NCI Laboratory of Molecular Biology
Oral History Project
Interview #2 with Dr. Michael M. Gottesman
Conducted on February 2, 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 February 2, 2009, and we are in the offices of the National Institutes of Health in Bethesda, Maryland. This is part two of an interview that began last Thursday [January 29, 2009]. 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: Thank you. Last Thursday we spoke a lot about success and I thought today we would start with a notable failure. This might be an experiment or something in life that didn't go as planned. My question is how did the disappointment affect you?

MG: I think most scientists try to turn failure into opportunity. One of my first supervisors, Bert Vallee, at Harvard [University] used to say, "What we have here is not a problem; it is an opportunity." Obviously a lot of experiments fail to give you the expected result but if they are well designed they give you a meaningful result that will allow you to move forward in the science.

My first major research project, which was to look for proteins that were excreted by malignantly-transformed cultured cells that might be angiogenesis factors, that would

stimulate angiogenesis, I would say was a failure. We did not find any such proteins. We did find some unusual secreted proteins that turned out to be lysosomal acid proteases. That project went about as far as I could take it in terms of characterizing the proteins and trying to figure out their function. We eventually dropped it because it did not seem to be leading to an understanding of either angiogenesis or invasiveness of tumor cells.

JG: At what point do you switch to something else?

MG: I think to some extent you switch when you have something better to do. In my case I think I began to work on the somatic cell genetics of transformation and drug resistance. My work on the cathepsins, the secreted cathepsins, just gradually became less and less important. It is also tied, to some extent, to personnel in the laboratory. If somebody comes in and they are committed to a two or three or four-year project working on something you tend to allow them to complete that project before dropping the project entirely. Although you do want your fellows working on those things that are of most importance to you there are practical realities of people completing work that they started.

JG: When we left off last week we were talking about your work with the Laboratory of Molecular Biology between 1976 and 1980. One of the things that is interesting is that for a period there were three people with the same last name in that laboratory. Describe that situation.

MG: Max Gottesman was the first person in the lab. He was recruited by Ira [Pastan] very early on because he wanted someone with a really basic understanding of molecular biology and bacteriophage. Max was one of the founders of the field of integration of bacteriophage into the genome.

JG: What type of scientist is Max?

MG: Max is a brilliant, very entertaining, very sharp-thinking scientist who I would say does not suffer fools gladly and seems to really enjoy manipulation of ideas and thinking about ideas. He, himself, was in medical school and one of the stories he likes to tell is about being told that they would give him his M.D. so long as he agreed not to practice medicine but instead go into molecular biology, which is what he did. He got a Ph.D. in that area. Susan actually came to work with Max on bacteriophage. When I joined the lab in 1976 Max was there and Susan was there and then I was the third Gottesman.

JG: Did that create confusion?

MG: It created some confusion. In order to dissipate some of that confusion we wrote a paper together. I was then working, as I said, with Marty Gellert before I joined the lab. That was, actually, earlier in the 1970s. We published a paper which was Gottesman, Gottesman, Gottesman, and Gellert, which was viewed alternatively as a legal firm or a funeral parlor. [Laughs] The intent was to establish that we were independent people. I

was the first Gottesman on that paper. It was about a bacteriophage called lambda reverse which had this peculiar property of being able to grow even though it was recombination deficient on recombination-deficient strains because it had picked up a previously unknown recombination system from bacteria.

JG: In 1980 you become chief of the Molecular Cell Genetic Section. Describe how that came about and the aspirations of that section?

MG: Initially Susan and I were recruited by Ira to join the laboratory. Part of the understanding was that we would have permanent or tenured status when we came. Ira and Al Rabson, who was the division director at the time, were able to arrange that. I don't know the details of how that happened. Subsequently I discovered that all those appointments are approved by the scientific director so there must have been some paperwork process. We were quite junior at that point; had not published a lot. Yet it was wonderful to have a sense of stability that came with a tenured position at the NIH. In 1980 my responsibilities were expanded and I was given a section to oversee. Along with it went some additional space.

At that point, I think Walter E. Heston, who had been Chief of the Laboratory of Biology, had retired and Ira was given additional space to grow his Laboratory of Molecular Biology. Some of that space was given to me as part of the section and it included a technician, a fellow named George Vlahakis, who had been in Walter Heston's group, and was a very accomplished tissue culture technician and cytogeneticist. I had at that

point one or two post doctoral fellows and the opportunity to start recruiting more people. We were still working on secreted cathepsins at that point and working more on developing somatic cell genetics in cultured cells and particularly doing gene transfer and selection experiments to see if we could get CHO [Chinese hamster ovary] mutants that were drug resistant. That work gradually became more and more successful. In the early 1980s we were approached by Bruce Chabner, who was the division director, he was a peer of Al Rabson's. The vision was the vision of chemotherapy, I think, and was much more focused on treatment of individual cancer patients and suggested that our work on drug-resistant cancer cells might be relevant to why drug resistance was such a problem in human cancer and asked if we would pick this up as a project.

JG: Describe the challenges. What is the problem with multidrug-resistant cells?

MG: The issue is that there are many treatments for cancer that are actually quite effective in reducing the number of cancer cells, and sometimes, apparently, eliminating them completely. When a patient who has a tumor that can't be removed entirely by surgery or local radiation, in other words, it has spread locally or metastasized elsewhere, but needs to be treated, about the only treatment available is chemotherapy. Nowadays people try immunotherapy and other biological therapies like cytokines. Ira has begun to work on immunotoxins as well. But, generally, chemotherapy is the treatment of choice. For some tumors, like childhood leukemias and testicular cancer, there are dramatic responses to chemotherapy. Anywhere from eighty to ninety-five percent of people will be cured with those diseases.

Sometimes tumors recur, and when they recur they are very resistant, not only to the chemotherapy to which they were initially exposed, but to all the different kinds of drugs, and that has been called multidrug resistance. It was not clear in the beginning whether that was the result of multi-step selection, with many different drugs over a long period of time in the patient, or whether they were a single mechanism of multidrug resistance. In addition, a lot of tumors simply do not respond to chemotherapy to begin with or respond poorly. Solid tumors, the so-called solid tumors like kidney cancer, colon cancer, lung cancer, liver cancer, pancreatic cancer, and brain cancer, basically do not respond very well to chemotherapy. You will get some response but not a great response.

