NCI Laboratory of Molecular Biology
Oral History Project
Interview #1 with Dr. Michael M. Gottesman
Conducted on January 29, 2009, by Jason Gart

JG: My name is Jason Gart and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is January 29, 2009, and we are in the offices of the National Institutes of Health in Bethesda, Maryland. Please state your full name and also spell it.

MG: Michael Gottesman. M-I-C-H-A-E-L—G-O-T-T-E-S-M-A-N.

JG: Terrific. Established in 1970, the Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, commonly known as LMB, currently has among its ten groups four members of the National Academy of Sciences. LMB has trained many other prominent scientists and its research has contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history project to capture recollections of prominent scientists currently and formerly associated with the laboratory.

I understand that you were born in Jersey City, New Jersey?

MG: That is correct.

JG: What year was that?

MG: It was 1946. October 7, 1946.

JG: What was the community of Jersey City like in the 1940s and 1950s?

MG: Well, I left before the age of two, so I have no direct memory, but Jersey City was at that point a middle class community. Lots of people with small businesses. It is very close to New York City, so it was a desirable semi-suburb of New York City. My parents were first generation Americans who were interested in establishing a stable family and Jersey City was considered to be a nice place to get started. We moved to Queens, New York, when I was two years old and I grew up in Flushing, New York, in a community which was sort of a typical melting pot in New York City. My particular community was mostly Italian and Jewish but there were a lot of middle class families, sometimes first or second generation, whose children later went on to academic careers.

One interesting anecdote about this is I was at a meeting several years ago on drug resistance and cancer and I got on a shuttle bus from the airport in Los Angeles with four people who were also speaking at the meeting. We began to talk about our backgrounds. We had actually grown up within about five miles of each other in Queens. So Bayside, Flushing, Forest Hills, Jamaica were the neighborhoods that encompassed that. Very ambitious families with upward-striving children. That was my background. I went to public schools there.

JG: What did your parents do for a living?

MG: My mother was a stay-at-home mom. My father early in his life was a watchmaker; worked with watch repair. Later on he had a small business. A little textile factory where they made textile novelties, hairnets, and things of that type.

JG: What were the names of your parents?

MG: My father's name was Jacob and my mother's name was Frieda.

JG: What were some of your interests as a child? I read that you experimented with model rockets and chemistry sets and that you were greatly influenced by Sputnik.

MG: Right.

JG: How so?

MG: I was eleven years old in 1957 when Sputnik was launched. Probably around that time I was extremely interested in space science. I think I had already been interested, and the fact that we could launch satellites and start to explore our local area of the solar system, was very exciting to an eleven year old.

Remembering back about the experimentation with rocket launchers—it was not a very organized activity and I think we were all very fortunate that no harm befell any of the people involved. We were pretty careful but we were not very old. We were eleven, twelve years old, and starting to mix rocket fuels together and put them in tubes and shoot them off. We read all the appropriate literature and so on, but it was not an organized activity. It was just kind of stuff we did in the basement.

JG: You would just shoot them off in the elementary school lot?

MG: Well, at that point, there were still empty lots in Queens and they did not go that far once they got off the ground. [Laughs]

JG: What did you read as a little kid?

MG: What did I read? I read quite widely. I think I was interested, as are most young boys, in dinosaurs and books about space. I read some biography. This is interesting because my wife read the same book and that was something we discussed when we first met. Paul de Kruif wrote two books: *Microbe Hunters* and *Men Against Death*. I think I was actually more influenced by *Men Against Death*, which was a book specifically about finding the causes of infectious diseases and treating them, whereas *Microbe Hunters* was much more the basic biology and genetics of bacteria. I think Susan [Gottesman] was more taken by *Microbe Hunters* and I was more taken by the public health aspects of *Men Against Death*.

JG: I have a little bit of a competitive advantage because I interviewed your wife. She mentioned that Paul de Kruif's book really captured her imagination and set her on her course towards biology.

MG: I don't know that that was necessarily true for me. I read a biography of Jonas Salk later on. I remember when I applied to college somebody asked me who I would most like to emulate and I said Albert B. Sabin because of his contribution to the polio vaccine which, by the way, was a big deal. Remember we grew up when polio was still epidemic. We were in the first test group of children receiving vaccine. I remember that because I was seven or eight years old and I remember them explaining to our parents that this was a potential vaccine. We were being tested and so on. The idea of testing something that could have a profound effect on public health in the human population appealed to me. That I think stimulated me as well. I read about Sabin, who was the person who had done the work initially on growing the cells and being able to grow the virus, which later led to a live virus vaccine, although we got the Salk vaccine, which was one with a killed virus. The whole intellectual atmosphere around creating vaccines and treating human populations also appealed to me.

JG: Had you known anyone that had polio?

MG: No. I remember my brother, who was in summer camp when I was a little younger, when I was four or five, was sent home from the camp because there was a case of polio. They

were shutting down summer camps all the time because the disease was very infectious and would run through populations. Subsequently I have known people who had polio, but at the time, I do not remember knowing anybody. I do remember as a child somebody in my second or third-grade class who developed leukemia. That was a period when childhood leukemia was not a treatable disease. There was a kind of a hush-hush about it, but we knew the child was sick, and within a month, heard that he had died. The concept of somebody who was our peer who was dying of this strange and unknown disease I think also influenced me in terms of wanting not to be powerless in the face of that kind of situation.

JG: How about your teachers at Flushing High School? Did the teachers there influence your career direction?

MG: I guess one important thing to know is that I was quite young when I went through school. I skipped a grade in elementary school. I went from the middle of the third grade to the middle of the fourth grade. I think it was just that the school was willing to deal with the fact that I wanted more stimulation and the easiest thing was to just put me in the next grade.

JG: Which they typically would not do nowadays.

MG: No, not at all. [Laughs] They would not do it at all.

JG: What was that like being the youngest of your peers in middle school?

MG: I think I remember relating more to my teachers than my peers at that point. I was always a very good student and I think the teachers reinforced that. I always felt comfortable in class. I had friends but not especially from school. I do not remember any particular interactions in school with specific individuals. There was no teasing. There is not a lot of memory that comes out of the actual kids in school. Although in the fifth grade I was in a special music class, which I think was a subterfuge for getting all the bright kids together in one classroom, because not many of us were that musical. I, for one, was not particularly. I was frequently asked not to participate in choral activities. [Laughs] Actually I learned how to play the clarinet which I carried all the way through high school and was a clarinetist in the high school orchestra and took piano lessons but not beyond high school.

