NCI Laboratory of Molecular Biology
Oral History Project
Interview with Dr. Mark C. Willingham
Conducted on October 7, 2008, 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 October 7, 2008, and we are talking via telephone. I am in my offices in Rockville, Maryland. Mark, please state your full name and also spell it and then also tell me where you are located.

MW: It is Mark Cauthen Willingham, M-A-R-K—C-A-U-T-H-E-N—W-I-L-L-I-N-G-H-A-M, and I am in my office at Wake Forest University School of Medicine in Winston-Salem, North Carolina.

JG: Terrific, thank you. 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.

Tell me a little about where you were born, your interests as a child, and what brought you to the College of Charleston?

MW: I was born in Charleston, South Carolina, but I grew up in a little town nearby called Summerville, and my father was a chemical engineer. He had instilled in both me and my brother, who was three years older, an interest in scientific things. Having done relatively well in initial elementary school and high school, I ended up actually skipping a few grades and came to the College of Charleston at the age of fifteen in 1961, having been born in 1946. My main interest was in scientific things, math, chemistry, that sort of stuff. That was kind of one of the entrées that I had when I went eventually ended up many, many years later at NIH in that I was younger than most other people. So that was my advantage. [Laughs]

JG: What career do you think you would have pursued if you did not enter the sciences?

MW: It is hard to know. I have a significant interest in engineering and sort of mechanical aptitude and that sort of thing. I am also a musician though, so at one point in the beginning, or I would say in my college, undergraduate college years, that was sort of the decision point as to whether I would become a professional musician or whether I would go into some scientific field. Probably I could have done fairly well going into electrical engineering, electronics, or chemical engineering but actually the school that I ended up going to, which was the College of Charleston, did not have an engineering major. It was not an engineering school, so just liberal arts, and the reason I went there was primarily economic. It was at that time a municipal college, it has subsequently become a state institution, but it was closeby. It was in commuting distance from my home. In fact all the four years that I went there, from the age of fifteen, when I could get a driver's

license, actually at the age of thirteen, in South Carolina at that time, I commuted every day to college. That school had a total student body of about 550 students and the advantage of that was it was fairly high quality education for that local area and that it was not uncommon for people to then go onto medical school at the Medical University of South Carolina, which at that time was called the Medical College of South Carolina, because that was the only medical school within the State of South Carolina. So that was also closeby and so that was one of the reasons that I ended up going there after I finished at the College of Charleston.

That decision as to whether to go into engineering and work for a company, or go into the sciences, and I at one point contemplated going to graduate school in physics, or to go into medicine was somewhat driven also by my father and by my older brother who had done essentially the same thing I had done. He went to college at fifteen, he then after graduating from the College of Charleston went to the Medical College of South Carolina, and I sort of followed in his footsteps three years later. My father had always had an interest in going to medical school where he grew up in Alabama and actually the only reason he did not go to medical school is because of the Depression. He ended up instead going into engineering. I think that had a major influence on both me and my brother in going to medical school.

JG: What was it like being a few years younger than everybody else in college?

MW: It was interesting, it was embarrassing, it was awkward . . . [Laughs] If I had it to do over again, and if I had the ability financially, I would probably not do that and spend the normal time in high school and end up going to college further away. Actually the first dormitory I ever lived in was when I went to medical school, and I was nineteen years old at the time. That has certainly been true with my children who all grew up in the Bethesda area, all having been born at the naval hospital [National Naval Medical Center] while I was at NIH. My oldest son went to Davidson College. My daughter went to the University of Delaware. My youngest son went to Wake Forest, which is one of the reasons I ended up coming to Wake Forest, and then subsequently went onto law school at George Washington. I would have probably gone to some more nationally prominent college had I had the choice but I was fifteen—what did I know? [Laughs] I got a reasonably decent education as it was. It was not very expensive. Actually the tuition to the medical school when I was in medical school was $600 a year.

JG: So your aspirations—it was pretty much set once you received your B.S. that you were going to go to medical school?

MW: Yes, about the middle of my college career I had decided that medical school made a lot of sense (a) that I was interested in medicine and (b) that I had the scientific aptitude. My real decision was should I try to be a professional musician, and try to go to Julliard, or someplace like that, or go into medicine. After realizing how much work it was to be a professional musician I decided to go into medicine instead. [Laughs]

JG: Talk about your mentors during that period both at the College of Charleston and then at the Medical College of South Carolina.

MW: Well, actually one of my major mentors at the College of Charleston was the professor of physics. It was such a small school that they only had one professor who taught all the physics courses and he actually was a really interesting guy named Harry Robison. He had been one of the participants in the Manhattan Project, or the residue of the Manhattan Project, I guess you would say, during the development of the hydrogen bomb. He knew a lot about nuclear physics and atomic physics and actually those were some of the things that he ended up teaching at the College of Charleston. He also was a bit of a commuter in that he lived in Pawleys Island [South Carolina], which is about 50 or 60 miles away from Charleston, and he would sometimes commute in his private plane and fly in and spend a few days. He was also a very engineering oriented guy as well. He used to build, one of the businesses he was involved in, was building racing engines for NASCAR. So I got some exposure to the engineering issues about how do you balance a crank shaft and that sort of stuff from him. He was, of course, very enthusiastic and encouraging and really made my college experience very positive. I owe a lot to Harry.

Once I got into medical school there was on the clinical faculty a couple named John and Maria G. Buse and they were in internal medicine. John was an endocrinologist, and Maria had been an endocrinologist, but in fact was the head of nuclear medicine at the medical school. John was originally from the South and was a very sort of good ole boy kind of personality but in fact a really brilliant guy. I did several externships and

research projects in Maria's lab. She did a lot of the research. Maria actually had the longest standing NIH continuous grant in that medical school which I think it was like forty-seven years or something. Anyway Maria is still alive, and I think is still on the faculty there, but John died a few years ago. But their children, two of them, are physicians. One is at Chapel Hill and a daughter is actually, I have forgotten what she got involved in, but anyway, it was a higher educational degree. They were very bright people, very nice people, and very motivating.