We talk about the first kind of resistance, that is, after an initial response the patient goes into remission and then resistant cells grow out, as *acquired* resistance. The second kind, that is, resistance that is there de novo in the tumor, as *intrinsic* resistance. It was not at all clear, and still is not actually clear, whether those are related phenomena. In other words are the mechanisms that cause acquired resistance already expressed in some tumors that are intrinsically resistant. We began to work on acquired resistance and actually, with Ira's help, we got together a group of people who were in the lab and in other labs who were interested in trying to solve this problem using the genetic approaches that we had been developing in the laboratory.

JG: What is the gospel of Bruce Chabner?

MG: The gospel, according to Chabner, as usually stated is "Resistance to chemotherapy is an impediment to the successful treatment of human cancer." I used to call that, and so did others, the gospel according to Bruce Chabner. That is still a correct statement. Almost all patients who die of cancer die with chemotherapy-resistant tumors because chemotherapy is virtually universally attempted on most patients with cancer. You could see that as chemotherapy failing in those patients and, therefore, drug resistance being the main reason for their death. It is a little bit of a chemotherapy-centric view of the world. For a chemotherapist that is how they think.

That was a sentence or statement that has appeared in probably several thousand papers in which people study drug resistance. They start by saying, "Resistance to chemotherapy is an impediment or a barrier to the successful treatment of human cancer." We began to work on that and we had a specific model in mind. We were going to isolate drug-resistant cells. Unlike most people who had attempted this in the literature, and I should say the background here is that there are probably two important discoveries relative to multidrug resistance. The first was a finding by a Danish scientist named Keld Dano, D-A-N-O, in the early 1970s, that you could isolate cells and tissue culture that were resistant to drugs like anthracyclines, doxorubicin, probably at that stage it was only daunorubicin, and that they appeared to express an energy-dependent efflux system which was really a brilliant understanding of what turned out to be important.

It was not clear what the range of multidrug resistance was but there was an energy-dependent efflux system. Then in the late 1970s Rudy Juliano and Victor Ling

published on some multidrug-resistant Chinese hamster ovary cells that biochemically had a protein associated in their membrane which they called P-glycoprotein which they saw in the multidrug-resistant cells but not in the sensitive cells. They just ran normal gels of plasma membranes and there was this big new band that had not been there before. There was an association of this protein with the drug resistance phenomenon and they called it P-glycoprotein for permeability glycoprotein thinking that it was an uptake defect and not really harkening back to the work that Dano had done showing that, actually, the problem was that there was an increase in drug efflux.

The question is whether or not this protein was responsible for the drug resistance. It was a correlative observation. Whether it was responsible for the whole phenotype of multidrug resistance. Whether this was a phenomenon limited to the peculiar situation of Chinese hamster cells or was true in human tissues as well. We set out to develop cell lines that were human cell lines that were multidrug resistant. I had at that point one of my first fellows in the lab, a fellow named Shin-ichi Akiyama, who was a Japanese scientist with an interest in somatic cell genetics. What he did was he looked to find a cell line that we could get that would be pretty sensitive to drugs and which we could select for resistance. He must have looked at a dozen or so different lines and found that the one that served our purposes best was the KB cell line, something called KB, which was supposed to be, according to the ATCC, which is the catalog of cell lines, a nasopharyngeal carcinoma.

Subsequently, maybe a couple of years later, we discovered that it was a cell line called HeLa, which is a standard cell line that is used in many laboratories. About fifty percent of the cells that are currently grown that have other designations in people's tissue culture facilities and in their freezers, they are called by other things, but are actually HeLa cells. They are able to contaminate existing cultures because they grow faster. They are quite drug sensitive. They clone very nicely. It is easy to get nice individual clones growing from a single cell. They are a wonderful cell line for doing the kind of work we wanted to do. We essentially rediscovered that HeLa cells were good to work with in tissue culture but they were called KB.

Actually, it is a source of some confusion. We try whenever we publish a paper—they still have KB designations—we always say in the paper that these are actually a sub-clone of HeLa cells. They were sent to us by the American Type Culture Collection. They were, in fact, HeLa cells. There is lots of evidence for that in terms of cytogenetics, gene expression patterns, DNA polymorphisms that are specific for HeLa cells.

JG: Is that something that is common in scientific research that you have conducted.

MG: It is quite common that the materials that people work with have properties that are unexpected or unknown and that there are contaminations. You can even get viral contaminations. Some cell lines are contaminated with mycoplasma which is an organism that grows in tissue culture. In this case it did not really matter for our studies

but it is important for people to know that these are HeLa cells because if they study them at some future time that information is useful to them.

JG: If the experiment had turned out differently you would have reported that it had not worked with that cell line when, in fact, it was another cell line altogether?

MG: Our main interest was in finding any cell line. For example although KBs were supposedly nasopharyngeal we were not willing or interested in drawing any conclusions about nasopharyngeal cancer but others might be. Someone interested in nasopharyngeal cancer could get the cell line from us under the assumption that it was a nasopharyngeal cell line. I think it has been incumbent on us to try to make it very clear that this is not a nasopharyngeal cell line even though it was provided to us under that rubric.

JG: Describe Dr. Akiyama.

MG: Akiyama was a very, very careful scientist. He cloned all the material that we started with. He isolated single-step mutants and we discovered two varieties as I have told you about from our Chinese hamster studies. Those that were specifically resistant to colchicine and those that were cross-resistant to other drugs. We wanted the cross-resistant ones; we wanted multidrug resistant ones. We imagined that if we continued to select for the same phenotype, that is the multidrug resistance phenotype, that we could select cell lines that would be useful for isolating the gene because at that

point Bob (Robert T.) Schimke had already published on methotrexate resistance which was due to amplification of the dihydrofolate reductase gene.

We thought we might be able to amplify either the gene or the gene expression that was responsible for drug resistance. This was an unbiased approach to looking for drug resistance genes. We selected cells in multiple individual steps cells that had increasing resistance to a specific drug. Now a lot of people will put drug in a tissue culture and then see what survives and then add higher concentrations of drug. What you end up with is a mix of different cells that are able to survive selective conditions. In our case, we picked individual clones, characterized them, and then reselected those individual clones. It was not a mass or a bulk selection; it was a selection of individual clones. The reasoning behind it was that that would allow us to amplify a single gene that might be responsible for resistance. As it turned out it did. Initially, we looked in those cells . . . This is work that John A. Hanover did. John was a postdoc in Ira's lab. I think you may be talking to John as well?

JG: I spoke with him, actually.