Then in the seventh grade I was put in something called a SP class that used to be called rapid advance, special progress, which is a much more organized way of advancing kids in school because it takes the seventh, eighth, and ninth grades and makes them into two years. I guess the notion is the less middle school the better. I started high school when I was twelve and high school was only three years: tenth, eleventh, and twelfth grade. I was in high school for three years and then graduated at age fifteen and went to college at age fifteen. This was to get background about the teachers?

JG: Right.

MG: I remember a science teacher in middle school where we took general science who was a very enthusiastic teacher and was very helpful in terms of getting kids involved in independent projects. I did an astronomy project for a science fair. I had a telescope at home and I used to take pictures through the telescope and I got fairly good at taking pictures of heavenly objects. I had this poster, which was for the science presentation, and he helped me assemble it. He suggested that instead of just saying telephotography, I call it "Telephotography and Romance." Being only about eleven years old at the time, I had no idea what this was about. It really appealed to the judges and it won some kind of award and they said "What a great catchy title." I learned a little about PR then from this guy. He was an interesting fellow and very enthusiastic about science.

JG: What was his name?

MG: That is a good question. Mr. Bleeker, I believe. Then in high school I had a chemistry teacher whose name was Abramson. Everybody was "Mr." but he was a "Dr." He had a Ph.D. in chemistry. He was a product of the Depression where a lot of people with Ph.D.'s found that the most secure jobs they could get were at public schools—particularly the New York City public school system. He was a real chemist. I think by that time I was interested in really learning a lot. He arranged for me to have a summer job at Albert Einstein College of Medicine where he was working part time in addition to being a teacher in the public schools. I think he was a sort of mentor. He recognized that

I was seriously interested in science and gave me opportunities, not only in the classroom, but after school to actually work in a laboratory.

JG: What was that like?

MG: It was my first lab experience. I think it was at the end of my junior year in high school and I had a summer in a laboratory. Now I was fourteen years old. We studied lipid micelles. How to construct lipid micelles from phosphatidic acid and cholesterol. I never thought I would go back to studying membranes but it turned out that what I learned was very interesting and important. We took phosphatidic acid, which is a lipid acid, and reconstructed micelles and studied their physical properties, the charge distribution on the outside. Most of what we did was simple analysis of charge and mass. I was pretty much supervised. I was fairly young then. I did that for two summers and then went off to college.

JG: What did your parents think of this?

MG: They were very supportive. In retrospect it was amazing how tolerant they were of me getting into situations when I was that young. But they seemed to understand that I was socially able and excited about the science.

JG: Did you have siblings?

MG: Yes. I have an older brother.

JG: Was he also ahead in his grade?

MG: He was one year ahead. He was in this special progress class. He was not particularly science oriented. I think the difference was I was really very much more interested in math than he was. He ended up actually becoming interested in social studies, history, and English. He taught high school for many years until his retirement a couple years ago in those subject areas—so no science at all. In retrospect, in talking to him, and discussing various things, he is pretty aware of scientific issues. I think he just, for some reason, never got into the mindset of wanting to be a scientist.

JG: You were the valedictorian of your high school class.

MG: I was.

JG: Did you do the speech?

MG: I did a speech.

JG: Do you recall the contents of your remarks?

MG: Yes. In fact, I have it someplace. I found it recently because we were cleaning out our attic and there it was. Of course, it is a little embarrassing to read what you write when you are fifteen years old. There has been some discussion recently about the things that, for example, our new president said when he was a certain age. It was mostly about the importance of using our talents, our gifts, to better mankind. It was sort of a very blatant, altruistic kind of valedictory statement from a very young person, who was maybe naive, but at the same time very hopeful and optimistic that we could do something. I remember reading this and being taken a little aback recently in seeing it. I made the statement in there that you should not just do art or science for its own sake but that it should have a function in society. I have a much more nuanced view of that situation now.

JG: You go to Harvard College. Did you apply to other schools?

MG: In those days you did not apply to a lot of colleges. I applied to three places. I applied to Columbia [University]. The other thing I had done . . . Columbia had a science honors program. It was actually a math and science program and I used to go on Saturdays to this math program at Columbia. I think you will discover from people who grew up in the New York area that that was a real magnet for people from all over the city. I met a lot of really smart people there. I got on the subway and I went up to Columbia every Saturday. I applied to Columbia because I knew the area and it was a local school and I was fifteen years old, after all. I also applied to Amherst [College] because I was told I should have a small school as well as a big school and I applied to Harvard. I was

accepted at all three. We used to say, "Harvard is never having to say you are sorry." [Laughs] So I went to Harvard.

JG: Were your parents concerned about you going to college at such a young age?

MG: At age fifteen, sending me off?

JG: Yes.

MG: They seemed fine. Maybe they were happy to get rid of me. No, I don't think so. I think they had some trepidation, but I wanted to do it, so I did it.

JG: You attend Harvard College from 1962 to 1966.

MG: Yes.

JG: What was it like?

MG: I did not have advanced placement. I was the youngest person in my class at age fifteen. I was sixteen in October of the year that I came in.

JG: Okay, so for that first two months, August and September, you were fifteen years old?

MG: Well, just September. It started in September. We did not start in August.

JG: You go into the biochemical sciences. What courses are you taking?

MG: The first year at Harvard in those days . . . You did not declare your major until the end of the first year, what is called the field of concentration. Everybody took general courses. People who were interested in science took more advanced science courses. There were social sciences courses, there were humanities courses, there were fine arts courses, and there were science courses. The first year I took an advanced math course. Not the most advanced. There were kids from New York, for example, who went to schools like Stuyvesant [High School] or Bronx Science [Bronx High School of Science] who had had more advanced science courses than I had had. I took a fairly advanced calculus course. I took chemistry, again, fairly advanced. I took Humanities V, which was philosophy, general history of philosophy, and Social Science I, which was the history of the world. Then we could audit courses and I ended up over the next couple of years auditing courses that advanced my general knowledge. I tried to get a liberal education. I was told I was at a very liberal arts college and I tried to take advantage of that.

JG: When you were applying for colleges what were your intentions for your career? What did you see yourself doing upon graduation?

MG: As I said, when I was interviewed, I said I wanted to emulate Albert Sabin. I intended to be a medical researcher.