After medical school when I first began residency, the decision point to go into pathology residency as opposed to internal medicine, which my brother had gone into, was based on sort of mentorship with an investigator who was in the pathology department who had spent a long career at NIH named Samuel S. Spicer. And Sam Spicer had worked with the famous Dr. Ralph D. Lillie who was in the early days of NIH when there were only six buildings on the NIH campus and he was one of the fathers of histochemistry which was this study of how stains interact with tissues and what the chemical basis of that interaction is. Sam was a very highly motivating kind of researcher who was—he actually died just a few months ago. He had come to Charleston after retiring from the U.S. Public Health Service Commissioned Corps and set up a histochemical oriented lab and was one of the early developers of these various immunostaining chemical techniques that are now the standard practice in pathology where you use antibodies to detect various kinds of antigens in tissues and that is used for diagnostic pathology routinely now. Sam was one of the pioneers in that field and actually one of the early presidents of the Histochemical Society, which was the international society for

cytochemistry, which was this newly emerging technique of labeling things in tissues, in the context of a tissue section, so you could see which cells expressed which and . . . Even though I did not realize it at the time this was actually cutting edge stuff because it was not until the late 1940s that people actually realized, for example, that the DNA in the cell was in the nucleus. This was right after those initial insights into the morphology of cells and how the biochemistry and morphology intersected, and histochemistry was a major part of that intersection where it demonstrated what a component was, what organelle it was in, and that then led you to a lot of information about how it might function, so that proteins that were associated with mitochondria you could see them in the mitochondria, or on the plasma membrane, or in the nucleus, or whatever. So that was origins of biochemical cell biology which eventually led to molecular biology. Sam was involved in that and he was a great mentor. He really guided me towards going to NIH after a research year spent with him and even though I had already actually applied to the NIH Fellowship Program before I had gone into Sam's lab, it was reinforced that this was a real opportunity for me to learn how to do research. Sam was a very important person during my career.

JG: Your colleagues while you were doing your internship, and then your residency, were they going into research or focusing on the clinical side of medicine?

MW: The history of that medical school was it was mainly a clinically driven medical school. Most of my classmates went into clinical medicine in that region. The Medical College of South Carolina, and it being the only medical school in the state, had existed since

1824. It was one of the very early schools of medicine in the U.S. and so it had a very long history. The strange thing about Charleston was that it tended to be very much an insular place where people would go through higher education there and then stay in that region. Many of the people in my medical school class were from families that were in part of society in that city and would then set up private practice in that city. I would say half my class probably stayed in the State of South Carolina even though it is a low population state. Its major industry now is tourism, but in fact, that was the historic precedent that you just stayed there. So that was unusual. When I went to NIH I was the only person from South Carolina in the entire NIH. [Laughs] The only other one who actually showed up as a significant person in the research community in the U.S. was Joseph L. Goldstein who then went on to get a Nobel Prize. He had gone through NIH as a fellow and he was from a little town about sixty miles from where I grew up. In fact, a friend of my mother knew his aunt. So it is a pretty small place in actual fact. Years later I communicated with him, and congratulated him for getting his Nobel Prize, and he said, "Oh yeah, he knew aunt so and so," and my mother was a friend of hers, so it is a very small world.

The majority of my classmates went into clinical medicine and stayed in that area although there were some notable exceptions of people who went into academic careers and went all over the country in different places. I think partly pathology tends to be a little more academically oriented and so not surprisingly some of the people who went other places were actually in the pathology program. I was attracted into the pathology program there in Charleston because the chair of the department, whose name was

Gordon R. Henniger, and he has passed away subsequently. He tried to take the top students in each medical school class and try to interest them in pathology because it tends to be an intellectual activity. I had interviewed at five other places for internal medicine residencies, again following the example of my brother who had done that, and I went to Vanderbilt Medical Center, University of Alabama, Emory, and Chapel Hill, and some places in the region. And he said, "Look, what are you really interested in?" I said, "I really want to learn how to do research and I was thinking of going to graduate school in chemistry." He said, "Well, Sam Spicer is here and he is doing cutting edge research in this new sort of field of cytochemistry and why don't you spend a year doing just nothing but research as the first year of your residency, and then go into the rest of the regular clinical residency program after that?" So it was an opportunity for me to learn how to do research right there and I already knew that Sam was a very good mentor. That is really what drove me into pathology was that opportunity to do that.

After the year with Sam Spicer I ended up doing a year of regular clinical residency and that was a sufficient amount of time that the program that I went into at NIH was called the Research Associate Program and it was designed to attract medical graduates who had already had at least a couple of years of residency into a research fellowship. The attempt to create this cadre of physician/scientists which are still very difficult things to create because it is very hard to be good at both the clinical part of medicine as well as the research part of medicine. But that was what the program was designed for and it was also at a time when there was a significant pool of people interested in doing that because the Vietnam War was on and the ability to do that would allow me to get through my

selective service obligation and yet at the same time be able to get some research training. So I thought this is a great idea and I applied for that. Nobody from my medical school had ever gotten in that program but I might as well try. I can remember going up for my interview to NIH and just saying, "Gosh, I'd give anything to be able to come here and get this training for these two years." My group interviewed with Al Rabson who was the director of that part of NCI, actually was the Chief of the Laboratory Pathology at that time, but he was handling this interface with these residents. There were six positions for the cancer institute for that year in that program and I got one of the six and I was just amazed that I had gotten into that program. Then subsequently I made a second visit to interview with individual lab chiefs and that is when I met Ira [Pastan] and that was the first insight I had into the actual research that was being done in the NCI at that time.

