Dr. Michael Sneller

Behind the Mask

April 7, 2021

Interviewed by Gabrielle Barr, Archivist, Office of NIH History and Stetten Museum

Barr: Good morning. Today is April 7, 2021. I have the opportunity to speak with Dr. Michael Sneller. Dr. Sneller is a Medical Officer with the Clinical and Molecular Retrovirology Section at the National Institute of Allergy and Infectious Diseases (NIAID). Thank you very much for being with me.

Sneller: My pleasure.

Barr: When did you and your team conceive of your study that's looking at the long-term medical issues experienced by some people who have recovered from COVID and whether or not they've developed an immune response to SARS-CoV-2?

Sneller: I first started thinking about this project shortly after it became apparent that SARS-CoV-2 was causing a worldwide pandemic—so that would have been the middle of March or so of last year. We were in the process of finishing up a study that we began in 2015 in which we were looking at medical complications of people who had survived Ebola. Having participated in helping lead that study, I was nearly certain that given the nature of the SARS-CoV-2 pandemic and the sheer number of people that were infected, there were going to be people who suffered long term effects of it, and it would be important to characterize those effects. We started thinking about it very early in the pandemic when most of the attention was still on how to treat the acute disease. The terms “long hauler” and “post COVID syndrome” didn't really exist. Again, that was based on a prior study that we had just concluded in West Africa looking at similar things in survivors of Ebola infection.

Barr: Very interesting. Can you speak about how you've designed your study, such as how many participants you hope to recruit, criteria for participating, your methodology, tools and equipment, and the duration of your COVID study?

Sneller: This is sort of a natural history study, looking at any possible clinical effects or sequalae of the infection, as well as having a research component to study the evolution of the immune response to the virus over time. Again, based on experience in Liberia, and given the fact that we don't have any prior medical information on people who will be enrolling in this study, it was very important to not only enroll people who had recovered from COVID and may or may not be having persistent symptoms, but also to have a group of controls who never developed COVID, and who are reasonably well matched for age and other comorbidities. We found that is essential. We're going to do extensive testing on this study. You really can't attribute any abnormality to COVID

unless you have a control group who never had COVID that undergoes the same series of tests. We designed it similar to the Ebola study in West Africa. Of course, we could do a lot more testing here at the Clinical Center than we could do in West Africa. We had a lot of other considerations, but it made it all the more important to have a COVID negative control group of people who had never been infected with COVID, but who undergo the same evaluation.

When we were starting the study, this was really a new infection; we knew nothing about what the long-term complications might be. It was possible to speculate what we might see based on other pandemics and other post-infectious illnesses, such as what was seen in Ebola virus survivors and what we might need to do. We decided the sample size we could enroll is probably up to 400 people who recovered from COVID, and at least an equal number of controls. We may not need to enroll that many, depending on what the findings are, but we have the ability to do that. We have currently enrolled approximately 150 people who have recovered from COVID and are just at 100 people in the control group. We're probably going to take a look at some of the data shortly to see where that leads us and how many more participants we might need to enroll based on the findings that we have to date.

Then there's the research laboratory piece, looking at the immune response—both at the antibody response and the cellular response. Those studies are being conducted somewhat separate from the clinical evaluations we're doing. We have some data coming out on that, but that's a separate piece. In the next few months, we'll have enough information that we'll probably be able to publish a preliminary paper that will provide a lot of information that is needed right now—both the clinical aspects and the immunologic aspects of people who are recovering from COVID.

For the COVID group, the people who have recovered from COVID, we're enrolling people who are at least recovered from the acute illness, so they have to be at least six weeks from their first symptom of COVID. And they have to test negative for the SARS-CoV-2 virus at a screening visit that we do, because we don't want people that were actively still infected and suffering from the acute illness. Really the only inclusion criteria for that group, the people who recovered from COVID, is that they have a documented positive COVID test. That test has to be a test that has emergency use authorization from the FDA. They provide us with that report, so we are pretty confident we're capturing people who really had COVID, as well as the typical symptoms. And they have to be 18 years old or older. That's really the only criteria; they do not have to have persistent symptoms. It's open to anybody that wants to join. The control group is sort of the opposite of that; they basically have no history of the COVID illness and be 18 years old or above. Otherwise there's no exclusion.