JG: Not clinical at this point?

MG: No, not necessarily clinical, but biomedical.

JG: Biomedical?

MG: Yes. At that point, I had had enough experience in a laboratory to know I enjoyed the hands-on part of being in a lab.

JG: What is Harvard College like in the Sixties?

MG: Okay, you are right. It was in the 1960s. We were in the Sixties. I was totally protected from the drug culture. There was none of that at all in my life. There was a famous editorial that was written about the three flavors of Cliffies at Harvard. There was Harvard and there was Radcliffe. Even at age fifteen I was very interested in the fact that there were girls there. I think the description of the girls, which were in terms of being chocolate, lime, or vanilla, those were the three flavors of girls and I think that went for Harvard as well. The chocolate were the hard working usually immigrant kids who had not gone to prep school and got straight A's in everything and were brilliant and were going to be successful professionally. I have to say that Susan and I were probably in

that category. Lime was the last of the beat generation. They were really unusual people who tended to be more artistic and sometimes had varying degrees of mental disability, either as a cause or a result of their behavior. They took drugs and so on and so forth. The vanilla, I think, was the preppies. Maybe that is the wrong flavor. It does not sound right. There was a third flavor who were people from privileged backgrounds. About half the people at Harvard were legacy folks. I mean there were people whose families were very rich—the Cabot's and the Lodge's and on and on and on. Some of them were extremely capable and others you wondered what they were doing there. My son, who in the next generation went to Harvard, we asked him the first week what it was like. He said, "Well, the people at Walt Whitman High School were a lot smarter." [Laughs] That was his general attitude. It is not that everybody at Harvard is brilliant. It is the environment that brings people from different backgrounds together that I think is special. Not unique, but special.

JG: Your tutor becomes William Beck.

MG: Right.

JG: Describe him.

MG: He was a hematologist who worked at the Massachusetts General Hospital which is a very famous research hospital. He was very interested in giving me a research experience, a real research experience in the laboratory, hopefully ending with something

publishable, which it did. We used to meet before we started in the lab. I declared my concentration the end of my first year and then got a tutor and started in the second year.

JG: And the concentration was?

MG: Biochemical sciences. We used to meet and the first thing that we did—

JG: I'm sorry, this was with a group?

MG: Yes. There were a couple of other people in my group. One was a guy named Jerry Angoff, I believe, who became a physician eventually and with whom I have not been in touch. I can't remember who the other was. I think there were three altogether. We separated when we went off to laboratories which was the next year. The first year was a tutorial in biochemical sciences. Remember we had had physics and chemistry. Well, we were starting physics in the second year, and chemistry and mathematics, but not really biochemistry. What William Beck did was he used the first sixteen papers that Arthur Kornberg published in the *Journal of Biological Chemistry* about DNA biochemistry as teaching materials. I learned very early how to critically read the literature, how to read really good papers, and I learned about DNA replication, basically, which became an area of interest later on.

Those papers were extremely formative and I still believe that one of the best ways to learn about science is to critically read the literature and discuss it in great depth. Not

only why they did the experiment, but what the results of the experiment were, how do they interpret these results, and so on. Kornberg's papers were brilliant. Charlie [Charles C.] Richardson was a co-author on some of them. Both of them went on to become scientific leaders. I can't remember whether Kornberg had won the prize [Nobel Prize] by then. I think he had. He had already gotten the prize for DNA polymerase.

JG: What type of scientist was Dr. Beck?

MG: He was a very smart guy. He also was the author of *Life: An Introduction to Biology,* which was a famous textbook originally authored by [George Gaylord] Simpson, which later became known as Simpson and Beck. He was interested in education as well and I think he had a rather broad view of science. He really did. He was a very good tutor. He was very well-informed, very knowledgeable. He had a lab so he understood scientific method. What he was doing was more systematic than it was brilliant, intuitive, creative science. I learned my way around a lab. I learned a lot about lab safety. I learned about designing good experiments with controls and interpreting data. I discovered that I was reasonably competent in the laboratory. There are people sometimes with good hands and not such good hands. I was pretty good.

JG: How so?

MG: Making dilutions that were actual dilutions, not spilling things, getting calibration curves that were straight lines. There was a lot of laboratory work in those days in the sciences

in college. Hours and hours of time spent in the laboratory. All the courses I took in chemistry or biology had laboratories. Quantitative analysis consisted of ten unknowns and you had to figure out what their molecular weights were and what they were. It was serious quantitative analysis. You learned how to be very careful.

JG: Your wife worked part-time in the laboratory of James D. Watson?

MG: Right.

JG: One of the questions I have been asking everybody is when did you learn about the discovery of the double helix structure?

MG: From Watson. I took Biology 2 and Watson was one of the lecturers. That was in 1962. Now I am pretty sure I was sophisticated enough to know about it before . . . I do not think we learned much about it in high school. I do remember that the New York State and New York City had exams called Regents Exams that were statewide exams. The exam in biology was way behind what we learned in high school. They used to tell us before the exam what answers to give to some specific questions—where the Regents answers were different from the real answers. For example, we were told if asked how many human chromosomes there were the answer was forty-eight even though we knew there were forty-six. As a result, actually, of a discovery made here in the Intramural research program. [Laughs] There was this disconnect between what the state thought were important facts and New York City. I am pretty sure I knew about DNA before I

went to college but it was not a driving force intellectually for me until I was really learning how to work with DNA and what its significance was in the laboratory.

JG: What other scientists did you get to cross paths with at Harvard?

MG: Oh, my goodness. Quite a few. Let me think of who taught my courses. The biology course was taught by Watson and others. They were all distinguished. There were four speakers who divided it up because it was a general biology course. It included E. O. Wilson. He was an ethnologist that worked on ants and was very well known. He had written a whole bunch of books.

JG: What was Watson like?

MG: He was brash. He was extremely entertaining. He constantly was making fun of other scientists and I remember being a little bit shocked by that as a young student. He was weird. He has a lot of personal mannerisms. He rolls his eyes. Those are all abundantly clear when he was lecturing. He did not seem particularly prepared. He would mostly reminisce about his experience in science. Obviously he was very smart. Part of being at Harvard is being exposed to these people. In economics it was John Kenneth Galbraith who was a legend.

JG: The Canadian economist.