JG: What were some of your first impressions of Ira and of his lab? How did he explain or describe what his group was doing?

MW: Well at that time, and this was probably, maybe two years, it was 1970, so maybe two years after the lab was started, and it was already split into the animals and vegetables. This was because Ira had an interest in cyclic AMP and cyclic AMP had a known role in endocrinology in regulating things in the liver and many other cell types and in addition it had been discovered that cyclic AMP had a role in bacteria. Ira was really interested in that. Ira is a very bright guy and so he obviously saw here is a way, like so many things that have been done subsequently, to use a model organism that is very simple and figure out how something works in that system, and then it could be expanded into what

mammalian cells do with it. The lab was clearly separated up into these two areas which Ira totally encompassed both of those areas, but Max Gottesman was already there and responsible for the bacterial part of things, and then Ira was mostly running the animal side of the thing. He had just maybe nine months or so earlier had George Johnson join as a fellow and Wayne Anderson was there as well doing the biochemistry of cyclic AMP as a starting point in the endocrine system that Earl Sutherland had originally done work related to signaling of hormonal signals. When I interviewed there it was a very small outfit. Ira had this little tiny office and we talked about the role of this weird little molecule, cyclic AMP, and these different things, but Ira was also interested in what I knew. I said what I am really interested in is learning how to do research. I have had limited opportunities up until this time and I guess partly my advantage was that I was young, and I was younger than everybody else, so he thought that . . .

JG: And they were young to begin with?

MW: Yes. It was just that I was twenty-four at the time, or something like that, and so the other thing was that I had a background in microscopy and morphology and knew about this new field of histochemistry and immunocytochemistry and then I explained to him how these experiments were done and how the antibody bridge principle works, which was a new sort of concept. He was really interested in that because it meant that there might be a way to find out where in the cell some of these things were happening. I suppose that was why he was interested in putting me high on his list, but I have really no idea why he did. [Laughs] And in fact, I did not really have much hope of really

matching with any of the labs I interviewed with because they were all people who were extremely smart and educated in very famous places, but it turned out I had already been picked for the program by Al Rabson's selection beforehand, and so I was going to go into some lab. I did not know which one and it turned out I got matched with Ira.

JG: Describe the NIH in that period, in the early 1970s, and speak about what Bethesda was like then?

MW: It was certainly very different. The thing was that NIH started with this initial six buildings that they built, I guess the late 1940s or the early 1950s, or whatever, on either one or two golf courses. I could never get it straight as to actually the origins of all those things. The National Cancer Act was passed about that time. [President] Richard Nixon signed that and it plunked $1 billion into the cancer research effort and that inspired a lot of money coming into the intramural environment for building new buildings. So Building 37 was underway when I first came to NIH. Of course, I interviewed actually two years earlier and it was a long process. There were the initial six little buildings and then there was a clinical center and then Building 37 was being built. When I first came to NIH I was actually in a lab in the basement of the clinical center and it was, as it probably is now, and that is, this enormous hospital with this huge brick facade on the outside of it. And yet Bethesda itself was kind of a residential community. The downtown part of it had businesses but they were these one-story kind of businesses like pizza shops and things like that and there were very few large buildings there. Much of the surrounding area was housing developments and the other big structure that was there

was the Navy Hospital, right across the street. The Navy Hospital actually had a golf course around it, and that was one of the perks that I had when I was first there, is that because I was in the Public Health Service I could get to go play at the Navy Golf Course. It was a nine-hole golf course which was for some reason mandated that it had to be kept as a golf course for whoever had donated the land or whatever. So the green fee on that golf course was $2.00. I got to play golf and that was really kind of nice. I was very upset years later when they built the military medical school there because they built it right in the middle of the best hole of the golf course and just ruined it. [Laughs]

JG: What do you learn when you get there? You mentioned that you wanted to build on your research skills. Describe Ira and his staff and the research skills that they helped you develop?

MW: The first thing that they were doing a lot of was mammalian cell culture and that was something I had not had any experience with because I had been in a pathology environment where that was all fixed cells and fixed tissues and so we were not dealing with live cells at all. So that was the first thing—I learned how to do cell culture. Actually some of the first projects we had derived from experiments I did in cell culture. Initially I started working how cyclic AMP might control the cell cycle and that sort of led me into getting an education on how cells control their growth as well how they control their morphology by sticking to plastic surfaces that they grow on. That eventually led to an interest in how cells really control morphology and what does it mean if one looks at normal cells versus cancer cells in culture, that they have differences

in morphology and why, and what does that have to do with the disease and people. That was a big area of controversy at the time. There were several assays that had been developed that claimed to be able to show a correlative difference between malignant cells and normal cells and many of those things turned out not to be true. Many of them derived from animal models of cancer and some had to do with how cells control their shape and it turns out that the major mechanism by which that really operates is how sticky they are, how well they adhere to the plastic or the glass or whatever they are sticking on. We got into the business of cell migration and how cells move. There had been some initial work in normal cell types in those fields but that led us into the use of cinematography in doing time-lapse microscopy and several different things all of which revolved around microscopy and eventually electron microscopy.

