often say that they are particularly interested in the brain or in isolating the viral genes and expressing them, or a particular gene that involves a specific function. Thus, the first real thing that I like to find out is who the student is, where are they coming from, what they are excited about. And if you get the student to really dig in, choose a project, understand it, and come to grips with it, then I think you have done the most important initial steps. Later, you want to help them over the times that experiments don't work, and you want to make sure they understand that if an experiment doesn't work, it's an experiment, it's not them. Separating and personalizing a failure at the bench from personal failure is a critical later point. No experiment works all the time and students don't know that; they haven't had enough successes. This problem of personalizing is often true for postdocs and it's even true for faculty.

It is critical that students get excited about something they've done and then know that they will be able to repeat that excitement in their future career. Beyond that, I think that you must provide a laboratory where you, or someone else in the lab, can make sure that students know the technology, are concerned about controls, mistakes, and other issues that involve the lab lore. The role of teacher and mentor has probably been one of the most satisfying aspects of my scientific career. I also have lectured for many years to medical students and to graduate students and I enjoy it. However, there is a time after lecturing and giving a course in virology and microbiology for twenty-seven years when you need a break. Over the last two years I have taken a break, but I have always enjoyed transmitting some of my own enthusiasm for virology and pathogenesis. Recently here in the department, John Mekolonis, John Collier, and I have given a course on molecular mechanisms in microbial disease for advanced graduate students. The excitement of this course is the reality that microbiology is coming together and many of the principles we think about for viruses are also relevant to bacterial parasites and vice versa. One of the advantages of lecturing and teaching is that you learn a great deal. There is no way like learning when someone asks you a question and you thought you understood it and you realize you didn't. Thus teaching is very important, and in many ways, involves interaction with colleagues and students and really getting to know a field. I have always felt that teaching is a very important responsibility.

SCHLESINGER: Now that we are back to talking about Harvard and the Department, I wanted to ask you some questions about being Chairman. I guess some questions would be what are some of the pleasures? What are some of the innovations that you made, and if you're willing, what are some of the problems?

FIELDS: Well, I think the main pleasure in the department is when it feels like it's a happy, productive department where people tell you about the positive aspects and you feel it and you see

it. I have enjoyed being Chairman because I haven't felt that it is a major chore because this department is very collegial and very high quality. We share a great deal and I feel that it's not that much work for me since I don't do everything. Everyone in the department shares some chore and members of the faculty meet regularly so that people know what is going on. The critical issue of running the department is, in my view, communication. I and the faculty have shared responsibilities, whether it be chores such as examining students, or committees that someone has to be on, or teaching. One important pleasure that I have gotten is in seeing the junior faculty develop into people who I have to compete hard to keep at Harvard. A difficulty in my position occurs when someone who you respect and like hasn't quite done enough so that you can keep them on the faculty with tenure. That, to me, is one of the most difficult parts of being Chairman. And the other things about the Chairman are—the Chairman does put his own personality on the Department, you set an absolute tone and hopefully it's the right one.

What problems have we had in the Department? I can't think of many. We've had problems where a postdoc had major problems with a faculty person where I had to get involved for damage control. Thus, the Chairman helps put out fires, and since you are dealing with a department that has twenty-two faculty and a lot of students (forty to fifty), an equal number or more postdocs, staff people, technicians, et cetera, there are going to be some interpersonal problems. But I have to say, I think it's a nice department and it has relatively little of that. I was very pleased when I came and there were some old, very old, minor wounds from an old history of this department. Bernie Davis had been Chairman and stopped being Chairman under less than ideal circumstances. I was very pleased to be one of the people to help bring Bernie back into the Department, where he is very comfortable. Overall it's a nice department and there's not much I can complain about. If you do it right, it doesn't have to take an enormous amount of time. Because we all have responsibilities and if we can share what we can do, the Chairman mainly is there to make sure that things are working well and that's been my view of the Department. It has not been an enormous burden, but parts of it that have been more time consuming are going to subcommittees to defend a tenure appointment, or going to a luncheon that involves Chairs, where you have to know what is going on. Thus, there is a certain amount of time that is unavoidable that you have to give up, but it's not bad.

SCHLESINGER: Have you been involved in any innovative programs?

FIELDS: Yes, we have been involved in the new curriculum, which was introducing case-based teaching.

SCHLESINGER: Did you teach in that?

FIELDS: Yes, I taught a great deal in the New Pathway and had some reservations, but I feel that the overall program is valuable. We give a certain number of lectures that are supplemented with tutorials involving illustrative cases. The students seem to enjoy the new curriculum more than the old and they are learning what we feel they need to learn. In some ways they are learning it better, because there is more self-starting and I'm more comfortable now. I was quite concerned about it in the beginning.

SCHLESINGER: Let's go back to science and talk a little bit about some of the recent interesting aspects of pathogenesis that you have been involved in, that your laboratory has contributed to.