MG: Right. Chemistry, it was [George] Kistiakowsky who was known, a very well-known physical chemist who had worked on the Manhattan Project on the trigger for the atom bomb. He was [President] Eisenhower's science advisor and he was constantly flying back and forth to Washington and telling us what was going on. Again, it was very chatty. [Laughs] You felt a citizen of the world at Harvard.

JG: What was Galbraith like?

MG: Oh, he was wonderful. He gave absolutely brilliant lectures. Now Galbraith was a Keynesian economist. This is not the Chicago School of Economics. He was explaining to us the vital role of the government in supporting social structure, in supporting poor people. It was a message to a group of people who tended to be liberal . . . In that day liberal was a perfectly fine word to use to describe people. I think it was a heady experience to have somebody with that stature reinforcing what you thought was the right thing to do and telling you that economically it was also defensible. We are beginning to hear a little bit about this again; that it is okay for the government to spend money in some circumstances. It is good for the economy.

JG: Looking back now how do you think those four years influenced your career?

MG: In many different ways. I was pretty young. I think it formed my intellect. I think it taught me how to think, how to think rigorously about problems. It taught me to be very

product oriented and to produce products that I could be proud of and that would pass muster through a peer review system. Everything got graded in those days.

JG: Did you have any publications?

MG: Yes. There was one publication that came out of my thesis work. My very first paper was in the BBRC [*Biochemical and Biophysical Research Communications*] with Bill Beck. That came out of my thesis project. He was interested in Vitamin B12. Remember he is a hematologist and pernicious anemia is a deficiency in Vitamin B12. It was not entirely clear what the basis was for the anemia and so he was interested in studying the molecular basis of the human disease. He used a model which was a Lactobacillus model, which uses B12 to make deoxyribonucleotide cells. The work was to find the mechanism by which B12 was involved in that and it turns out it was a hydrogen-transfer reaction. It was a little bit of chemistry more than biochemistry. I think that was an interesting paper. It made a reasonable contribution to the field, small but reasonable. It was a good start for me. It gave me a sense that I could accomplish something.

JG: It is 1966 and you decide to go to medical school?

MG: Yes. I guess Susan told you that we met when I was a sophomore and she was a freshman. After a few months of dating it was clear that we were meant for each other. We were very close. All the decisions, the subsequent decisions that we made, we made

together. We were married in my senior year; Susan's junior year. She will tell you it was because she needed to get out of the dormitory. I am sure she has said that. [Laughs] It was a really wonderful period. Again, we were very young. Both of us were young. It was fairly amazing that both sets of parents, who got along well with each other, lived ten miles apart . . .

JG: Really?

MG: Yes. Well, Susan grew up in Roslyn which is about twelve miles from Flushing where we lived. There was an easy comfort. We had very similar backgrounds.

JG: They were supportive?

MG: They were supportive. I think they realized that this was a match that actually could last. I think forty-three years later it is fair to say that they were right. We were right too. [Laughs] It happens occasionally in life; you find the right person early. We talked together about what we wanted to do. Susan had another year at Radcliffe to finish. I applied . . . There were two M.D./Ph.D. programs at that point. It was clear to me that I wanted a medical degree, I wanted a medical education, but I wanted to be able to apply that to biological problems.

JG: Why not just a Ph.D.? Why did you seek out the M.D.?

MG: As I said, even from the beginning I was interested in medical problems. I thought I wanted to be able to solve medical problems and that I needed the education in medical school to do that. I still think that if you are really interested in figuring out what important problems are it helps to have a medical education. More and more people with Ph.D.'s are getting into medical things. In those days a Ph.D. was not a degree that enabled any kind of medical research except in a support role. I applied to the Albert Einstein M.D./Ph.D. program and I got into that program. I applied to Harvard Medical School and to medical schools in the Boston area including Tufts [University] and BU [Boston University] thinking that I would probably end up staying in Boston. I got into Harvard and again it seemed like the reasonable thing to do. There was no M.D./Ph.D. program at Harvard at that point. There were only two in the country. One was at Einstein and one was at Duke [University].

JG: How did you like Boston compared to New York City?

MG: We loved Boston. Being a student in Boston is a very positive and heady experience and we loved it. I think we imagined we might end up staying there. This was a time, the war in Vietnam was already fairly much underway, and that had a huge influence on personal decisions as well. As I went through medical school it became clear that there would have to be some sort of decision made when I graduated about public service in place of military service. That is why we ended up coming to the NIH program.

JG: What was Harvard Medical School like?

MG: It was a much more disciplined sort of rigorous curriculum than it currently is. We basically had classes ten hours a day. We would start early in the morning. We would have class and then we would have labs in the afternoon every day for the first two years. I think someone said that you learn more new terminology, new words in the first year of medical school than during the first five years of your life learning how to speak. Thousands of new terms. I was great at that; I was terrific at that. It was no problem at all. It was really a piece of cake for me to learn all those things. I have a good memory and I was fascinated by all the biology that I was learning. It is a huge amount of information. Nowadays, my daughter went to medical school and there is three times as much information that they cram into the medical students. It is just an amazing experience, medical school.

JG: You worked with Dr. Bert L. Vallee?

MG: Yes. I think during the first two summers of medical school I worked in Vallee's lab. I am trying to think how I got into that lab. He was one of the people who taught us. In the first year he had a clinic that he ran on the role of metabolism in human disease. It was kind of inborn errors of metabolism. I thought that was interesting. His lab was one of the bigger labs that took students. There were several other students there. I worked with someone named Robert Simpson who was an M.D. who was getting his Ph.D. at the time. He was a physician who was getting a Ph.D. with Vallee and I was assigned to him

as a student for the first couple of summers. Bob was a terrific mentor. We were on the same wavelength because he had a medical background but was a very rigorous scientist.

There was a laboratory that worked with metalloenzymes. A question, of course, was what is the role of metal in the catalytic site of the enzymes? We worked on an enzyme called alkaline phosphatase which is an enzyme that removes phosphate groups from a variety of different substrates. We also ended up publishing a paper. It is a zinc metalloenzyme and we took out the zinc and put cobalt in. It was still an alkaline phosphatase but all of its properties changed. Its pH optimum, the various kinetic parameters for the reaction, and so on. You could learn a lot about the relative role of zinc versus cobalt by just changing the metal. It was a fairly controlled environment in which you could learn something important.

JG: You mentioned that Dr. Simpson was a very rigorous scientist.