MG: You talked to him. His job, because his background was in glycoproteins, was to see if we could detect this P-glycoprotein which was already in the literature in these cell lines. We were unable to. We had pretty highly-resistant cell lines. We did not have P-glycoprotein. In retrospect it turned out that the problem was with the techniques we were using. This is a protein, a high-molecular rate protein, when you boil it in the buffer

that you need to put it on the gel to see the band on the gel, it aggregates, and so it does not enter the gel. What we were doing was changing the protein in a way that did not allow us to detect it. At that point we thought we had some unique cell lines that did not express P-glycoprotein. We started to see if we could identify what the responsible resistance was.

Then I would say serendipity struck. I was at a meeting—a Gordon Research Conference. These are meetings that are put together by the Gordon Foundation. Small meetings where scientists talk about their work. I think it was a meeting on somatic cell genetics. One of the posters was by a young postdoctoral fellow named Igor B. Roninson who was developing techniques for identifying amplified genes. Since we had set up these cell lines with multiple steps so that perhaps the genes that we were interested in had been amplified we said "Would you be interested in looking at our cell lines?"

He began to use his technique which was a clever technique involving isolating DNA from both sensitive and resistive cells, digesting with an enzyme, and then denaturing and renaturing the DNA, and then cleaving it with an enzyme that cleaves single-stranded DNA. The idea is that anything which is present in high copy number is more likely to renature because of the number of fragments available. If you have twenty copies of a gene you will have twenty fragments on each DNA sample that could find each other, as opposed to a single-copy gene, which is only one fragment. The conditions were set up so that single-copy DNA would not have time to renature and the multi-copy DNA could renature and then would be resistant to the enzyme.

You digest away everything that is not multi-copy and you get gels that show bands. In the sensitive cell you see some bands that correspond to known repetitive sequences in the human genome and in the resistance cells you see the same bands plus some new bands that correspond to the amplified genes. You cut them out and clone them, sequence them and so on. That was a clever technique. It is, again, an unbiased technique. It is just looking for amplified genes, assuming there are amplified genes, and there were.

JG: What year did you meet Dr. Roninson?

MG: Good question. It must have been in early 1983 or something like that. When I look back at this strategic plan there is no mention of this technique. You can see that we were thinking along the lines of amplification and gene transfer to detect amplified genes, but not using this technique, which Igor had developed. Presumably on September 28, 1982, I did not know about this technique yet, so it must have been some time after that. The paper describing the cloning and sequences was in 1986 in *Cell.* It must have been someplace around 1983 or maybe 1984.

JG: How long did you work on this project?

MG: I am still working on this project. [Laughs] I guess we started thinking about this in 1982; probably started the work in 1983. The gene of interest was cloned and sequenced

in 1986 and then subsequently all the work was done to try to understand the function and how we could use that information to reduce the burden of drug resistance in uterine cancer.

JG: You mentioned that it was published in *Cell*. How was it received?

MG: Oh, with great interest. The story is even more interesting than that. What we did was we were able to sequence some of the cDNA [complementary DNA] fragments that we cloned out of the gel. As we got the entire sequence of the cDNA it became clear that there were, embedded within the larger sequence, homology to two bacterial transport systems. One is called malK and one is called hisP. Both of them are transporters that move either maltose or histidine into *E. coli*. Having a background in bacterial genetics was helpful because we could immediately try to understand what was going on. Looking at the sequences it became clear that there were sequences that had ATP binding sites. There are certain recognizable signatures of ATP binding. We had a homology between the ATP binding sites of a human protein and of a bacterial protein. The bacterial one, we knew the function, which was a transporter to move things into the bacterial cell. It was kind of a heady exciting moment when we discovered that. Igor and I were on the phone back and forth quite a lot about this.

JG: Where is Igor today?

MG: Igor, at that point, was at MIT, I think. He was a sort of senior fellow. Eventually, he moved to the University of Illinois, College of Medicine. Now he is in New York at the Albany Medical Center. Igor was a wonderful collaborator because he was extremely bright and read widely and had a very good sense of what was important and what was not. It was Igor who first noticed the homology among the ATP sites of these transporters.

When we got the full sequence, we were able to start thinking about whether or not the protein that we had the sequence of, which looked like it had two ATP sites, and two big transmembrane regions, so therefore it was likely to be a membrane protein, whether it was the same membrane protein, the P-glycoprotein that had been described years earlier. We had one paper, actually, with Victor Ling in which we exchanged materials and antibodies and demonstrated that what we had cloned in the human, based on an unbiased gene amplification process, and what they had observed in the Chinese hamster were, in fact, the same protein. We had a short paper together that demonstrated that. In general, there has been a lot of cooperation in this field although people are competitive because the research is important and it has impact. The people who founded the field have tried very much to work together and to acknowledge each other's contributions.

We were probably the first to make a full-length cDNA which had all the sequences and all the functionality and transfer it into human and mouse cells and demonstrate that it could confer resistance to multiple drugs. Until this point all the data were correlative. We had an amplified DNA; Victor's lab had a protein. We knew they were one and the

same except his was hamster and ours was human. What we wanted to do was show that this protein was capable of conferring drug resistance. Do you know about Koch's postulates?

JG: No.

MG: [Robert] Koch was a very famous German microbiologist who worked on mycobacterium tuberculosis. He formulated the concept of proving that a specific agent was responsible for disease. If you had the agent, if you were sick and someone cultured the agent from your pathological tissue, or your sputum in case of TB, that does not prove that that causes the disease. It is just associated with the disease. What he said is you have to isolate it from the disease. You have to be able to grow it in a pure state in culture. The equivalent for our protein would be cloning it so it is free of any other kinds of proteins and then you have to reintroduce it into the organism, in the case of TB, into an animal model. In our case, into a drug sensitive cell, and show that it reproduces all the symptoms of the disease, in his case tuberculosis, in our case multidrug resistance.

We were satisfying Koch's postulates for cloned molecules by doing that. Conceptually it is rather important in science to be able to complete that cycle. The world is full of associations which have nothing to do with causality and so demonstrating causality is important. Now that does not prove that it is important in clinical cancer and I would say that for the last twenty years we have been trying to understand what the role is of these transport systems in conferring resistance in patients that actually have cancer.