I had been there for two years and Ira asked me to stay on one more year, and I had training in electron microscopy from my pathology experience, and so I actually set up my own little EM, not a facility, but actually the prep lab which was making thin sections and doing that sort of stuff. I knew how to do that stuff and I was actually using a microscope two floors down in Building 37 which we had moved over to Building 37 by that time. My staying at NIH at the end of that third year was the consequence of Ira deciding that this morphologic stuff was kind of useful and that it was nice to be able to correlate the biochemistry with what the cells looked like and where stuff was located and especially the electron microscopy part of it was useful. He offered to get an electron microscope and I could set it up as a lab and I could stay in a more permanent position and do that. That was another decision point for me in my career and that was—my

original plan had to been to go there for two or three years and then go back to residency and finish my residency and get my boards—a big decision as to whether to continue doing research in an environment I has having fun doing it and it was very important stuff. On the other hand to go back to a residency position and finish my pathology residency and get my boards which was an element of security. That was really a major decision point because it meant if I didn't do that I would be committed to an academic career in research. Ira actually was happy for me to go back for a couple of years and finish my residency and then come back. But I finally chose not to go back into residency and just to stay there because we were doing things that were really exciting at the time. I do not know if I would ever do that differently—now I might, but you have to make a decision one way or the other.

JG: Did you publish papers when you were at the LMB or had you published before?

MW: I had published one paper before I got there and then within that three years we probably published ten papers. So I can look up in my CV and see because there was a lot of different projects going on and the other thing was that I was sort of comfortable collaborating with lots of different people. And as Ira was expanding his lab there were people both in the animal part as well as in the vegetable part who needed morphology help either electron microscopy or light microscopy. I had collaborated with them as well as a few other people at NIH. It was a very collegial kind of atmosphere where those collaborations were easy. And unlike the world out here in academia where you are dealing with grants, it was much easier to initiate a little pilot project or something with

someone because you didn't really have to worry about where that money was coming from or to have to justify as part of a grant process.

JG: When you made that decision, and I guess it would have been 1975, when you became a senior investigator, how did you think that your career would then progress. It was a big decision to not . . .

MW: It was a very big decision.

JG: You mentioned before that your older brother was also a physician. Had he gone the clinical route?

MW: Yes, he did. Actually all of my generation was also driven by the draft and the things that it then required of you. For example, one of the things that I had applied for, which everybody coming out of medical school applied for, was the Berry Plan. The Berry Plan was to give you a deferment until you finished your residency. If you are an orthopedic surgeon, or something, you go into the Army as an orthopedic surgeon—not as just a general medical officer. That gave you then more experience in your area of specialty. That was the big advantage of doing that. I applied to the Berry Plan and actually did not get it. My brother did. He went into the Navy for two years, and however he was able to do it after his initial residency, he had switched from internal medicine to psychiatry. He was in the Navy as a psychiatrist for two years and then he came out and then went essentially into private practice. Although the place he went was actually the Ochsner

Clinic which is down in New Orleans and is kind of an academic private practice setting. He has continued in private practice in psychiatry ever since. I was sort of in the position where it was either research or go in the Army and the research opportunity was really terrific because not only was I learning how to do research and satisfying my selective service obligation at the same time but it was good research and it was well respected. I had one paper published in 1971, which represented work done back in 1969 and 1970, and then once I got into Ira's lab by 1975, I was on ten papers by that time and among them were two papers in PNAS [*Proceedings of the National Academy of Sciences*]. That also was the two areas of major interest I had which was an immunocytochemistry, of how cells move, and so myosin was one of the components we were dealing with, trying to figure out where it was in cells, and then the other one was how cells control their shape. I actually had a *Journal of Cell Biology* paper about the effects of cyclic AMP on cell shape and the distribution of microfilament and microtubules and that was in 1975. That also was about the time that we were just starting these experiments trying to track the entry of fluorescently labeled hormones into cells and that was a new technology in amplifying the amount of light coming out of a microscope and that was a real interesting area for me and so that was another of the projects that I was interested in pursuing. Those papers were not published until a couple years later but that is what we were involved with at that time.

JG: During the 1970s the laboratory is impacted by the recombinant DNA controversy and I am wondering what your observations were on that?

MW: I was out of that and the reason was that I did not really personally work with any of those techniques. The bacterial geneticists in the lab who were working with lambda, the bacteriophage lambda, were really at the heart of the technology that was involved in doing recombinant DNA. Those national controversies that started about then were by people with a longer view of nature and how things work and the relationship between different organisms. I was not that expansive in my vision at that point. I was much more focused on these very narrow areas, especially having had pathology training, of the difference between cancer cells and normal cells. That was my real area of interest and I viewed the recombinant DNA stuff as kind of "Gee, it would be nice tools if we could do in animal cells what we can do in bacteria." My guess was it was going to be fifty years before we could do that. Well I was wrong—it turned out we could do it a lot sooner than that. [Laughs] That was where people like Michael Gottesman, for example, had a much broader view of what was potentially going to be possible and he really had a better handle on it than I ever did. I really did not use the technology. I just benefited from it but I really did not use it personally.

JG: Who do you think the laboratory was competing against at that time? Was the laboratory competing against institutions like the Rockefeller Institute or Stanford University?

MW: It was not so much institutions as it was individuals. In the early days of cyclic AMP in animal cells there were controversies depending on what cell type people worked with as to whether cyclic AMP was a growth inhibitor or growth stimulator. So several other labs have faded into oblivion since then because they worked on very pivotal experiments

early on the days of cyclic AMP which have subsequently turned out to be not so important. But I can remember going to a meeting in Florida and I remember it very vividly. It was Marco Island, Florida, and Ira had been invited to come give a talk because it was the initial experiments that George S. Johnson and Ira had done on how cyclic AMP inhibits cell growth. There was another camp, one guy's name was Sheppard, and the other guy's name was Pledger. They both had published stuff about how cyclic AMP was a growth stimulator and much of it boiled down to the techniques of the assays to measure cyclic AMP and that was not an easy thing to do. It was a little tiny molecule, most of the techniques used radioactivity as a readout, and there was a lot of controversy about what the best method was to measure cyclic AMP. I had not really gotten involved into worrying about that controversy but I was sent as a representative of the lab and presented my data. Immediately the controversy came up about how Pastan's lab says it is going up, and our lab says it is going down, and blah, blah, blah. I was kind of shocked. You guys are worried about this? [Laughs] So that was the first of many times that I ended up getting an opportunity to go to a national meeting, or an international meeting, because Ira had been invited but he did not have time to do it. That was really a good thing because it gave me an opportunity. I would have never been invited myself. It gave me an opportunity to meet all these other scientists and go to these high profile meetings and that really benefited my career a lot in my overview of what the world of science and its politics are. I can remember calling up Ira from Marco Island, Florida, and saying—because I hadn't really realized there was that much controversy on whether things were going up or down or whatever—this guy Sheppard is saying that it is different from what George published. Ira said don't worry about it. Just