FIELDS: Well, we have spent a lot of time in what seems like a simple problem. That is, what happens when you swallow a virus. In fact, it's not so simple. It passes through the stomach, enters into the small intestine, but then how does it get out of the small intestine? In many ways the virus is like a needle in a haystack. Some years ago, we learned something very important about how you find the needle in the haystack. Don Rubin had spent two years as an Infectious Disease Fellow in the lab trying to find where the virus went following its introduction into the stomach. We kept looking in the lining cells of the gut, which make up 99 percent of the cells, but we couldn't find the virus. A student by the name of Arlene Sharpe went to a lecture on the anatomy of the GI tract, came back to the lab, and said that there is a newly-described cell called an M cell that sits over Peyers' patches, which are collections of lymphoid tissues in the lining of the small intestine. Since M cells sit in such an interesting place (i.e., over Peyer's patches) we went back to the old experiments that Don Rubin had done with Jackie Wolf and Jerry Trier. In fact, I said to Jerry, "You have got to go back to the original samples that we prepared years ago and look at the M cells." When the samples were examined, the cells had enormous numbers of Reoviruses on their surface and entering the cells. This was a very interesting observation because the M cell is a site where a variety of microbes, viruses, and antigens enter with extraordinary efficiency into direct and intimate contact with the immune system. These observations also helped explain one of the ways that microbes (in this case the particular virus) penetrate the mucosa to enter into the host and start a systemic infection. Over the last few years, poliovirus, cholera, salmonella strains, and an increasing number of microbes, perhaps HIV, have been discovered to use the same pathway. Thus, Reoviruses were the first, and maybe best, example of what is a new understanding of a very important step: where infections are initiated in the host. We were also able to discover how much the virus changes before it ever gets into cells. We showed that the intact virus is really built to be like a "spore," a very stable structure. When Reovirus reaches the lumen of the small intestine, enzymes of the pancreas start working and the Reovirus undergoes dramatic conformational changes—all taking place in the gut lumen outside cells. If anyone ever tells you that a virus is inert until it gets into a cell, tell them they are wrong. Important changes occur that prepare the virus, "activate" it in order to allow it to enter a cell. In fact, for Reoviruses, unless activation takes place, the virus will never cross M cells to enter into the host. It turns out this dynamic process between the form and the function of the virus is a centrally important principle: there are different structures ("forms") that the virus takes during different stages of its life cycle in the host. The questions that we have always been interested in are: what are the steps in the viral life cycle and what are the genes (and gene products) important at each step? What are the viral structures involved at each step and how do they relate to principles of pathogenesis and infectious disease? And this is the theme that we always return to. When a student comes to me and says they want to study in great detail the factors involved in transcription, I tell them other labs that are studying transcription. It's not that transcription is not important or that I'm not interested in it, but transcription is not the problem that we are trying to solve. Other labs are more enthusiastic about studying transcription. Most labs, in fact, are more interested in transcription than the kind of problem (pathogenesis) that we are trying to solve.

SCHLESINGER: And are you studying M cells, themselves?

FIELDS: No, M cells still have to be studied in a very complex system by taking out the gut of a mouse, or of a mammalian host, and studying the organ. It's not an easy system, but you learn how to study M cells in mice and can learn quite a bit from those studies. M cells are fragile cells that have not yet been grown outside of the intestine. The study of M cells does illustrate another point: that most of the people who have been in my lab will have at least done some animal experiments because unless you do an animal experiment, for example, you would never know about an M cell. Molecular biologists study viral structure, take viruses apart, and look at the sequence of nucleic acids and proteins. I'm interested in these issues as well, but most molecular biologists would not care how a virus crosses an M cell, because they didn't feel comfortable studying the host. My religion in virology is that the animal is where the biologic truth often has to be tested. Often you cannot even get to know the question without studying the animals.

SCHLESINGER: I know you have been sick and diagnosed with a serious illness, I wondered if you wanted to make some comments about that?

FIELDS: Sure, I'm happy to say a little about my illness. I developed some symptoms about nine months ago of malabsorption that eventually led to a diagnosis of cancer of the pancreas. That diagnosis was made in July of 1992, and was obviously upsetting. The word "upsetting" does not describe my feelings, which were very powerful. My diagnosis was made at the time that I was planning to go to ASV [American Society for Virology] to host two dinners, give a talk, and be with friends. Thus my scientific community knew about my illness rather earlier than they might have. It was a very difficult experience because suddenly whatever future we all think we have was removed from me, since cancer of the pancreas has a rather grim prognosis. In my own personal case, I was fortunate to go to a physician at the Dana-Farber [Cancer Institute]—Bob Mayer—who immediately changed my perspective and pointed out that I was a statistic of one, and even though I know the statistics of cancer of the pancreas, he said, "Let's see what happens with you." I started chemotherapy in the summer of 1992 and started trying to deal with my feelings about the disease. It was a process that I had to go through that involved intense pain, anxiety, and the need to find comfort. My wife and the rest of my family were very important and critical in the process. I started to meditate, which was extremely helpful to me in finding comfort. The amazing thing is that I am still alive and we are now talking eight, nine months after the onset of my illness. I can honestly say on December 8, 1992 that after a horrendous beginning of the summer, I've had a nice Fall. For whatever multiplicity of reasons, the tumor has not progressed the way pancreatic cancer usually does. I've had chemotherapy. I may have been fortunate in having a brisk immune response at the outset of the disease—the pancreatitis it started with. And for those or whatever other reasons that I can't fully account for, the disease regressed. Even though surgery seemed not to be feasible in July, I will be undergoing surgery next week. I can only say that the mind is a rather extraordinary organ. I would never have thought five, six months ago that I would have had a productive and fun Fall. I also wouldn't have thought that I would have been here and would

have had a future. Now I am gently taking steps that involve projecting a little longer into the future, since it seems that my tumor has been indolent enough to even regress. We'll see what the next step is.

But regardless, there is an interesting literature about cancer that exists and is quite helpful. I think the most important thing is to say that I have had a quite remarkably wonderful Fall, in spite of knowing that I have this tumor. I guess I should thank the tumor and accept the fact that it's very important never to really give up hope when you have a disease like cancer because you don't really know the future. It's very easy to talk yourself into giving up. Also say—be lucky in your doctor, be lucky in your friends and spouse, and hang in there because there are no absolute numbers that relate to you as an individual. These thoughts have been very helpful to me and we'll see what happens. I think that's probably about all I can say other than I wish myself luck next week as I have some pretty big surgery. I hope that I continue to be luckier than I thought I would be. That's about all I can say for now.

[END OF INTERVIEW]

NOTES

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