One requirement, of course, for the protein to be important in cancer is to demonstrate that it is present in cancer cells. We began working . . . This was work that Ira was extremely interested in and supported with fellows and so on. What we would usually do is, I would have a few fellows working with me, and Ira would have fellows who he would assign to multidrug resistance projects. Although Ira was directly mentoring them, they would be working with my group. One such person was Lori J. Goldstein who was a clinical oncologist. We were, at that point, occasionally getting oncology fellows who wanted to do research rotations in the laboratory. Lori's project was to isolate as many human cancers as she could, take RNA from them, and show that they were expressing or not expressing the gene for P-glycoprotein. She published a paper in the JNCI [*Journal of the National Cancer Institute*] which I still think is a classic in which she quantitates RNA expression using techniques available at the time and showed that about half of human cancers express significant amounts of Pgp. By significant we meant enough so that if that amount were present in cultured cells, they would clearly be drug resistant.

We thought that was the beginning. Again it is correlative data that there was enough expression of RNA, and as it turned out protein, to account for drug resistance in a lot of tumors that were drug resistant. What are those tumors? They are all the solid tumors that I mentioned to you: liver, colon, kidney, pancreatic cancer, not lung cancer as a matter of fact. Susan Cole and Roger Deeley, ten years later, showed that lung cancer expressed a different transport system and I will get to that in a moment. We were seeing a tip of an iceberg. Many solid tumors expressed P-glycoprotein (MDR1). Many tumors

that had been selected for resistance expressed it. Sometimes you would see a tumor that started out not expressing it but even in the absence of selection evolved into a tumor that could express Pgp. In all of those cases there was some correlation between the extent of drug resistance and the amount of Pgp that was expressed.

Early on the clinical efforts were aimed at trying to understand how much P-glycoprotein you needed and whether or not if you inhibited it you could have an effect on the efficacy of chemotherapy. The key person there was Takashi Tsuruo who was a Japanese scientist who recently died, he died this year, who was the first to observe that there were drugs that could reverse the drug resistance of cancer cells. These are cells expressing MDR1 or P-glycoprotein. When you added the drug, and he started with something called Verapamil, which is a drug that blocks calcium channels, then you could reverse resistance. He assumed initially that calcium flux had something to do with drug resistance because he was using what he thought was a specific agent. As it turned out there are so many different drugs, both anti-cancer drugs and other drugs that are handled by the transport system. What he was doing was simply giving another substrate, which was a competitive inhibitor, and the pump was busy pumping Verapamil, having nothing to do with calcium channels, and so did not have time to pump the anti-cancer drug, and so the anti-cancer drug could get into the cell. To be a good inhibitor of Pgp you can be a substrate but you should be non-toxic because, obviously, you can't be as toxic as a cytotoxic agent. These competitive inhibitors will reverse drug resistance. Later discoveries have indicated there are a whole variety of different kinds of inhibitors but

those are the major classes. So there was this phenomenon of reversing drug resistance and that looked like a great way to treat human cancer.

Some trials were initiated, clinical trials. Also around that time we had in the lab a fellow named [Antonio] Tito Fojo who was an oncologist who was one of Ira's postdoctoral fellows. He was very interested in clinical applications. He did some nice work in the laboratory on the gene amplification process and the expression in normal tissues. When he got out on his own he was really interested in it and has run a few trials. There are a few other oncologists who have really been pursuing this. A fellow named Brandy [Branimir I.] Sikic, who is at Stanford, has done some work in this area. Sid Salmon worked on myeloma at the University of Arizona. There have been isolated clinical efforts, some of which have shown some effects on reversing drug resistance, and others not very much in the way of effect. Over the years we have taken stock on why this does not seem to work as well as we expected. The obvious reason is that P-glycoprotein is not the only mechanism of drug resistance.

When you have a tumor that has been treated multiple times with chemotherapy it has accumulated many, many different mechanisms. We call that multifactorial multidrug resistance. Eliminating one of them does not cure the cancer; there are just too many other mechanisms. That is one possibility. The other is there are problems with the experimental design. Many of the tumors that people have tried to treat do not actually express P-glycoprotein. People tried to use reversing agents on lung cancer and it tends not to express Pgp which raises the whole issue of why they did those studies in the first

place. Some of it is because the technology for measuring P-glycoprotein, which can be present at pretty low levels, but that are significant. Those technologies are not great and some of the antibodies are not specific. Some of the RNA tests are too sensitive. There are a variety of reasons for people getting misinformation. Some trials have not even begun to look at whether the Pgp is expressed. They will take a tumor where maybe ten percent of the cells are expressing Pgp and assume that is representative. It is not. You would not be able to pick out a response in ten percent of the cells. A lot of the problem has to do with the agents that reverse resistance. Early on the so-called first generation reagents were things that had been identified because of other biological properties, calcium channel blockers, antihistamines, antiarrhythmics, and so on, that were in clinical use but tended to be not very specific in their action. They clearly had other actions which is why they had not been originally developed as reversing agents.

Companies began to look at second generation agents which were versions of existing compounds that had been slightly altered. For example Verapamil normally is an optical isomer that has D and L forms and only the D- form is actually a good calcium channel blocker. The L- form, L-verapamil, is not a calcium channel blocker but actually also inhibits P-glycoprotein. You could reduce the calcium channel effects but still use the same compound. Cyclosporine, which is an immunosuppressant agent, had an alternate version that had been developed that was not a very good immunosuppressant agent. It was a mildly-altered form but turned out to be a good inhibitor. The second generation agents were agents that were similar to the first but lacked the initial biological activity but were still good Pgp inhibitors. Third generation agents, where we are now, were

developed specifically because of specificity and did not seem to have other toxic effects but were specific Pgp inhibitors. The jury is still out on whether those are going to be better agents. Again it is a matter of designing the right trials. My own feeling about this is that what is needed is experiments that are done much earlier in the evolution of a tumor. Let's say early on in a tumor ten percent of the cells are Pgp expressing. Normally, when you would treat you would kill ninety percent of the cells but not the Pgp expressing ones. That is the point at which you add the agent that reverses drug resistance so you kill that remaining ten percent of the cells *not* after those cells are grown out and after several cycles of resistance.

The FDA is not particularly kind to clinical trials that add multiple drugs together because here you are talking about a chemotherapeutic and a reversing agent. Designing those studies is very hard and I think we still have not come up with an ideal study design, even for the third generation agents. What we need is a tumor that expresses Pgp where we can demonstrate that expression, either pathologically or by imaging technology, in which you can demonstrate that the reversing agent actually increases the amount of drug getting in the tumor and then see what the effects are. We need much more sophisticated study design to answer the question.

JG: Is this the work with Mark Willingham on imaging techniques?