tell them what your data is and that is okay. It was kind of a pep talk long distance because I thought "Gee, doesn't everyone agree with us." [Laughs] This was a nice education in what science is really like.

JG: What was NIH like for a young researcher or scientist?

MW: Well it was a pretty small environment even though there were lots of buildings and everything. Ira had lots of specific connections related to either labs he had worked in or other people who were interested in bacterial genetics or interested in endocrinology. I got exposure to those people and that would frequently lead to some collaborations across campus. I got to know several other people in other labs. It was actually quite possible to be very insular, even though there were 10,000 people working on that campus or however many at the time. You did not necessarily interact with them all. The big advantage, of course, was that if you wanted to go to a seminar and hear about a certain topic there was one every week. There were enough people that they used to put out—I do not know what they do now—but they used to put out . . .

JG: The yellow sheet or the green sheet?

MW: Yes, the green sheet. It was a weekly summary of all the seminars that were going to be presented. If I really wanted to hear something about a certain topic I just walked down to Building 36, or went to the clinical center, or whatever it was, and just walked in and sat down. There was nothing formal about it at all. There were these really first line

scientists talking about . . . That was how I learned about a lot of other techniques and other strategies. By going to people's seminars and just listening to them and sitting. We also invited people that would come over and give seminars in the lab. That was a great thing about NIH. There were just so many good scientists there who were constantly giving talks that you could really learn whatever you wanted to learn.

JG: Walk me through your next position. You are chief of the ultrastructural cytochemistry section from 1980 through 1991?

MW: Yes. Things happen for strange reasons. I had stayed on because Ira wanted to set up an EM lab and so we did that and finally at that point . . . I basically viewed myself as a fellow. I was just learning and eventually some of the stuff that we were publishing and whatnot was getting some national recognition and people realized that some of the things we discovered were novel and no one else had thought about it in that way. I remember specifically one time we had a collaborative visit from Keith R. Porter. Keith Porter, I do not know if you are familiar with him, but he was the father of cell biology especially as it related to electron microscopy. George E. Palade, for example, had worked in Keith Porter's lab. George Palade got the Nobel Prize, but Keith Porter did not, and so that was fun. But anyway, Keith Porter was at Rockefeller, and then eventually I guess at Harvard. So Keith Porter actually was unlike a lot of famous scientists in that he was relatively pleasant to talk to. [Laughs] He came and visited and he had just published a paper which I had read. Those kinds of papers were in the *Journal of Cell Biology* and that is a totally different kind of journal now, but back then it

was mainly related to morphology and the biochemistry that goes with it. He had published a paper about cyclic AMP's effects on cell morphology in the area we worked in a lot. I looked at his data and said "Well, we knew *that* two years ago." So eventually we published a paper in the *Journal of Cell Biology*. He came and visited and we were sitting in the conference room and were just discussing some of our findings and Keith Porter was saying that cells that are flat like this don't move as much and they don't grow as fast. And I said "Oh well, that is obviously why because of such and such." So he implied "You know a lot about this stuff don't you?" He said, "Where did you learn your cell biology?" I had really not thought anything about it, that I knew anything unique. But he was actually discovering some of these things himself for the first time. And I do not know if this offended Ira in some way because I said "Well, I learned a lot of it with Sam Spicer." The guy who I had worked with in Charleston. And in truth I guess I learned some of it with Sam Spicer, but I learned a lot of the cell culture stuff with Ira. Keith Porter knew Sam Spicer and he said "Oh, well okay. He is in South Carolina." But the realization came to me—because I had great respect for Keith Porter, he was a very famous guy—that the work we were doing was actually on the cutting edge. These well-known people . . . I had never gone to school at Rockefeller or Yale or Harvard or anything and yet these people who were the famous people in that field really did not know a whole lot more about it than I did. So that gave me the feeling that being in Ira's lab, in that environment, and having the freedom to do the kind of work we were doing, was really a very good thing.

JG: Tell me about the video intensification microscopy.

MW: Right. So this gets back to my engineering interests. Ira was interested in looking at where insulin goes in cells and at the time, and this is actually forgotten now, but at the time there was a fairly major dogma in the endocrinology field that hormones, even hormones that are peptide hormones, like insulin, would bind to cells and then go into the nucleus and control the regulation of genes in the nucleus directly. There had been quite a controversy in the field of steroid hormones that in fact that was what was going on, and in fact it turns out that in steroid hormones that is what is going on. They actually go inside and there are receptors that they interact with in the nucleus itself, and that directly regulates gene expression. Well that is not true of most peptides. That was before the days when people actually realized about these concepts of signaling cascades that come from the outside of cells. Ira was very attuned to that because cyclic AMP was viewed as a second messenger. There was a receptor at cell surface and then that adenylyl cyclase created this other signal and that small molecule went into the cells and eventually interacted with DNA, or whatever it did, in the nucleus. But that was not the dogma for these peptide hormones. And so our interest was initially in looking at insulin and its interaction with cells.