Barr: Are you interested in the variants, how the people who've had the variants have recovered, and if they have more severe symptoms afterward than those that had the original virus?

Sneller: Well, we would be interested in that, but remember, the variants didn't exist when we started this study, and they're only now in the last few months coming to the United States. You would have to sequence someone's isolate when they were acutely ill, and we don't see them when they're acutely ill. While that would be interesting to look at, I don't know that we're going to be able to do that since we won't have the original

sample of the viral RNA to sequence, which is a labor-intensive test to do, to know whether they got the variant or not. For the vast majority of people, we're not going to know that.

Barr: That's interesting. There are lots of different tests and things that the participants have to undergo, like physical examinations and things like that. Can you speak a little bit about what they have to go through?

Sneller: Sure. The baseline visit is probably the most involved. At the baseline visit, they undergo a thorough history. We query them on all the symptoms they might be having or not at the time and do a physical examination. They have a battery of routine laboratory tests, looking at blood counts and kidney function, liver function, and evidence of any ongoing problems with blood coagulation or with any heart problems. We do a number of laboratory tests on the people who have recovered. We do a chest X-ray routinely. We don't do a chest X-ray on the control group, but otherwise the control group gets the same evaluation. We also do an investigation looking at lung function with a series of pulmonary function tests and exercise testing. We do echocardiogram, which is a way of looking at the heart and the function of the heart. And on a subset of people, we actually do cardiac MRIs, which are an even more sophisticated test, looking for evidence of involvement of the heart or persistent inflammation in the heart after COVID.

Barr: What's the criteria for the people you do that for?

Sneller: We initially did it on the first 50 survivors and the first 50 controls. That's what we're finishing up now. We're going to again look at that. That's a very intensive study. We have a limited number of research slots that we're able to get the MRI machine, but it's basically the first 50 that were selected. They don't have to be having any symptoms or anything. Some of them did have persistent symptoms, some didn't. We're just finishing up doing the same studies on our group of 50 from the control group—the COVID negative group. Once we have that data and look at it, we'll see if we need to do any more or not. The echocardiograms everybody gets, regardless of symptoms or anything else. Cardiac MRIs are done regardless of symptoms.

Barr: Why is the leukapheresis optional?

Sneller: That's just a technique we can use. It's in the Blood Bank. It allows us to collect large numbers of lymphocytes that we want to study in the laboratory from the peripheral blood without drawing a lot of blood. It's optional because you have to have good veins. It requires an IV in each arm for blood to flow through a machine that separates out the lymphocytes. Not everybody has good enough veins to be able to have that done, and not everybody wants to have it done. We made it optional for those reasons. It's also that, again, we have limited resources for doing leukapheresis. It's strictly a research procedure. It's not therapeutic at all. It's just to obtain cells. We only have a finite number of slots; especially given the way the Clinical Center was operating for most of the last year under restricted clinical rules. We can only bring a set number of patients in.

Barr: I understand. What happens to the participants on their second visit and other subsequent visits? Do they do other tests or questionnaires?

Sneller: For the baseline visit, there are still some other things they do. I described parts of them, but also, for the first 100 patients we had a team of psychiatrists that are part of the study. They did formal psychiatric interviews of all patients, and all the COVID recovered people and all the controls have a whole series of questionnaires they do at every visit. They're not always the same questionnaire, but they look at the functional aspects of their life and how any symptoms are affecting them. There's a series of mental health questionnaires. We do cognitive testing on an iPad. There's a set of cognitive tests that people undergo at the baseline visit, at the end of the one-year visit, and yearly visits thereafter. There's a whole series of mental health evaluations that are also done, mainly through questionnaires. Again, a subgroup of the first 100 recovered COVID individuals and the controls also get an in person, one-hour, formal psychiatric interview. Again, this is regardless of whether they have any symptoms or any history of any mental health problems. Everybody gets the same thing.

Barr: Did you create these questionnaires? Or did you get these questionnaires from other places or base your questionnaire off of standard questionnaires for these sorts of things?