MG: Yes.

JG: How so?

MG: Well, I learned probably the most that I have ever learned about managing laboratory equipment, for example. How you actually measure something on a Mettler balance and how you autoclave things. He was just absolutely . . . It was very important to him that laboratory work was done properly. He designed very careful experiments as well. Very

bright guy who later ended up at NIH who unfortunately died a few years ago in an accident but was here for many years in the NIDDK [National Institute of Diabetes and Digestive and Kidney Diseases] and then moved to Penn State.

JG: Was this common for the medical students to also get laboratory experience or were you starting to do a different track?

MG: No, it was fairly common. In terms of summer jobs I think some of the medical students sought out more clinical kinds of experiences. I would say at Harvard probably half of the class was interested in some kind of research. There are many laboratories in the Harvard Medical area and many would find summer jobs.

JG: How about clinical training? Did you also interact with patients as a medical student?

MG: Yes. The first two years not very much. There were clinics in which patients were brought in and findings were demonstrated. At the end of the second year of medical school we did something called Physical Diagnosis which was the opportunity to actually start to examine patients. My tutor there was—we had tutors again—was a guy named Stu [Stuart F.] Schlossman who was a very well-known immunologist. He taught us how to listen to the heart, how to listen to the lungs, and how to examine patients. How to take a history and a physical. That was kind of exciting. It was amazing how easy it was to pass yourself off as a physician even though I was twenty years old. [Laughs] Put on the white coat.

JG: Did you ever consider moving to the clinical side?

MG: Yes. I think I was good at it. The patients liked me. I was a good diagnostician. I was not particularly good in procedures with patients, starting IVs, passing nasogastric tubes, and doing cut downs. I did all those things but I remember during my anesthesiology rotation the anesthesiologist said, "You know, some people just are better at thinking than they are doing some things." [Laughs] He picked up on that. I was not ever really comfortable manipulating, hurting people, basically. I knew it was for their own good, there was no problem justifying it, but they were unpleasant procedures for most people, and I did not particularly like that.

I particularly could not stand doing it in pediatrics. I loved the kids and I loved studying the diseases but I found it extremely difficult to have to do any harm to a child or cause them any pain. That was really difficult. I knew I was not going to be in pediatrics, even though some of the areas that interested me, the genetics and the infectious disease, were things that would involve pediatrics.

JG: You are in medical school from 1966 to 1970?

MG: I started medical school in 1966. In 1968 we start our principal clinical year. There was a year in which you do only rotations in hospitals. That is what happens in 1968. Then in 1969 and into 1970 there are a few rotations which are elective but are not required.

Then the last six months I spent in the laboratory. I had an elective period which was entirely laboratory and I went back to Vallee's lab and finished publishing a paper. At graduation, there were a couple of research awards, and I won some awards.

JG: Which ones?

MG: Something called the Soma Weiss Award at Harvard, which I actually shared with Ron [Ronald H.] Schwartz, who is now still a colleague at the NIH. He is an immunologist. We were friends with the Schwartz's. Joan is a member of this office actually, currently. All of us were at Harvard Medical School; Susan and Joan and Ron and I. Susan and Joan were at the medical school in the graduate department and Ron and I were in the medical school. It was somewhat disturbing that we were both competing for the same award but we actually both got it. They decided we would share it which was fun. There are a couple of other awards and I would have to look on my CV. I do not know all my medical school awards. I did graduate from college in biochemistry summa cum laude and magna cum laude from medical school. Phi Beta Kappa from Harvard College. I also got the James Tolbert Shipley Prize. These awards were at graduation for research. They were research awards and they are still there. They still give them.

JG: Were you or your wife active in the antiwar movement at all?

MG: We would attend as many peaceful student demonstrations as we could. We were obviously pretty busy as I just described. There was a medical school organization for

peace. It was mostly aimed at the war more than global peace—the war in Vietnam. We have a photo someplace of us. Where did I see it? Susan must have it someplace. There is a photo of us, me in my white coat, and Susan standing there with one of these peace armbands. We were active but there just was not enough time. We were really busy. These were all peaceful protests by the way.

JG: Duly noted. [Laughs] You do your internship at the Peter Bent Brigham Hospital?

MG: Right, which is a Harvard teaching hospital. There were four Harvard teaching hospitals. The Peter Bent Brigham, the Beth Israel, the Mass General, and there was a Harvard section for Boston City Hospital. The Brigham was where my laboratory experience was with Bert Vallee. I felt really comfortable and wanted to stay there for my internship. It was obviously considered one of the top internships in medicine.

JG: Describe the year.

MG: It is a blur. When I was a medical intern we were basically on every other night for a whole year except for a couple of months that were more elective time. That meant you came in at 7:00 a.m. to go on rounds of day one, and rounds lasted several hours, and then you admitted patients starting usually in the late morning usually two, three, four patients. In those days we did everything for our patients. We did the blood tests; we did the urine tests. We had a little laboratory where we did a lot. Some things went down, for more complicated tests, but we did virtually everything on the patients. Then you

were up with your patients all of whom were really acutely ill. We did not admit patients to the hospital who were not really very sick. The wards that we were on were like intensive care units, basically. You would stay up essentially all night. You were lucky if you got one or two hours of sleep.

What you learned to do as an intern was write orders for the nurses that covered every conceivable contingency so you could at least sleep an hour before something unexpected happened to one of your patients. There was almost no sleep at night and then the next day you went on rounds and you stayed generally till four or five in the afternoon to tidy up the patients. Then you passed on your patients to the other intern who was on the night alternating with you. You are not only admitting and taking care of patients but you are taking care of the whole ward during this time that you are on. That went on for month after month after month. We figured it out so we could arrange to be on and off every other weekend. There are some weekends when you would be on for three days in a row with only a couple hours of sleep. It was very difficult. During the end of my medical school years our first child was born in 1970. I started my internship with a five-month-old child at home and used to come home every other night and see him for a while and then fall asleep. We slept about the same amount, my baby son and I, when we were home. [Laughs]

Susan was a graduate student during this period. We had a babysitter who did not come in. We took Daniel to the babysitter, or Susan did, because I do not remember what I was doing for that first year. I was very busy. She was very tolerant. It was amazing in

retrospect that she lived through that. After one year we decided we definitely needed out and so we came to the NIH after a year.

JG: How did the internship influence your career?

