Interview with Frederick Miller, M.D., Ph.D.

Conducted on October 13, 2020, by John Maruca
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JM = John Maruca, interviewer
FM = Fred Miller, interviewee

FM: Hello, my name is Fred Miller, and I'm the Chief of the Environmental Autoimmunity Group in the Clinical Research Branch, Division of Intramural Research at NIEHS.

JM: Have you always been interested in science? How did you get started?

FM: In terms of my interest in science, I have always wanted to understand how living things develop and work. And I think this came first from my times as a child, when my father and uncle would take my sister and I out naturing, as we called it, on most weekends. This involved walking the trails and the fields and woods around the Ohio farm town we grew up in and they would teach us about the flora and fauna they knew about. They were remarkably patient and would take a lot of time for us to wade in the streams and collect butterflies and other insects, tadpoles, frogs, salamanders, and many other critters. And we would often keep these for a while along with our other pets so we could watch their behavior. I enjoyed those days very much, and they were my first real encounters with what I call observational science in a small Ohio farm town.

We didn't have that many options for specific scientific training back in those days. But I did have afterschool opportunities with several of my teachers that did allow me to do some very simple experiments in physics and biology. And I had a couple of friends with whom I would build various devices like incubators, in which we would grow slime mold, and ant farms in which we would put ants and watch them do their thing. So, I did have those opportunities and I did take full advantage of those in terms of my academic background. My family had been harness-makers for over a hundred years in this small town in Ohio, so of course, many expected me to continue that business. And I must say, I do still love the smells of leather and their oils. They always bring back such rich and vivid memories of that time.

JM: Briefly describe your academic background.

FM: Regarding my academic training, I was more drawn to understanding living things, and while I wasn't sure what I really wanted to do in life, I eventually moved in that direction. After experimenting with a number of majors, I finally settled on Zoology at Miami University, where I went to undergraduate school in Oxford, Ohio. During college, my dad developed and died from melanoma, and at that time I was amazed how little was known about it and what little could be done to treat it. So, this influenced me greatly and made me decide to pursue medical research training at that time, which as I explored it further meant obtaining both M.D. and Ph.D. degrees. As I understood it, there were really few combined programs, though, that taught both M.D. and Ph.D. degrees at that time. I applied to a number of them, and I was accepted at all of them, but decided to go to Case Western Reserve University in Cleveland, partly because of its proximity to my home, but also because it was more a flexible, but still a rigorous, training

program. Over the next six years there, I worked on understanding the composition of malarial protein synthetic machinery in the Anatomy and Developmental Biology graduate school program, while I also studied medicine.

In the first year of graduate school there, you would spend a little time in each of the labs and then choose an advisor that seemed to be most appropriate to your interests and who wanted to take you on as well. After spending some time with all the advisors, the ones that seemed most interesting to me were Drs. Joseph and Judith Ilan, who had developed a project based on some preliminary data that the malarial parasites actually use part of the host ribosomal protein machinery to make proteins. This concept was quite different than what was thought at that time and generated a paper in Science that became very well known. So, I took on the project of more careful evaluations of the ribosomal proteins and ribosomal RNAs from the malaria parasite.

I used the rat/mouse malaria model at that time and found that the Ilans' prior findings were probably misinterpreted. And that, in fact, the malarial parasite has a completely different protein synthetic machinery from the host with its own unique ribosomal proteins and ribosomal RNAs. It was difficult for my advisers to believe this, of course, given their prior publications. So, I had to repeat the same experiments three times to convince them that these were the true findings.

When I finished my M.D. and Ph.D. program, the philosophy of my mentors at that time was to go to different training programs for medical internship, residency, and fellowship to allow you to get a full spectrum of different biases from different groups. So, I decided to do my medical internship training at Emory University in Atlanta, where I thought a more hands-on approach would complement the more theoretical training that I had at Case Western Reserve.

My internship at Emory was an amazing experience as it allowed interns levels of responsibility in patient care that I don't think are available today. But I did miss research. So, I decided after my medicine internship to spend a year at the Emory Clinical Research Facility, studying serum and urinary biomarkers for cancer. During that time, I was offered a medical residency at Stanford University Hospitals and decided that would be a very different training and living experience in California. And, in fact, it was. I ended up living in a wonderful log cabin in the virgin redwood forest there.