MG: Right. One of the early questions we asked was what is this P-glycoprotein? Why was it in some cancer cells? What was its normal function? Mark was very instrumental in

answering that question. What Mark did was he used immunohistochemistry, using an antibody again that we had gotten from Takashi Tsuruo which was specific to human Pgp, and then doing an analysis of both normal tissues and cancer tissues. The distribution in normal tissues was striking.

It was in barrier organs, it was lining the GI [gastrointestinal] tract, it was in excretory organs, in the liver and the kidney, and the parts of the liver and kidney that are responsible for excretion of drugs into the bile, into the urine. It was in barrier functions, like the blood-brain barrier, the blood-placental barrier, the blood-testis barrier, blood-ovary barrier where you want to protect germ cells and fetus and brain. It was blocking uptake, it was increasing efflux, and it was affecting distribution in the body to keep it away from vital organs. That was exactly what you would predict based on a transporter that was responsible for protecting us from the bad stuff we eat everyday. In an evolutionary sense, it, or related proteins, were present in all organisms.

Clearly, the price that cells paid when they put membranes around themselves was a security system that would keep out toxic compounds. The plant world is busy making toxic compounds. The microorganisms are busy making these all the time. They are part of the war between vegetables and animals. I do not know if you are aware but one of the ways that plants protect themselves, being unable to run away from omnivores and vegetarians and herbivores, is they can make toxic materials so that when the animal eats them, the animal gets sick.

JG: Or a bad taste?

MG: Could be a bitter taste, alkaloids, or something really toxic. I do not know if you remember ever eating something that made you immediately sick. You do not eat that again. There is something in humans and in all animals called gustatory visceral conditioning. It is a conditioned response. That plant made me sick. I am never going to eat it again. Even primitive peoples are well aware of that. These are compounds that allow the vegetation to sustain itself because nobody is going to eat it. Some of them are insecticides also, natural insecticides.

Many of these compounds are handled by the transport system that we discovered in cancer cells as a way that cancer cells protect themselves. It is a really neat system. All of these ideas began pouring out in the late 1980s and early 1990s. I would say by the early 1990s we had a pretty good idea of the function of the protein, what its normal function was. We still did not know exactly how important it was in cancer but it was clearly an exciting new discovery of a whole new class of transport proteins.

As I mentioned, in the mid-1990s, in I think 1995, Roger Deeley and Susan Cole found in a lung cancer cell line, using the same paradigm that we had, that there was overexpression of another protein which was called MRP1, multidrug resistance related protein. Susan and Roger went on to characterize that protein. It turned out to have homology in the ATP binding parts and to look very much like P-glycoprotein. Then several years later in the late 1990s, Tito Fojo and Susan E. Bates, groups at the

University of Maryland and a couple other places, discovered a third major multidrug transporter which was called breast cancer resistance protein (BCRP) at the time. Now all of these transporters have ABC designations for ATP-binding cassette proteins.

It was an international congress, or an international nomenclature meeting, and for some reason, they called P-glycoprotein, which was the first to be discovered, they called it ABCB1. ABCA1 was reserved for a lipid transporter which had been discovered many years later. I do not know why that was "A" and we were "B" but we are B1. There were A through G, ABC transporters, and each had many members. Mike [Michael] Dean who has been doing the enumeration of these transporters in the human, he is up at Frederick, found that there are forty-eight human transporters. So suddenly, in a matter of years, at the end of the 1990s and early 2000s, we went from having one or two or maybe three transporters to having forty-eight transporters. There was no reason to think that any of them were any more important than any others.

We knew that the first one we had discovered was probably the most active, had the highest turnover number, had the broadest spectrum of resistance, which is why it pops up whenever you select. We did not know whether the others were contributing in some way, certainly to the metabolism of drugs and maybe to resistance in cancer. One of the things we have tried to do is understand the array of different transporters that are responsible for resistance. It still looks like B1, C1, and G2 are the most important. Certainly in clinical cancer G2 and B1 appear time and again and seem to be playing an important role. The other transporters were a little bit mysterious. You could

demonstrate individually that if you transfected, if you took the gene and moved it into a sensitive cell, that you could get some pattern of drug resistance. Even in a few cases you could select for that pattern of drug resistance and get increased expression of those other transporters. We wanted to get some sense of how many of these transporters were likely to confer drug resistance.

I had two fellows in the lab, Gergely Szakacs, who was a Hungarian M.D./Ph.D., and Jean-Phillipe Annereau, who decided that they wanted to try to do a more systems biology approach to looking at this whole system. We had an interesting data set, which was, NCI has at least 100,000 different natural products that are potential anti-cancer drugs. They have tested their ability to kill sixty different cell lines. These are cancer cell lines that have been established and they are growing and NCI uses them as standards. They represent many different human tumors. They know what the killing curves are for all of these 100,000 different drugs.

What we knew, based on studies that Jean-Phillipe and Gergely did, was the level of expression of all forty-eight ABC transporters. It turned out that with the help of John Weinstein, who has pioneered bioinformatics approaches, that you can develop a mathematical model, which is called Pearson correlation coefficient, to ask whether the expression of the gene across this family of cells, each of which has a different amount of expression in the gene, correlates with the resistance or sensitivity to any of the drugs. You have got 100,000 drugs. The reality is we have good data for maybe 20,000 drugs and sixty different cell lines, imagine all the data points, and forty-eight transporters.

Believe it or not we got pretty good correlations at high statistical significance with about half the transporters conferring resistance to one or more drugs.

When you go back and you recreate, you take a cell line and you transfer in the transport gene, this is Koch's postulate, you can actually show that the correlations are correct, that you can actually confer resistance to these different transporters. We have not done it for all the transporters.

JG: So you worked backwards or reverse engineered in a sense?

MG: Reverse engineer it to test the hypothesis that there is a real correlation. And you see resistance. We have not done the whole set. It is a huge amount of work.

JG: This is all possible because of advances in computing technology.

MG: Just using standard computational approaches. You need a fair amount of computational power because there are so many variables.

JG: Yes, I can imagine.

MG: You get a statistical number. The likelihood that the correlation occurs by chance can be as low as one in ten million or something like that. Then you go in and you test. The problem, of course, is it is measuring RNA levels, not protein levels. In order for this to

work the amount of resistance has to be proportional to the amount of protein. It has to be quantitatively proportional. There can't be something else that is limiting for resistance. Yet we found a lot of correlations and we have confirmed a lot of them. We think about half of the transporters probably are likely associated with resistance to one or another transporter.