MG: Well, it gave me an incredible substrate of human disorders to think about in terms of things that I might be interested to study. People with tumors, with cancers, a lot of the patients at the Peter Bent Brigham were deathly ill in one way or the other. There were a lot of alcoholics too. It was adjacent to a community in which alcoholism was fairly rampant. Low-income community. In those days the sickest people were the alcoholics. Now it is the people with HIV. People who work in inner city hospitals tend to get exposed to very sick patients such as immunosuppressed people who get all kinds of infections. Alcoholics have their own set of problems. I learned a lot about the ravages of alcoholism. It is a way of learning how to deal with almost any medical emergency. It gave me a huge amount of confidence. Surviving that year, it is like a year in the trenches, gave me a sense that I could solve virtually any problem and that it was just a matter of choosing problems that were tractable in a laboratory. I think it gave me both confidence and an exposure to what human disease was like and where advances needed to be made.

JG: What were some of the areas that you really started thinking about?

MG: The two areas that I was interested in at that point were infectious disease and oncology. They both seemed fairly well suited to my intellectual background which included bacterial genetics and a little bit of an interest in biochemistry. Those fields looked like they were amenable to scientific discovery.

JG: Your colleagues and other interns where did they go?

MG: Many of them at the Brigham were interested in research experiences. Some of them ended up at NIH actually. George C. Fareed was in my class. He is a very well-known SV40 [Simian virus 40] virologist. I would have to reconstruct but I think probably four or five of those people came to NIH eventually not necessarily after their first year. Some of them waited till after their junior residency. Others still are here. There is a group of people who trained in Boston. This is the so-called Boston-NIH axis. There is just a huge number of people. During the period of the so-called "Yellow Berets" when people were recruited here in the place of military service there were 400 to 500 physicians who came in a ten-year period between the mid-1960s and the mid-1970s. Maybe a hundred of them were from Harvard. There was a huge percentage from the major academic medical centers: Harvard, Yale, UCSF [University of California, San Francisco] and so on. NIH was getting the pick of the top medical students at that point.

JG: You move to Bethesda.

MG: Yes.

JG: You were accepted into the research associate program at the National Institute of Arthritis and Metabolic Diseases (NIAMDD)?

MG: Yes.

JG: What had you known about NIH at that time?

MG: I talked to a lot of people up in Boston, many of whom had been at NIH, or knew NIH'ers reasonably well, about who a good mentor would be. Particularly I think I must have had a lot of discussions with Bob Simpson who himself was interested in coming here and knew people. There were a few people . . . I interviewed with Maxine Singer. At that point, I think you had to specify an Institute, and it looked like NIAMDD was the most basic science oriented. It had a very strong basic science program. This was before the heyday of the NCI.

JG: What was Maxine like?

MG: She was very no-nonsense. She seemed a little bit distant to me. Not particularly warm and not necessarily interested in having an M.D. in the laboratory. She is a Ph.D. She did not know quite what to do with me and did not feel that I was as trained as the post-doctoral fellows that she could easily recruit. I talked to Marty [Martin] Rodbell and I remember he was all over the place, enthusiastic about GTP. I thought "Did he mean

ATP? What is this about GTP?" He was at that point still working on G-binding proteins for which he won a Nobel Prize. I did not quite get it. I could not get from him exactly what it was he was doing. It was partly because I did not know the field very well and it was such a new area. I interviewed with Marty Gellert who also implied I would take-it-or-leave it. It was not like he was going to live or die depending on my coming there but I really liked Marty. I liked the way he thought, I liked the way he talked, I liked the science he was doing. I decided to ask for that laboratory and he obviously felt that I had done well enough to come.

When I arrived I started working on DNA ligase which was a subject that he was interested in at that point. My project was to do bacterial genetics to isolate mutants that were defective in DNA ligase and analyze their phenotype. The theory was that ligase had something to do with DNA replication and DNA repair. We isolated a mutant which had reduced amounts of DNA ligase. Somebody else had isolated a temperature-sensitive mutant that was actually temperature sensitive for growth so we knew it was an essential enzyme. A guy name Thomas Lindahl, who was Swedish. I learned all the tools of bacterial genetics.

Fortunately, Susan, at that point, had a Ph.D. in bacterial genetics. I think she influenced me in terms of this kind of approach to science. I did some heteroduplex mapping which is using an EM [electron microscope] to map where genes are along DNA. My general approach to science has been not to be technique limited. To identify a problem and then learn whatever techniques you needed to solve it. Some people are much more focused

on using a technique to learn new things. Techniques were not so important except as tools to learn something about problems. The problem was how does DNA replicate in *E. coli*. The mutants we got turned out to be defective in closing what are called Okazaki fragments.

There is a leading and a lagging strand in DNA replication. One of the strands you can make with three prime to five prime DNA polymerization and it can go on forever and ever until you come to the end of the replicon. The other strand, though, sits in the other direction, so the only way you can make it is in little pieces that have to be knit together with this DNA ligase. We studied that process and the mutants were very useful. There were spin-off projects. I isolated a bacteriophage for a gene that was right adjacent to the DNA ligase gene. It was by accident because we were looking for DNA ligase and we got this other gene that was involved in sugar metabolism in *E. coli*.

I became interested in jumping genes, what we call jumping genes in those days, which was related to antibiotic resistance. We were one of the first people to map a translocon for a jumping gene in bacteria. These are important elements for multidrug resistance in bacteria. The chloramphenicol locus, we did some work on that. I was generally exposed to a very stimulating group of people in the group that is called Lambda Lunch. I am sure Susan has told you about that and I had an opportunity to present my work and to have endless discussion about various aspects of it. I felt that I could hold my own and I enjoyed the repartee and the science. It was a great time.

JG: After your internship had you looked at other positions or had you just focused entirely on the NIH?

MG: The only options for not going to Vietnam were the CDC [Center for Disease Control], the NIH, and the Indian Health Service. The NIH was far and away my first choice. I did not even consider the other options.

JG: You mentioned that you liked the way that Marty Gellert talked and his style. Describe his style of science?

MG: Marty has a very logical mind and before he does an experiment he thinks about what he wants to do. He thinks about the various options in terms of experimental design and in terms of being able to come up with results that are unequivocal and where the interpretation would be clear. He was trained as a physical chemist and so is very knowledgeable about chemical reactions and chemical processes. His way of choosing problems was not by accident by any means but by thinking about critically important problems. For example, this work on DNA ligase, it became clear that based on what we knew about DNA replication that there had to be an enzyme that was involved in knitting together these fragments and DNA repair and putting them together. He set about to develop an assay to be able to detect and purify such an enzyme. He was the first person to isolate DNA ligase.