Sneller: These are all validated questionnaires that have been used for other studies, sometimes for years, to look at these aspects of mental health and measures of disability. These are well-standardized forms. It's the same for the cognitive testing that we do; there were pre-existing tools and questionnaires that are validated in the U.S. population.

Barr: You were talking about the six-month visit?

Sneller: The six-month visit is a little bit less—we do a little bit less. We don't repeat the X-ray or the lung function tests. We don't repeat an echocardiogram, or a cardiac MRI for that matter, unless the initial one had some abnormality that we felt needed to be followed up on. The number of questionnaires is less—they still do some but not all of them. We collect less information on that. The one-year visit is more like the baseline. We do repeat the lung function test. Again, we don't repeat the echocardiogram ever unless it's abnormal and the same for the cardiac MRI study, but we will repeat the pulmonary function tests on everybody at one year. The mental health evaluations were also done again—more extensively at the year visit. The total duration of the study is three years, and the visits are always six months apart. Since we didn't know when we were designing the study exactly what we were going to find, as this is a new infection, we also have the ability to basically do any standard diagnostic test that is indicated based on any abnormality we pick up on an exam, on history, or on any of the other testing we do. If we're concerned about somebody who has problems with their brain, we can get a brain MRI, although it's not part of the protocol, per se. We can really just do a thorough medical evaluation of any symptoms that individuals have with standard testing.

Barr: Are all the participants being screened at NIH or are some of them being screened at other locations throughout the United States?

Sneller: No, this is only being done here at the Clinical Center, so everybody is seen here at the Clinical Center. Just because of the numbers of people we're getting, we're limiting enrollment to the immediate NIH area of

Virginia, D.C., and Maryland. Even with doing that, right now we have a waiting list of probably over 100 people that are waiting to get their first visit.

Barr: Wow, that's great. You spoke about this a little bit, but what made you interested in the long-term effects of those who have COVID? It's an interesting angle. What are you most excited about with your study?

Sneller: Well, what initially got me interested was the experience with looking at Ebola survivors in West Africa, and how before we did that study there were all sorts of not very well-done studies—or they weren't really studies—claiming a variety of sequelae of Ebola virus infection. We were able to actually look at that in an organized fashion with a control group and show that many of the things that had been attributed to Ebola infection occurred in similar frequency in the Ebola negative control group. It was a very important study, and it has sort of defined what the post Ebola syndrome is and what it is not. We did that by having a control group that underwent the same evaluation. At the time, it was apparent, at least to me, that this was going to be a big deal and that this was going to affect tens of millions of people in the United States. If even a small percentage of them develop some sequalae of COVID-19 , it could be a major health problem given the huge number of cases. And so, this clearly needed to be done. We've done it before in West Africa. We now had much larger, better resources at the Clinical Center to do an even more detailed study here. My main area of research was in immune based therapies for HIV, but our studies were severely limited by the COVID-19 pandemic. We eventually had to close some of them because of COVID—it wasn't possible to conduct those trials. This has taken pretty much my full time since last March, for the last year, to do this study. I think it's an important study. And certainly, it's kept me and my teammates busy through this time.

Barr: Can you talk a little bit about your role in this study, as well as the team that's helping you with this study?

Sneller: I'm the principal investigator of the study, which basically means I'm responsible and in charge, and also responsible for everything that's done on it and making sure everything is done right, including the data collection and so forth. I'm involved. I tried to see every patient that enrolls in the study. That's not always possible, because there are so many of them now, but I have a team of other doctors who are co-investigators, as well as a nurse practitioner and physician's assistants to also help you see the patients. We have a whole group of data analysis experts. We have subspecialists in pulmonary diseases, cardiovascular diseases, and psychiatrists and psychologists for those pieces of the study. They're all working and lending their expertise to this, helping collect the data and interpret the data. My role is to oversee and make sure that it all runs. I mean, we have a number of nurse study coordinators who are responsible for screening the patients, making sure they're eligible and bringing them in, and doing the very difficult task of trying to coordinate all these studies that the people need over a relatively short period of time. Everybody's working very hard on this study and doing a fantastic job. I'm just privileged to be able to work with all these people. I think we're going to have some very important information that will come out of this study. We got a big head start because no one really thought about doing these studies and studying the sequalae of these infections until really just the last six months or so.