In fact, there is no anti-cancer drug that anyone has come up with where we cannot find a transporter that does not transport it. Again, this does not prove that those confer resistance but I think it gives a sense of how flexible the human response is to handling drugs. Now the FDA, which has to deal with drug-drug interactions, has begun to appreciate that these transporters are probably a major player in why when you take drug A you become more sensitive to drug B. It is because drug A is a competitive inhibitor of the specific transport system or metabolizing system and drug B is no longer subject to transporter metabolism because the enzymes or the transporters are busy working on drug A. It is free of interference to get into the body. You have to be very careful.

The FDA is trying to understand . . . There are reports in the literature of specific drug-drug interactions but they are trying to create a data set that would allow prediction based on known substrates or known transporters and so on. You would say this drug and this drug should not be used together because they are likely to interact. I think the whole area of pharmacodynamics and pharmacogenomics has been developed through an understanding of the complexity of these transport processes. I should add as an addendum that it turns out that this is drug efflux.

Drug uptake is a whole other interesting kettle of fish. The human genome projects has revealed about 350 uptake transporters in the genome, about thirty to forty of which are credibly, based on their known specificity, involved in transport into cells of anti-cancer drugs. If you do this correlative analysis looking at the uptake transporters you also start to get examples where, if you transfer in the uptake transporter, you get increased sensitivity. It could be, through some cancers, resistance relates to loss of an uptake transporter or increased efflux pumps. The process is complicated. The more we learn the more ignorant we become for any particular cancer about what are the components that determine the set level for the sensitivity or resistance to drugs.

JG: In 1990 you become chief of the Laboratory of Cell Biology. I assume you are now taking on more administrative responsibilities?

MG: Yes.

JG: Let's walk through what is occurring on the professional side, non-research. You become acting director of the National Center for Human Genome Research?

MG: Yes.

JG: And then deputy director for Intramural Research at the NIH.

MG: Right.

JG: Walk us through these appointments.

MG: Some of this story may have to wait for my memoirs but I will give you the outline of it. How did I become deputy director for the National Center for Human Genome Research? At that point Bernadine P. Healy was director of the NIH. Bernadine happened to be a classmate of mine from medical school. She graduated from college and she was a year ahead of me when she entered medical school. She took a year off to work in Bernie [Bernard D.] Davis' lab at the Harvard Medical School and then came back, joined my class and graduated in my class.

Although I did not know her well as a medical student, because remember, the third and fourth year of medical school, people are dispersed into hospitals, she knew who I was and I knew who she was. She was interested in finding someone to replace Jim [James D.] Watson because, first of all, Jim was publicly very derisive and negative about her leadership and there were some other major differences. The decision was that he would step down and she needed someone to be an acting director of the genome project. She told me, in retrospect, that she actually asked Gary Felsenfeld. Do you know Gary?

JG: No.

MG: Gary is a very senior, very distinguished scientist in the NIDDK who studies chromatin structure and he was not interested. He is a decade or more older than I am and he was not interested at that point in an administrative position. She called me in and she said she would like me to replace Watson. I knew Watson reasonably well. You remember why?

JG: Because of your wife.

MG: Because of Susan.

JG: Right. She did not sit at his table for lunch, if I recall. There was a table for young researchers and then there was a table for the senior scientists.

MG: Is that right? She was not allowed to sit at the table because she was just a technician?

JG: Well, it was not something that you were allowed or not allowed. It was just something people did.

MG: Right. [Laughs] Interesting. There are a lot of stories about Watson that are far more interesting than any stories I could tell. But this involves Watson so it is kind of interesting. Watson was always very outspoken and he said some things that aggravated Dr. Healy. She wanted to replace him and I said, "Well, I know Jim very well. I think it is really a disappointment that he is leaving genome because he is able to galvanize

support for this project." I also said, "And maybe I am not actually a strong believer in sequencing the entire human genome as a bypass for budget." You remember at that time there was a big discussion about whether this was a good way to spend government money.

JG: Right. The project came out of the Department of Energy.

MG: The Department of Energy had sort of conceived it. They were not making a lot of progress and it became clear that in order for this to really work that it had to be done by NIH. Watson, you know, is a visionary and saw this as a very important contribution that only the government could make. That there was no way in which the private sector was going to do this.

JG: There were many at NIH that believed that it would be taking money away from other programs.

MG: Not so much in NIH, although we were of the same mind, I think, as scientists outside of NIH, but there was a general feeling that this was not a good use for government money that could be spent on RO1s [Research Project Grants]. There is still an argument. The Director's Roadmap, for example, which uses NIH money for infrastructure support, is still viewed by some scientists as money taken away from individual research grants.

JG: Right and it speaks to the fact that there is such a limited budget.

MG: Many of these big projects actually move forward with the support of scientists when it becomes clear that there is new money that will support them and that that money would not be forthcoming except for those projects. Then suddenly the money is coming in and people are jumping on the bandwagon. The scientists are practical people and that is exactly what Watson was able to do. He was able to diffuse the criticism by pointing out that this would be new money that otherwise would not be coming to the NIH. That by whatever process, trickle down or conversion, people would be seeing this money, and they would not otherwise see it. I think he eventually convinced people. He was a very effective spokesperson for the human genome project.

I said I would like to talk to Dr. Watson before I made a decision. I did not want to be in the position of undercutting his position. Dr. Healy said to me, "No, you will not leave this room until you decide, tell me what you want to do." I sat for a while and I said "I guess this is an opportunity I can't turn down." This will be a chance for me to try my administrative wings. Of course it was a high-level position. Being even an acting director of an NIH Institute was a pretty high-level job. I agreed to do it. I subsequently discussed it with Jim who was delighted. He had already made the decision to step down and there were others in the community to whom I spoke who said they would certainly be very supportive. I said my major job would be to help find another permanent director of the project, who turned out to be Francis S. Collins.

I was acting director for a year and it was actually an interesting job. I got to understand a lot about how the extramural program works. There was a fair amount of power in the hands of an Institute director and the ability to make decisions usually in concert with the National Advisory Council, but frequently, more on the spur of the moment about what priorities were. I, for example, made the decision to fully sequence the yeast genome for which we had the technology and everyone agreed would be a wonderful addition to information. This has revolutionized yeast genetics and to some extent human genetics because there are homologs for almost all the yeast genes in the human and you could actually do studies on what their function were in yeast that you could not do in human. That was my major contribution.

Of course, there was already an ongoing strategic plan. The genome has had five-year plans to make accomplishments and my job was to reassure the staff that we would keep on track to go out and talk to various center directors and reassure them. Along the way I learned a lot about how extramural programs work, about how to manage big offices, and I think my people skills and my organizational skills were rewarded by the success in eventually recruiting Francis Collins who, of course, has been a magnificent director of the genome project.