There were other competitors at the time but I think the work was just beautiful. There is something about science, there is a way in which people tell a scientific story which is clean, and where anyone listening who is interested can follow step two from step one, step three from step two, and say, "Yes, that was the right thing to do." The clarity drives not only the future science but is a way of describing the past science. It is just—I think the word is elegant. There is an elegance about it. It is an aesthetic property but it is also a property of mind and a property of communications that some scientists have and some do not have it.

There are scientists who are perfectly successful who lack those skills entirely. I was attracted to being able to tell a complete story. There are other people who can do that. I think Ira [Pastan] is actually wonderful at explaining what he is doing and so on. Harold E. Varmus, who was the director of NIH, used to always say when we set up a lecture series "Let's get people who can tell a good story." By story I do not mean mythology. I mean a story of discovery—accurate, complete, where you can follow from step one. For students who are learning how to do science that that is really the best way to learn.

JG: What was Bethesda like in 1971?

MG: There were cows inside the Beltway. [Laughs] We lived in a little house just outside the Beltway and we arrived in July and for the first two months we did not see a single human being on the street because it was so hot. We thought we were living in a ghost town. These were very small, these are small three-bedroom tract houses.

JG: Wartime housing?

MG: Probably postwar housing. Now of course they are being replaced with $2 million McMansions and the property is worth a fair amount. It turned out nobody was out on the street. There were people with children but because it was so hot in Washington people just did not go outside in the summer. We were not used to that because in both New York and in Boston summer was a time when people went outside. It was a little weird. We used to ride our bikes to work which was a problem because on Old Georgetown Road all of the grates and the sewers were parallel to the road so the tires used to get stuck. You had to swerve out in the street to avoid the grates. Some of the land which is now housing tracts had farm animals on them inside the Beltway because the real estate taxes on farmland were a third of what they were on other land. People would put a cow there. They were obviously speculating. Now all that has been converted into high-density housing.

There were two restaurants in Bethesda. Bish Thompson's [Seafood Restaurant] and North China [Restaurant], not counting the Tastee Diner as a restaurant. Bish Thompson's was a seafood restaurant. It is gone. North China, just a year or so ago, got sold to another Chinese restaurant but it was there for many years.

JG: When you arrived did you think that this would be a place that you would spend your professional career?

MG: I think for New Yorkers and Bostonians it was a little bit suburban. [Laughs] That, of course, has changed. Yes, I think we felt this could be a place for us. Downtown Washington, D.C, was a great place obviously. At that point we had a child and we were thinking about having another and it seemed like the schools were good. We knew that. It seemed like a good place to bring up children. We could imagine more permanently being here. Initially, I think, the intent was to serve, in my case three years, and then go back and finish residency because remember I had just had an internship. Then probably stay in Boston. That was our original plan. We bought a house when we went back.

JG: You return to Boston in 1974?

MG: Yes.

JG: What was your residency like? Susan mentioned that there was some discussion that you might not return to do the residency. I am not sure if that is correct.

MG: Yes.

MG: There was discussion. At that point we were alternating choosing what to do. I think Susan chose to go back because she wanted to be at MIT. She worked with David Botstein, as you have heard. I think she felt that she was not quite ready to make the NIH decision and I was perfectly willing to go back. We never got into conflict over it. I

think it was sort of an agreement that we would go back to Boston. I think we always felt that I was more mobile than she was, that having the M.D. meant I could go anyplace, pretty much. Given my background in research I was I think a reasonably hot commodity. It was clear that Susan favored more going back at that point than I did.

I was able to do a year of senior residency. I skipped my junior residency so that is another year that I skipped. To some extent my life has been aided and abetted by a lot of people being willing to be flexible about programs which are now much less flexible. In terms of my overseeing the Intramural program I like to think that we look at the individual and we try to be very flexible in their career pathways. We have already heard about three years of my life that was not spent doing things I did not really need to do. Two years in school and then I skipped a year of residency.

Gene [Eugene] Braunwald was my chief of medicine. For a physician, chief of medicine when you are in training is an important figure because they are the main mentor. George W. Thorn was my chief of medicine when I was an intern. He was close to retirement, and when he retired, he established the Howard Hughes Medical Institute. He was the first scientific director of HHMI. He was a very senior figure in American medicine. He was the first person asked to be the scientific director. He established the principles.

JG: Right, in 1953.

MG: No. No, Howard Hughes Medical Institute did not exist until the 1960s. Maybe it existed on paper but it did not exist as an entity. I would have to go back and look. I am pretty sure he was the first person who was asked to put together a scientific program for HHMI. I left in 1970 and he maybe was at HHMI in the early 1970s. My next chief of medicine when I came back as a senior resident was Gene Braunwald who was a very famous cardiologist who had been scientific director, clinical director, of the National Heart, Lung, and Blood Institute (NHLBI) so knew NIH. He was very favorable to having me accelerate my training. Then through my connection with Bert Vallee I was offered an assistant professor of anatomy position in the anatomy department.

JG: Do you think that you missed anything by accelerating the residency?

MG: No, because I was not primarily interested in practicing medicine. What it enabled me to do was complete my training, take my boards in internal medicine, and be board certified. I knew enough to do well in the boards.

JG: How did you choose internal medicine?

MG: Again, pediatrics was pretty much ruled out by my sensitivity about dealing with children who were sick. Internal medicine, at that point, was a fairly common choice for people who were interested in research careers. It sort of segued in recent years into pathology. I actually enjoyed the patient work. I enjoyed dealing with patients.

JG: What was the board certification like?

MG: It is an exam. It was an all-day exam. It was at the end of my senior year of senior residency so I figured I should know all the medicine. Like many of these things the questions were written by the people who, by and large, had been my professors. I had heard a thousand times what they expected the answers to be. I may have studied a little bit. In medical school you take second-year boards and fourth-year boards and then you take boards after your internship. There are three points and you can't be licensed unless you pass those three boards. Then for internal medicine there are specialty boards beyond that. I did not spend a lot of time studying for any of those I do not think. I assumed that my training was sufficient to get me through.