Barr: What have been some challenges that you and your team have experienced to date? You said that the findings haven't quite come in, but are there any observations that you've made?

Sneller: We had a whole campaign for recruitment lined out for ads and various things. It turns out, we didn't ever need to use any of that because as soon as this trial got posted on the clinicaltrials.gov website, we were inundated with calls and emails from people who want to join—and have been inundated since then. The biggest challenge has been because the Clinical Center initially markedly curtailed its outpatient visits—and still we have to do them in a different way than we did before. We can't have waiting rooms anymore; each patient has to have their own room. The biggest challenge was just operating within that limited system to try to get these people in and evaluated. And that still remains part of why we have a backlog of people waiting to enroll. It's really a challenge, when you have to institute precautions for COVID-19 and limit the number of patients coming here, to actually still get the study done in the setting of an ongoing pandemic. That was the biggest challenge and remains the biggest challenge. Hopefully, with vaccines coming out, this will improve. As far as results, we're just starting to look at the data. I don't really have anything I can report right now. But we certainly have collected a lot of data, and I think we'll be able to make some interesting and meaningful contributions to this important area.

Barr: Definitely. You've spoken a little bit about Ebola, but how has your work with HIV and other viruses informed how you've approached SARS-CoV-2?

Sneller: This is a very different kind of study than I was doing with HIV, in which we were testing various therapies in controlled trials and there were interventions. This is more of a natural history study. Instead of giving a relatively small number of people a drug and then controlling the drug or placebo, and then looking closely at how that drug worked or didn't work or whatever, this is different in that we're enrolling large numbers of people just passively. We're not intervening in any way, but we're collecting large amounts of information. The only experience I had doing such trials previously was the Ebola study. That was a very large study with several thousand people. Certainly, that study made it much easier for me to design and to carry out this study. I learned a lot during the Ebola study from a lot of people who also worked on the study. That was sort of why I was asked to do this study and why what I learned in the Ebola study has helped me a lot.

Barr: Transitioning now from you as a scientist to you as a person who's also living through the pandemic, have you been mostly working on campus, at home, or hybrid, and what has that been like?

Sneller: Well, for the first few months of the pandemic, I worked mostly from home, but since the protocol began, which was June of last year, I've basically been here five days a week—pretty much every day—seeing patients. Also, we have some other duties. I'm part of the infectious disease staff here at NIAID. We rotate when there are clinical trials looking at therapeutics with people with active COVID, and with this most recent surge in infections, the Clinical Center also took patient overflow from other Maryland hospitals when their ICUs were full. We would take some patients here, and our group was part of the group that cared for those patients. Separate from this protocol I would rotate responsibilities. Occasionally, I've seen people with active COVID and provided treatment for them. In the first six months or so, clearly, there was always concern about sometimes

seeing patients most days. Even though they were recovered or the controls, there was still a potential for transmitting the disease. That's a thing I've shared with many people. Certainly, after the vaccine became available to health care workers, and that really took hold, that made coming here less stressful, I would say. I was at least partially protected. Looking back on it, I think I was thankful to have something to do during all this time. I was able to come in and work and do what I'm trained to do. A lot of people couldn't do that because the studies have been shut down or have been limited. To me, I'm actually glad that I was able to do it and that I'm still able to do it.

Barr: That's great. You've talked about it a little bit, but what have been some of the personal challenges and opportunities for you that COVID has presented?

Sneller: Well, the challenge is basically to get the study up and running and to keep it running and keep it going. It's got lots of moving parts and lots of very good people involved, but it just requires a lot of effort. I spend pretty much all my time just doing this. That's always a challenge, to keep everything running smoothly and everybody happy and the patients and participants coming in and trying to help them as much as we can and collect as much information as we can. But again, those are some of the rewards too—to basically have something useful to do.

Barr: Yes, definitely. Well, is there anything else that you would like to share as an NIH scientist and clinician, but also as a person who's living through the pandemic?

Sneller: I would just say to other people out there that I think I'm very hopeful that things are going to get much better in the near future. Everybody who has the opportunity to get the vaccine, please do it.

Barr: That's a great thing. Well, I wish you the best on your study, and I hope that you, your family, and your staff continue to stay safe.

Sneller: Thank you.

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