JG: Harold E. Varmus taps you to be deputy director for Intramural Research?

MG: Right. At that point there was a change in Presidential Administrations. In 1992 the Clinton administration came in and the Bush 41 administration went out. Harold was sort

of hanging around for a while because it took a while for his appointment to be confirmed by the Senate. I do not think there were any specific problems. Clinton, as you may remember, took a long time to make his appointments.

Part of the issue was that Harold was chosen as a result of a search, which was a process that Donna E. Shalala was comfortable with because she had been president of the University of Wisconsin—a university president. As an academic she thought you should search and find the best people. A committee was put together. Bruce M. Alberts, who was the head of the National Academy of Sciences, was chair. They came up with Harold who had never run anything bigger than his ten person laboratory at UCSF but had been involved in a lot of issues related to the politics and practice of NIH-supported research, and was a clearly brilliant scientist, and quite accomplished tactician, I think, or strategist. Connie Casey, who is his wife, you may or may not know, was the daughter of a congressman from Pennsylvania so she was pretty comfortable in D.C.

JG: Senator Bob Casey's daughter?

MG: Maybe. One of the Casey's. There are two Congressmen Casey's. I think the one from Pennsylvania. I should know this, actually. She was comfortable in Washington and I think early on made him feel a little more comfortable because a lot of the NIH director's job is relating to Congress, the congressional staff, and getting support. Harold, who had not done very much of that, became comfortable with it.

When his appointment was known, even before he was here, we were undergoing an outside review. Congress had mandated that the intramural program be reviewed for the size, for the role, and for the cost. Ruth L. Kirschstein, who was acting director, had asked me to be the co-chair of a committee that was helping to work with this outside committee to review the intramural program. I became very familiar with all the details of how intramural programs are run, including the foibles and the pluses of intramural research. We got a very helpful report. When Harold came in, he asked me to stay on first as acting deputy director, because Bernadine's deputy, Dr. Lance Liotta, was asked to step down at that point. Then later on, after a search, I became the permanent deputy director for Intramural Research in 1993. I have been in the position since November of 1993, which is what, seventeen years? It seems like a long time.

I guess that was a job that suited me well. First of all, it was, by and large, a science job. The deputy director for Intramural Research used to be called the NIH deputy director for science. I was the person who represented the interests of intramural scientists to the NIH director. The NIH director, Harold, was extremely supportive of intramural research but we wanted to really make sure that the programs were well reviewed and that there were standards of practice across the intramural program with regard to appointments and tenure. I got involved in implementation of some of the recommendations that had come out of the report, which is called the Marks-Cassell Report because Gail Cassell and Paul Marks were the two chairs.

JG: There is more emphasis on training?

MG: Much more emphasis. Well, I mean, there were many good things in the intramural program but I think what we did was we standardized and made sure that everybody got the same kind of treatment. We started a whole bunch of training programs. One of the ones that I am most proud of is the Postbaccalaureate Intramural Research Training Award (IRTA) Program, which was intended to bring relatively disadvantaged populations, minorities and women for example, after college, to give them a year or maybe two years of experience working in a laboratory. They could decide that they wanted to go to medical school, they wanted to go to graduate school, or they wanted an M.D./Ph.D. That has been a fabulously successful program. We have 600 or 700 students here every year. They get a very good exposure to science. They can make informed decisions about whether they want to go to medical school or graduate school or both. Some of them decide not to stay in science at all because of the experience they have.

JG: You also work to get Ph.D. trained scientists into the Montgomery County School District. I thought that was interesting.

MG: Yes. We have a program, there are just a whole laundry list of things, and I could give you that at some point. Susan and I have always been active in Montgomery County Public Schools, as PTA presidents, we were PTA presidents in elementary school and in middle school, not in high school. We got to know the people in the central administration fairly well. We were approached because there was a shortage of teachers

of science, particularly biology and chemistry. We worked up this idea about offering to our postdoctoral fellows who are interested in working in the public school system a truncated training program in education. They need to be somewhat conversant in educational techniques.

JG: Of course, you do not need an education background to teach at the university level, which is always kind of bizarre.

MG: No, you do not need any skills at all. You just need research skills. But it is reasonable at a high school level. You need some skills. You have to handle more than just intellectual problems. There is a very truncated version that allows them to get their license, their teaching license. Then they have a period of student teaching for a year. All during this time they can continue to work in the laboratory. Eventually they can be placed as teachers. I would say over the years, five or ten fellows have ended up teaching in Montgomery County Public Schools, with maybe a few more trying it out and deciding it was not for them. It is not a particularly lucrative career. In fact, fellows who are not paid very well get paid as well as teachers do. Most of them have the opportunity to earn more than that later on.

I do not think it is the money that attracts. It is the opportunity to work with students and some of our fellows really enjoy that. We have tried to provide career pathways. Not everyone here is going to end up being an independent head of a laboratory. There are other careers in science and science teaching that people can pursue, and we have tried,

through the NIH Office of Intramural Training & Education (OITE) to support all kinds of career opportunities. To bring a very diverse group of people here, to give them exposure to the very best science, and then once they have decided what they want to do, help them with their careers. That is the goal. There are just a lot of programs.

There is an academy for students who are interested in health disparities. That is a postbaccalaureate program. There is a graduate partnership program. Harold was very interested in bringing graduate students here, as was I, and we created a series of partnerships with existing universities that would allow us to bring students here, make sure the universities give them credit, and then they graduate with degrees from their home universities. Some of these are formal programs with contracts and agreements. Others are individual students who want to work with people here and I have had a couple of graduate students in my own lab. It has been very rewarding. They are very different from having postdoctoral fellows which through normal training are here.

JG: Speak a little about mentoring. You mentioned that mentoring is a two-way street. Describe that process. Your first postdoctoral fellow was Fernando Cabral?

MG: Cabral.

JG: Where is he now?