Well we had just gotten some really good fluorescent microscopes, Zeiss microscopes. Really a lot of this is driven by the instruments you have available to you. So we had gotten some really good Zeiss microscopes where we could look at live cells. We had employed fluorescence as a way of detecting things and put some fluorescent markers on insulin, or on other types of little peptide hormones like that, and tried to see what they

did when they interacted with cells. Of course, it was very hard to see because you are talking about a single molecule maybe having five or, at the most, ten molecules of a fluorochrome, one of these markers, and that is not a whole lot of fluorescent light that it produces. So we started thinking about how we can we make this better and one of the challenges is that if you turn the light up brighter it actually kills the signal because the chemicals that are putting out the light, the flourochromes, actually get bleached, they get damaged chemically. You can't turn the light up so the only option you have left is to somehow gather more light that is coming from that and amplify it in some way.

We looked around in the technology of the world as to how can you amplify light and that actually was something that was being done by astronomers because they had the problem similarly that they could see a star but it was not very bright and they could not get photographic film sensitive enough to record an image. They had invented this technology called image intensification. The company that had made the most successful image intensifiers for astronomers was EMI. It is sort of the RCA of England. They had these big image intensifiers which were sequential stages of fluorescent screens and high voltage electronic accelerators, and then another fluorescent screen, and a target, and so forth. And these were not video cameras. These were just big boxes that you put a little bit of light in one end and you get a lot of light out the other in the reference to the x-y positions of an image. I actually went to Cambridge to visit the EMI factory when I was going over there to a scientific meeting and looked at one of these image intensifiers and they were very expensive. They were something like $25,000, but in those days that was a lot of money. We eventually were able to purchase one and it had this enormous power

supply. It was not transistorized, it was all vacuum tubes. This huge image intensifier weighed about fifty pounds or so and we had to make adaptors to microscopes and things. But the nice thing about it was that at the end of that whole process we could get an image of these little tiny dots that were associating with cells that you almost could not see by eye. If you really, really tried with low magnification eye pieces, and whatever, you could maybe see them. This thing would actually give you an image—so that was terrific.

But in actual fact some of this technology was just at the brink of being classified. That was because there was a lot of interest in developing night scopes for the Army. The way I found out about this stuff was I called up a guy. That is one of the advantages of being in Washington . . . I called up a guy over at what was called the U.S. Army Night Vision Laboratory and I was discussing with him this technology of image intensifiers and finally at the end of the conversation he said "How did you get my phone number?" It turned out that the person who had told me did not actually realize that this was a classified lab and that the technology they were working on for night scopes was in fact not out on the shelf somewhere. Our application of hooking this thing to a microscope was a new idea that nobody had actually employed.

Subsequently companies began to make video cameras that had these little intensifiers. RCA made one for surveillance purposes so you could get a picture of a parking lot with no lights on. We went further from our initial big image intensifier to these video cameras and now CCD [charge-coupled device] cameras are really, really sensitive. It is

no problem. You do not have to use intensifiers anymore. But that was how it all started from a technology standpoint and it was driven by the need to be able to see these little tiny molecules—collections of molecules of hormones bound to the surface of cells to try to figure out where they went without killing the cell in the process.

JG: Walk me through to 1991 and your decision to leave the NIH.

MW: Well, that decision was very much just financially driven. My oldest son was getting ready to go to college . . . There are certain advantages and disadvantages to being in the intramural environment at NIH especially for someone who is an M.D. where you have the other option of going out into the academic world or going into industry. When I was first married and had little children and living in the Bethesda area—which was not all that expensive to live in—you could actually swing it on the kind of salary that you could make. I was a Commissioned Officer and so basically it was like being in the Navy. It was not too much of a stretch. But by the time I had been there fifteen years I was making about half of what I could be making somewhere else. In looking forward to when my kids were then going to have to go to college—my oldest son and my daughter were fifteen months apart, so they were both going to be hitting college about the same time, and then I had another son who was a few years younger—it was very clear to me that there was no way that I was going to be able to afford sending them to college on the kind of salary that I was making at NIH. I decided to stay there until I could retire at twenty years which, because I was in the Public Health Service Commission Corps, was a very big incentive to stay. I think I would have left earlier, and some friends of mine who

were in a similar position, some of them left after ten years. The decision was basically either leave after ten years or wait until twenty.

JG: Right.

MW: I interviewed for several jobs during that time—some as department chair at various places. It was just worth it from a security standpoint to retire and be able to get that retirement income that is why I stayed on for twenty years. But there was not much of a decision that had to be made in terms of the amount of money involved when your kids go to college. You are devastated by the bills you have to end up paying and so that is why I left and went back into an academic environment. If I had made that decision to go get my boards early on, and finish my residency, I could have then had the option of either going into an academic department or going into private practice where I would make four times as much instead of two times as much. I have still stayed in academic medicine and I have been happy doing that. It has worked out pretty well. Initially I went back to Charleston, which was the department where I had done my residency, and was offered a job down there to help with a research program. Then subsequently about six years later a friend of mine who was the chair of that department actually was offered the chair of the department up here at Wake Forest which is a little bit more well known, higher level of grant funding kind of research institution, and so for that reason he decided to come here and I came with him. So that is why I am at Wake Forest now. It had some other incentives like tuition concession for your kids to go to Wake Forest undergraduate and it is a really good school. My youngest son ended up going to

undergraduate at Wake Forest which he was very happy about when he finally got there because it is a terrific school . . .

JG: Do you have more time for a few more questions?

MW: Sure.

JG: You have 427 publications. Talk about the role of citations in science and how that has changed over time?