While I was there, I was told by my mentors, though, if I really wanted to do medical research as a career, I needed to spend a few years at NIH. So, I applied to NIH after my residency, planning to only spend a few years in Bethesda and to then return to Stanford. Among all my medical rotations at Stanford, Rheumatology was by far, the most intriguing, as each patient was his own mystery. You first had to sort out the diagnosis, then figure out what organ systems were involved and then finally, how to best treat them. So, I applied to and was accepted into the NIH rheumatology fellowship program in the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

JM: Tell me about your research.

FM: In terms of my research history and evolution, one of my first patients at NIH when I was the fellow on the ward — which in NIAMS really meant that you did everything that normally in an academic settings, medical students, residents, fellows and attendings would do — was a patient who had an autoimmune disease called dermatitis herpetiformis who was being cared for by Dr. Steven Katz, who then headed up NCI dermatology. This patient was now developing new severe dermatomyositis, a different autoimmune disease that involved inflammation of the skin and muscles, right before our eyes. And Steve brought him to me and said that he's getting far too sick for the dermatology service and asked if he could transfer him to rheumatology. My attending at that time, Paul Plotz, and I of course jumped at the chance to learn more about this rather rare and unstudied, autoimmune skin and muscle disease, so we accepted him. The patient did become very sick, and his illness included severe lung and joint disease, as well as terrible skin rashes and muscle weakness.

So in fact, it was because of this patient, and my realizing that very little was known about autoimmune muscle disease at that time, that directed me to focus my research efforts for the next nearly four decades at NIH on these diseases that involve chronic inflammation in muscles, known as myositis.

JM: What brought you to NIEHS, and how has the institute contributed to your success?

FM: After my fellowship was completed at NIAMS, I had set up my first independent lab at the Center for Biologics Evaluation and Research in the FDA on the NIH Bethesda campus, where I continued my myositis work while doing regulatory work on cell and gene therapy and monoclonal antibodies for the FDA. In the late 1990s I was asked to give a talk about the genetics of autoimmune diseases as part of a NIEHS-sponsored symposium on the environment and autoimmunity. Many folks there were impressed by my presentation, and it was particularly Drs. Ken Olden, Carl Barrett, and Perry Blackshear that thought I would be a good choice to develop the first NIEHS clinical program in the NIH Clinical Center.

Although I did study the genetics of autoimmunity, I'd always had a strong interest in the environmental causes of disease and had already begun to work in that area, realizing that most genes were neither good nor bad but only their environments made them so. And actually, I'd formed several collaborative groups, including in the American College of Rheumatology, to begin to understand and define environmentally-associated autoimmune diseases. So, I thought this would be a great opportunity to expand my work in that area.

It was a major task to essentially single-handedly initiate a new institute in the Clinical Center on the Bethesda campus. I needed to set up new NIEHS adult and pediatric clinics, in-patient and day hospital facilities, new IT connections with RTP that required separate computers as we were on different incompatible networks then and add NIEHS to many of the NIH Clinical Center programs and databases. I also needed to find appropriate administrative and clinical support staff to add to Lisa Rider and Terry O'Hanlon who were the only people in my group then. As there was no clinical space allocated to NIEHS in Bethesda, we made arrangements with the FDA where I was working to allow my group to "rent" space there as it were, and for me to do half-time FDA review work to "pay" for this for the first several years.

The first NIEHS clinical study in Bethesda involved twins and close siblings, where one had recently developed a systemic autoimmune disease and the other did not. We began by

assessing possible environmental triggers, such as stressful life events, drugs, vaccines, ultraviolet radiation and so on, as well as studying the genetics, immunology, transcriptomics, epigenetics, and proteomics to try to understand the mechanisms of systemic autoimmune diseases like lupus, rheumatoid arthritis and myositis.

We have made much progress over the years in these areas through the great support of NIEHS, and we have continued to make new discoveries in many ways relating to the environment and myositis and other autoimmune diseases as well. And this really would not have been possible without the many fantastic collaborations with numerous stellar scientists and clinicians at NIEHS, NIH, and around the world that I've had the honor of working with.