JG: You take an assistant professorship position in the Department of Anatomy and you briefly work as an attending physician at the West Roxbury Veterans Administration Hospital.

MG: Right. I was chief medical resident. The senior residents had a chance to be chief resident for a month of the year at this VA hospital. That is significant because it really gave me complete responsibility for the medical services as chief resident. It also convinced me I did not want to do the next year of medical training which would have been as a chief resident someplace. That was not up my alley. I needed to get back into the lab. Other than medical school, actually, even in medical school, I never went for more than a year without having some time in the laboratory.

I went through this whole process with research in summers, elective time, a year of internship and then three years at NIH, senior residency, and then went into my own lab. I had a lab and I was working on tumor angiogenesis with Judah Folkman and Bert Vallee but I had my own project. My angle was since we knew that angiogenesis was happening we needed to figure out what angiogenic molecules were. My approach was to look at cells that were malignantly transformed and see whether they were secreting anything that had angiogenic activity. They were secreting interesting things. None of them had angiogenic activity and that led to some other projects that we have been working on. [Laughs]

JG: You and Susan returned to Bethesda.

MG: We returned. Why did we return? Part of medical school was anxious to keep me but Susan was not happy at MIT. She was not unhappy in her laboratory but they made it clear that faculty-level positions were not likely. She and I have a different memory of this. I actually remember a conversation in which she was told at MIT that because she was married and had a child, by that point two children, she should look around her and see how many faculty members at MIT were in the same situation. There were hardly any women at all and the women that were there did not have families. It was just unheard of. We decided NIH was a far more hospitable environment for people with families and for women's careers.

JG: Was that just a sign of the times?

MG: Yes. No, I think it is. I would say that both Harvard and MIT still have a problem with women in senior positions but they are doing better. They are trying harder. They certainly would never say what I just reported to you about their environment. Although Larry Summers pretty much said the same thing. It just seemed right coming back to NIH. We were comfortable coming back and we were well-liked here. Ira and Al Rabson provided us both with fabulous opportunities.

JG: Susan was recruited.

MG: Susan was recruited primarily by Ira's lab. Ira said "Well, we can probably use Michael too." He and I have had a great collaborative relationship.

JG: Speak a little about Ira and how you first met him.

MG: Well, I think I first met him when Susan was in the Laboratory of Molecular Biology with Max Gottesman as a postdoc. I got to know Ira a little bit and he got to know me. We did not have any direct scientific interactions until I came back. There were two people responsible for our recruitment. Ira for sure. At that point his lab was expanding and he had space and opportunity. He wanted to bring in not people working in a particular area, but people who he could talk to, who would provide intellectual stimulation.

JG: What was his lab working on at that time?

MG: He was working on cyclic AMP. He moved from cyclic AMP in bacteria to cyclic AMP in mammalian cells. Earl Sutherland had just gotten a Nobel Prize for cyclic AMP as a second messenger and Ira was interested in what cyclic AMP could do to cell biology, to cell growth, to cell shape, to various other things. He had published a few papers on that.

What I forgot to say is that as a postdoctoral fellow here with Marty Gellert, Marty really encouraged me to get interested in a new field which is called somatic cell genetics. In fact, at one point I was supposed to do a journal club. He said, "Well, there is this paper out by Ted [Theodore T.] Puck about using Chinese hamster ovary (CHO) cells to do genetics in culture cells." It is not genetics in the sense that they do not have a sex life but they are somatic cells that divide and they transfer DNA from parent to progeny. You can introduce mutations and study the effects on the biology of the cell. That actually got me very interested. When I came back I thought setting up a laboratory that could study important processes related to cell growth using cultured cells would be a great thing to do.

Ira was very supportive and from Lou [Louis] Siminovitch in Toronto, Canada, I got some CHO cells. He was very generous and we began, in as organized a way as possible, to clone them, to get cell lines that we knew were highly reproducible. They grow extremely well. They double every eleven or twelve hours which is fast for mammalian

cells. You could put a cell down and get a colony there five or six days later. You could actually do experiments. It is not like bacteria where you would put one down and then the next day you have a colony. It was a week. You had to do seven experiments during that time. Fortunately I am a good multitasker so I could do that. Colony formation did not take three weeks so that by the time you came to the end of the experiment you could not remember why you had done it in the first place.

I got interested because of Ira's interest in cyclic AMP and isolating mutants that were cyclic AMP resistant. We did some of that work together but some of it we did separately and you can see in the CV that we started to have papers together, some separate and some together. It turned out that was a great way to do science. Irene Abraham in my lab learned how to transfer DNA from one cell to another so we could do DNA transformation experiments. That was a field still in its infancy. There had been a couple of reports and we got fairly good at DNA transfer and cloning cells.

After the cyclic AMP work we became interested in resistance to anti-cancer drugs because that seemed to be an important problem. Here Bruce Chabner who was another division director, scientific director at NCI, had an influence because he suggested that if we were interested in studying drug resistance in cancer we could do it in some of the cell systems we had established. We started to study drug resistance. In the early studies using anti-cancer drugs we got two classes of mutants. We were using antimicrotubule agents like vinca alkaloids and colchicme.

We got mutations in tubulin, which is a separate interesting area, and actually, one of my fellows went off and has worked on that. We also got mutations that were not in the target for the drugs but seemed to be mutations in a system that kept the drugs from getting into the cells. At that point, probably by the late 1960s, there was a guy named Keld Dano who was a Danish scientist who had reported on the presence in cells of an ATP-dependent drug efflux system and there were a few papers out about that. Victor Ling and Rudy Juliano had described in some of these cells that were multidrug resistant a protein on the surface which they called P-glycoprotein which they thought blocked the uptake of drug. We began to work on multidrug resistance as a second class of these resistant mutants that were cross resistant and did not seem to accumulate drugs.

We sat down in about 1983 and we wrote a strategic plan for studying multidrug resistance in human cells. That is really interesting. First of all strategic planning in science is a very difficult thing. We had a few people, and we were assigning tasks, and the idea was to try to figure out as best we could how to most efficiently determine what the mechanism was of drug resistance in human tumor cells. It was kind of the culmination of all of this training, interest in human disease, and finally, being able to manipulate cell systems. It all came together.

JG: Let's leave it there today and we can pick up again on Monday.

MG: Good stopping point.

JG: Terrific. Thank you.

[End of Interview]