MW: Well it depends on the field. The biological medical research field has one sort of standard and then there are other fields like chemistry, which from my understanding, people publish ten times more papers than we do in biology. [Laughs] I think it is different with each field of science as to what the impact of that really is. I know that in the academic environment, extramural universities, that the number of publications is a significant factor, it is sort of a yardstick that people use to measure productivity. The other factor is grant funding. Those people have two different things going on at one time and they therefore tend to have fewer papers published because they are spending so much of their time trying to get grant funding. In the intramural program at NIH there was no issue about grant funding. It was an issue about being productive and publishing papers. The measure of productivity was really publications at NIH. There was a tremendous amount of emphasis on that. Now subsequently, with all of the different peer review systems they have got now it may be different. It was not at all unusual to publish

ten papers a year and basically you did research and that was it. You did not do teaching, you did not do clinical activity except for some of the people over in the clinical center, they probably did, but it was mainly just the research activity, the measure of which was publications at the end of it.

So it is different in that environment than it is in this extramural environment and in the universities where there is a goal of having people who are physician scientists. People who have three different agendas, and sometimes four, that they have to match. There is clinical activity which actually is a major generator of money for the support of the institution. There is teaching which usually does not generate any money and therefore it is somewhat de-emphasized especially in private institutions, and yet many of the faculty still have to do it. There is research which is measured more in extramural environments by money, by grant funding, than anything else. And then there is administrative duties and that is sort of just tacked on at the end of it and can then occupy an enormous amount of your time but really does not reflect any kind of funds generation. That is really especially in a private institution. The first institution I went into was a state institution and so there was an emphasis on generating funds to cover the budget. It was not as severe as it is in these private institutions where they do not have any other alternative except to try to balance the budget every year on what kind of money the faculty can generate and that is between clinical grants and then in some cases clinical trials with industry or something like that. So teaching ends up being the reason for having the institution exist, being an educational institution, and yet it generates no money and therefore it has the lowest priority. In my situation most of the teaching I am involved

with is with graduate student teaching, whereas a major chunk of the clinical faculty are involved with medical student teaching. Of course there are two parallels. One is teaching one-on-one in the clinical arena with residents, versus teaching one-on-one with graduate students and postdoctoral fellows in your lab when you are doing research. It is hard to quantify, and what happens in private institutions is they have an excessive need to quantify and micromanage things. They want to know where is the money coming from and how much of your time you spend on whatever activity. One agenda says don't spend so much time doing that because it does not generate any money. Another one says well do that because that makes us famous because it is an important mission of the institution, whether it is teaching, or research, or whatever. There is this constant conflict about what a faculty member is supposed to spend their time doing. I sort of try to ride the wave in between all of them and do a little of everything. [Laughs]

JG: You had gone to NIH as a very young researcher and you leave the middle of your career—

MW: Yes, I was forty-five.

JG: What did you learn about responsibilities to younger scientists? How do you teach young scientists and researchers to scrutinize errors and also to balance both skepticism with creativity? And what is the status of the profession?

MW: Right, well in the case of graduate students, who are the ones that are basically doing a lot of the research, their training beyond these formal courses is really one-on-one training that is almost train by example. They see what their mentor does. You have some conflict that occurs. How does the mentor handle it? Not all mentors handle things well. They also have interaction not only with other faculty in their department but they also have interaction with, in the case of graduate students, with a thesis committee. The thesis committee is five people, not always from the same department, some from outside departments, who they can talk to. Those people can talk science, they can talk ethics, they can talk personal stuff. I have often wondered in a way why people want to go to graduate school at all. [Laughs] If this is a career that you want to go into, that is, emulating the kind of career that your mentor has . . . So your mentor, your primary advisor, is existing in this bizarre environment in which they are allowed to apply for money outside, that is basically it, their guarantee of salary, security, space, support is very tenuous in this kind of private institution where I am now. You look at the graduate student and say you want to be like this person who has no job security, who is dependent on whether they get the next grant funded, who submits ten grants before they will get one funded, who is constantly worrying. You really want to do this? It turns out that in this kind of . . . We are sort of a middle of the road kind of institution, and I'll probably say that ninety percent of our graduate students end up going into industry. Now they don't do it immediately of course. They go do a postdoc fellowship, or something like that, and they really see how broken the research funding situation is in this country. They are smart enough to realize that this maybe is not such a good decision.

Now when you are dealing with physicians, and especially with MD/PhD students, we have many instances in which they do the MD/PhD program because often they will get their stipend paid for and they don't have to pay for medical school—but of course they are extremely bright students. That is how they get selected for that program. They go through their research time with their research mentor where they are like a graduate student basically. They have done a couple of years in medical school. They go into this research program and they can be there for four or five years and then they come out and they do their clinical years in medical school. The question is how many of those people actually go into academic medicine? A lot of them do not. A lot of them come out, and you would think here they dedicated their lives to this idea of being a physician that does research, and they learn that in the current environment of pressures of how this stuff is done that it is not such a great career. It is a very insecure competitive kind of environment where they have an alternative and that is just to go into clinical medicine. For all of its disadvantages and all the red tape and everything that clinical medicine has in it today a lot of them still choose that. Especially if they are in a clinical specialty like pathology, which tends to be a fairly intellectual enterprise anyway, and where you can almost do it and keep your sanity as opposed to a surgeon who is showing up in the wards at five o'clock in the morning and going home at midnight. These kids are not dumb. They can see what this does to people and how really broken our research funding mechanisms are in this country. And they end up getting attracted to the drug industry and that is the only place that has money. So you have the choice of government labs which depending on the political climate at that moment you are dealing with either the disease of the month or what the latest pressures from Congress are; then you have the

academic environment where you are constantly being berated about getting funding to do anything other than doing your clinical activity; and then you have physicians in drug companies where you can have a nine to five job and do not go insane. [Laughs]

So it is really amazing that anyone ends up being a physician scientist in the first place. That was the whole idea behind that clinical associate program—the reason I ended up at NIH in the first place. It was people who had the insight and the forethought to think that we have got to train people who interface between the world of clinical medicine and the world of research. It is almost an impossible task. Ira is one of the few people who has maintained his sanity in the middle of all of that and continued to be productive for years and years and years. There are many other people who have just given up because it is just so difficult to do that.