MG: Buz Cabral is a professor at the University of Texas in Houston in the pharmacology department and he has enjoyed NIH support and has worked on a subset of drug-resistant mutants. He continued to work on the non-multidrug resistant version of what we started working on together in the laboratory and that is the tubulin mutants that you isolate if you use anti-microtubule drugs rather than the permeability mutants. That went with him when he went. One of the things I have tried to do with fellows coming into the lab is I have let them take their projects when they leave. Between the ones who directly work with me and the ones who work with me because they were assigned to me by Ira, we have had sixty or seventy fellows over the years, virtually all of whom are still doing science, practicing science, or in something related to science. There are a handful who are in science-related fields, not in the laboratory, although now some of them are beginning to reach retirement age and I am hearing about people retiring. [Laughs]

I think an important thing, the mentoring process, obviously, requires that the student or the trainee have a sort of relaxed relationship with the mentor. That the mentor consider not only the project, which of course is an important part of the learning experience, but what the individual goals are of the person. People want to have a successful project. It really reinforces their desire to stay in science. Over the years I have had a lot of people who decided that they are not competitive enough to stay in science. In particular, there have been women in the laboratory who needed reinforcement to stay in experimental science because they felt that they could not compete. One of the things we have discovered in doing an analysis of women in science at the NIH is that women are far more likely as postdoctoral fellows to lack the confidence to apply for independent

research positions irrespective of whether they are equally qualified as men. In many cases they are. The men are more likely to have the confidence to go ahead and say, "Well, I can be an independent scientist," and the women less likely. We see a drop-off at the postdoctoral level. Fifty percent of our trainees here are women. They do equally as well as the men in all respects. When you look at applicants for tenure track positions, which is the next stage in a researcher's life, most of them are men. Seventy percent are men and thirty percent are women. Women do equally well in competing for those jobs, thirty percent of the jobs, but there are not as many competing.

When we ask why the main thing we get is, "Well, we just don't think we can make it." Now a lot of things are going on in women's lives at this point. They are starting to have families. In many cases they are burdened with more responsibilities than men have. They may get the short end of the stick when there is a discussion about where to move and so forth. It is a complex difficult situation and women are not equally powerful in some of those relationships. One of the things that I have tried to do, particularly with women in the lab, is encourage them to remain actively in science, reinforce the success of their research. By and large most of the women have stayed in science through this transition period. Probably my role model is my wife, who seems to have no problem at all competing and being successful in the field that, of course, is dominated by men. I think that most women are quite capable of doing that and they just need reinforcement. That is part of the mentoring process.

The other part, as you mentioned, is a two-way street. People should have multiple mentors. They should talk to different people about what their aspirations are and what their intellectual interests are. Hopefully they will choose mentors who are not at odds with each other about what the best advice is. Sometimes a supervisor is a little too close. They might supervise and might say, "You have to keep working on this problem," when in fact that is not a good idea. Somebody on the outside would say "Give it one more shot but then I think it is time to move on. You should change labs or insist on another project."

JG: What about the selection of research topics? I have read that it is important to choose a topic that people are going to be interested in?

MG: Well people are always interested if you have interesting results. If you do science carefully and you are open to new ideas there are a lot of opportunities to be successful, even in projects that are not perceived by the community as a whole to be important.

JG: If you were mentoring a young scientist, and they wanted to do something that they would have difficulty getting funding for, would you tell them to pick another topic?

MG: This is the conflict at NIH between our mandate to do high-risk research and our mandate to train fellows who can produce something that will allow them to get a job. We all have this balance. The usual way to do it is to develop some sort of equipoise between the risky projects and the more routine projects that are guaranteed to produce data. The

data can be interpreted, the smarter the person is the more likely the data will be interesting, and it will move a field forward incrementally. There should also be an opportunity to pick up a project which is very high risk, where likelihood of success is small, but the impact of that success is very large. Those projects make careers, obviously. If somebody can discovery something entirely new about a system, then that will be something. As director of NIH, Elias A. Zerhouni used to say, "The guy who invented tennis was the world's champion for a few months until other people learned how to play." That is really what you need to do in science. You need to invent something new, establish yourself as an innovator and a creative scientist, move it forward as quickly as you can, but eventually, there will be competition and you will be just one of many people working on a project. You could still be outstanding, but you will no longer be the innovator.

JG: What about the lifestyle of science? You have considerable freedom to organize your day. Talk about how you balance of work and life.

MG: I have to say I have much less freedom. My administrative day is totally packed with meetings. Scientists should have a fair amount of free time. I think there are beginning to be more and more responsibilities that science has to deal with, regulatory responsibilities, committee responsibilities. In the intramural program we try to minimize those and the scientists themselves can protect themselves particularly once they are at a senior level by just saying "No" and nobody's going to say boo about their refusal to be part of the administrative process. Most people will do some administration.

But there is no teaching; there is no grant writing. It is just a wonderful environment for a scientist. You have a range of involvement that you can choose from zero to whatever you like. I took on far more administrative responsibilities than most scientists would. Part of it is that I am basically a multi-tasker. I am not really happy unless I am doing ten things at once. I have also been very fortunate to be able to recruit people into my lab who are relatively independent and sort of nurture their independence along.

JG: What is it like being married to a colleague? Do you get to see each other during the day?

MG: Rarely. We are on opposite sides of the campus. We do not have lunch together. We occasionally will see each other in seminars. Because of my position Susan is not on that many high-level committees at the NIH, so I do not even see her at those. She used to say that the best thing that ever happened to her was my becoming the Deputy Director for Intramural Research so the DDIR stopped putting her on committees, which is true. [Laughs] I do not put her on committees because committees that I chair, particularly, would be a little bit tense.

JG: What about balancing the personal life?

MG: We carpool. We come together. We leave together almost all days. Because of the stages we are in our careers we do have conversations about scientific matters. Susan is very involved in all kinds of training and educational activities and I learn from her in the

trenches, so to speak, what is actually going on with our training programs. It is quite useful. I think for her I am a source of unimpeachable information about what is actually happening at the NIH. [Laughs] A shortcut.

JG: Last question. If you had one lesson learned, one piece of advice you would like to give a future researcher ten or fifteen years down the line, what would that be?

MG: Do not be afraid to try new things. Do not be technique limited. Use whatever techniques you need to solve problems, and choose problems that are important, either because they give you some basic biological information, or they actually have clinical relevance.

I actually just gave a talk about this this morning. If you are interested in this, I gave a talk to some students who are here on a program that NIAID [National Institute of Allergy and Infectious Diseases] is running about the future of biomedical research. Part of it was about what the science problems were going to be, but a lot of it was how to prepare yourself to be a successful researcher.

JG: What about hobbies outside of science?

MG: I read. I have two granddaughters who live next door to us. On a daily basis every free moment we have we try to spend with our granddaughters because that is a constantly exciting area. To see them developing and growing is just amazing.

JG: You can report back to your wife that you both answered that question exactly the same way so you should be very pleased.

MG: Thank you.

JG: It was my pleasure.

[End of Interview]