JM: Which of your discoveries was most surprising?

FM: I think the most surprising and interesting research finding I have made was that whereas myositis was previously thought of as a rather small group of diseases defined by specific clinical features, there are in fact, over a dozen mutually-exclusive, stable and very homogeneous subgroups of myositis patients. And each of these is defined by characteristic immunological features called disease-specific autoantibodies that are predictable in terms of their unique genetic and environmental risk factors, clinical presentations, laboratory test abnormalities, responses to treatment and prognosis. And of note, the risk factors for the development of some of these phenotypes are protective factors for other phenotypes, possibly explaining why patients only develop one type of disease that stays with them for life.

So, the myositis syndromes are much more complex than we thought, and yet understandable by a careful evaluation of all these different parameters in a large number of patients. And I think, in fact, this is true for all of our diseases. In many ways, clinical researchers are blind men sort of feeling different parts of the elephant right now, looking at our own particular areas of interest, but not integrating them into a whole picture and seeing the great complexity of human disease in terms of the impact on human health.

I've taken a very broad view of the myositis syndromes. As I've mentioned, these syndromes are systemic diseases that can really affect many different organ systems, and I decided to understand all their aspects that I could. And I must say, it's only at the NIH that I could have had the freedom and flexibility to spend decades carefully assessing and evaluating thousands of patients using the unique laboratory, imaging, and collaborative resources in Bethesda, and later in RTP, to allow me to eventually see the patterns among what turned out to be these very different phenotypes of myositis. I began by first simply cataloging the many ways that these patients can clinically present, but then trying to understand what the immunological abnormalities were, the specific laboratory tests that we found, what were the genetic and environmental risk factors, and how can we best assess and then treat these systemic autoimmune diseases.

JM: Does your work have an impact on human health? If so, how?

FM: I think the clinical impact is that now by talking with a patient on the phone, I can, in most cases predict which of these groups each patient will fall into and be able to not only predict what their future clinical presentations might be, but also the best ways to assess them and perhaps

to treat them going forward. And it's been through these approaches, which are now widely promulgated and used by all the physicians in the field, that I think we can now really make great progress in decreasing the morbidity and mortality of myositis.

JM: What scientific advances you like to see in your field in the next five or 10 years?

FM: In terms of the advances, I'd like to see in the next five or 10 years, my findings, I think have general implications for many other diseases. And by applying similar, but even more expanded evaluations and approaches, we can make much more progress. I think we need to be much more aggressive and expansive in our thinking about human diseases and the use of big data approaches to fully phenotype each patient and then fuse all these evaluations together to discover new patterns of disease. And this should ideally include a full clinical evaluation with, of course, pathology, laboratory and imaging studies, as well as all the new “Omics” studies that are available now, including genomics, epigenomics, exposomics (the environmental exposures we've experienced over a lifetime), transcriptomics, proteomics, metabolomics, etc. We then need to use big data and machine-learning approaches to integrate all these elements and assess trends and new paradigms that I think could for the first time really allow us to truly develop individual precision medicine approaches and understand the mechanisms of disease.

JM: Name one skill that you think every scientist should possess.

FM: As others wiser than me have said before, curiosity and persistence are the main things that are really needed in every successful scientist. Because if you're persistent, but not curious, you're really not good at figuring out the most important questions. And if you're curious, but not persistent, you can define the questions, but you really can't answer them. Of course, it also helps to have a well-rounded education and an open mind to new ideas, as well as some good luck, since as Louis Pasteur rightly said, “chance favors the prepared mind.”

JM: If you had not become a scientist, what career would you have chosen?

FM: What would I have done if I hadn’t gone into science? Well, many random events in our lives are so important in altering our perspectives and our paths and our choices, so it is really difficult to say. But I suspect that I probably would not have gone into my family’s leather harness-making business, but rather I still would have gone into medicine, if not research, and tried to help people that way.

JM: What advice would you give young people who are interested in a science career?

FM: The advice I would give to young people who are interested in a science career is very simple. Follow your heart and your passion and only do the things that you really love doing, as life is too short for anything else.