JG: That leads into my last few questions. How do we attract young students into the sciences?

MW: So the basic attraction to science is taking advantage of the curiosity of young people. When you are just learning about the details of the world young people can have an awful lot of enthusiasm about being curious and wanting to know how does something work and they can have the luxury of focusing in on a really narrow little area. It is like when I was a kid and I would take a clock apart to see how it works. Of course, that doesn't mean I could always get it back together. There is inherently in young people, especially smart-oriented young people, who are able to think and communicate with others, that

discovery. The idea would lead some people into forensic pathology. The clues that are unfolded in front of you in trying to find the answer that is hiding there somewhere. There is a great drive to be involved in that process, so science has that really going for it, because it does not discriminate in terms of your inherent talents or anything like that. If you have got the curiosity the answer is there. It is just hidden from you and if you use your brains you will figure out a way to get to it. Whereas lots of other things in society depend on all kinds of political and social factors that nobody has any control over. There is a big impetus when people are young to be curious and want to be involved in something where they enjoy going to work. They enjoy the challenge of figuring something out.

Now when they get into the middle part of their career is when reality sort of strikes home and that is that the real world has a lot of other pressures involved in it. Pressures of surviving in the security of a job and being expected not just to be curious anymore but doing seven million things worth of administrative paperwork or being interested in the fiscal condition of your organization, especially big organizations, which are really a pain in the neck. And trying to get consensus—as they say a camel is a product of a committee trying to create a horse. It is that same kind of thing and then it gets into human psychology. That is very frustrating because it is exactly opposite of the curiosity about the way things are already in existence in nature, and nature is not trying to hide them from you. You have got to figure out how your curiosity can be allowed to function whereas in mid-career you are suddenly inundated with all these other responsibilities and all these other priorities and it can very easily quash your curiosity. That is where

somebody like Ira is so unusual because he continues all throughout his career to have this immense curiosity about nature and about how mechanisms work and how to go about uncovering that. Of course, he is extremely bright, so that helps, because then he puts out feelers into other disciplines and other fields and encompasses those as well and understands how they work. I used to just sort of give up. I would start to try to understand some arcane part of physical chemistry and I would just give up and say I can't do this. [Laughs] But that never seemed to happen to him. He was always able to understand and get the real message out of some other discipline. Anyway getting young people started in science isn't as hard as maintaining careers in science and the pressures that end up on people as they go through careers become overwhelming and they just lose their curiosity. It is very sad.

JG: What about your hobbies and your other interests? Have you continued your interest in music?

MW: Yes. I play the piano all the time and it is a very relaxing activity and I enjoy that a lot. I also still like doing things that are sort of engineering related. I still build model airplanes, radio controlled model airplanes, and I occasionally get an opportunity to fly them. I enjoy fishing a lot and I still do that. I actually now have got some property in the country where I have got a big pond on the property and am doing all sorts of scientific experiments about my fish populations and what happens to them.

JG: Are you really?

MW: I am tagging them and figuring out how they are expanding and contracting and how they are related to each other. It is a lot of fun.

JG: So you are really tagging them?

MW: Yes. I actually have an aquarium in my house where I have some of the tiny offspring from one of the species and I am trying to figure out which species it is now. I have had a long standing interest just in nature in general. In gardening, in trees and rocks, and it is fun to live in an area like I do. It is very close to a rural environment and so I am able to get to that pretty quickly, which is another of the reasons I left Bethesda. Washington had changed, or Bethesda had changed, from a sort of sleepy little residential community to an urban center and that is an entirely different environment. Not only is it more harrowing on your senses but it is also extremely expensive and that was one of the reasons to leave also. Anyway I still do those sorts of things and now I have grandchildren and so they are a lot of fun to play with. I have four grandchildren. I am building a little cabin out on my property in the mountains, so it is actually a lot of fun.

JG: Last question. If you had one piece of advice, one lesson learned that you would like to pass on to a future scientist or researcher operating ten or twenty years in the future what would that be?

MW: That is a good question. Well I would say that just looking back at my career as to what has been positive, and what things I have learned, one thing is being a good collaborator. If I have had any success much of that success is the function of working with other people. That was one of the surprising things I ran into when I came back into academic medicine is that that is not necessarily an attitude that is shared by a lot of people. Even in this extramural environment, being willing to help other people without any kind of guarantee of return or anything, just using your expertise in an area you know a lot about helping someone who doesn't know a lot about that and making their life easier, it will always come back to you in a positive way whether it is five or ten years down the road. That was partly something I learned at NIH. The intramural environment was an extremely collaborative environment. People could walk down the hall and say "would this work"? Here I have this problem and this technique and I am not real familiar with it but I understand you do it some and you know is this a strategy that might work? And then the people would sit down and say sure, that will work, and I will do the pilot experiment for you. There was no issue of can you contribute some money to pay my technician or can you buy some supplies for me—nothing. The financial part of it never entered your head in that intramural environment and so it was by far the most efficient way to do research that I have ever been exposed to. Things got accomplished in a much shorter length of time with really high quality results. I would say to somebody who is just starting in the career to value collaborative interactions. Do not be so self absorbed as to not share your data with other people, to not share your expertise. Be willing to put in a little bit of effort to help somebody starting up because even if that person does not pay you back in the long run somebody will. It really leads to positive things. I would

say that it is an important lesson to be collaborative and not be necessarily as ego driven as a lot of people have to be in this kind of environment.

JG: Well thank you very much. It was very enjoyable.

MW: Sure, thank you.