Dr. Oliver Laeyendecker

Behind the Mask

October 7, 2021

Barr: Good afternoon. Today is October 7, 2021. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Oliver Laeyendecker. Dr. Laeyendecker is an epidemiologist in the International HIV and STD Section in the Laboratory of Immunoregulation at the National Institute of Allergy and Infectious Diseases, and he also has appointments as an associate professor at The Johns Hopkins University School of Medicine in the Division of Infectious Diseases and also at the School of Public Health in the Department of Epidemiology. Today he's going to speak about the multiple COVID-19 research initiatives that he has been a part of. Thank you for being with me.

Laeyendecker: Thank you very much for inviting me to talk.

Barr: Yes, so when did you and your team decide to start investigating COVID-19?

Laeyendecker: So that was in early March of 2019. We were supposed to go to the conference on retroviruses and opportunistic infections in Boston, and that conference was really thinking about [if they] were they going to cancel. Were they going to keep going? At that point in time, many European countries were not allowing their infectious disease specialists to travel to the United States and that wasn't for fear of them getting infected, but the government officials felt the need to keep all their infectious disease people at home in case they were having outbreaks in their home countries. There was a meeting with the Biogen executives that occurred a couple days prior to the other conference I was going to, and they did have a number of Biogen executives all get infected with SARS-CoV-2. The meeting got cancelled.

At that point in time, I felt it was necessary that we start working on SARS-CoV-2, and considering that we have a lot of expertise in determining how well different ELISAs [enzyme-linked immunosorbent assays]–different antibody tests–work in different parts of the world, we could jump right in and do that. I went into the lab, and I told my lab manager, “Buy me as many kits as you can from as many different companies. I don't care. Let's just get them in.” Then I contacted some of my collaborators who work in the Pathology Department here at Johns Hopkins University, because I'm physically based at Johns Hopkins University. It's where our section has been based since 1983. Often when you have clinical tests, they take a while to get validated in the lab, which is then going to be used for clinical purposes, and so it is sometimes very difficult for them to add new tests. We could help by screening out which tests don't work and giving them other information about how well all these different assays perform to help them in their decision of which assay they could test.

Barr: How many [SARS-CoV-2] tests were available for you guys in the beginning, and how did you learn about the new ones that were being put out there?

Laeyendecker: I think we've gone through about 30 tests. In the beginning, part of the problem was getting samples from positive people who we knew were infected. That was a problem for a lot of different groups. The Department of Health here in the State of Maryland had trouble getting those samples, and because Johns Hopkins is a fairly influential and well-respected medical research institute, many of the cases that were in the Maryland/D.C area came to Johns Hopkins, and we could get a lot of those samples from those infected individuals to help with determining which assays worked, which ones didn't work. We could coordinate with the Health Department and help them make their decisions, help them get some positive controls. We have tons of negative controls from different studies, which are basically okay to allow us to test for these different types of developmental tests. We had lots of samples also from subjects who we knew had been infected with other coronaviruses so we could work on that.

And it was also the kind of thing where–and this was pretty amazing–early on, I just noticed there were a lot of different researchers and professionals that just changed course. It almost felt like a lot of the HIV and hepatitis C and other viral infection researchers really just put the brakes on in terms of the direction they were going. Their research turned 90 degrees and they started working on COVID, and that happened fairly smoothly. I think there was a real spirit of cooperation. I still think that goes on. It was really, " What do you need?" "Well, how can we help?" "What is the… you know?" " Can we put our technicians on working on your projects?" "Where do you need help?" " What are you missing?" "What information do you need?" And that has been truly wonderful. That has been really quite unique; I mean in infectious disease research, there seems to be a lot of cooperation; there's a lot of collaboration. That has been my experience in all the years I've worked in this field, but this brought that to a different level so that was really quite wonderful.

Also in terms of working with the young people in the lab where it's actually pretty scary, you've got a new virus, we don't know really any of the long-term consequences then, this was in the Spring of 2020, everybody wanted to work on it. There was really no hesitancy; they all felt like this is our chance to really help. Part of my responsibility was determining which assays worked, what's going on with antibody responses to SARS-CoV-2 because it's actually quite different from other viral infections that I'm used to. In most infections when somebody gets newly infected with a virus, you have an initial IgM [Immunoglobulin M] response, and then as your antibody response matures, it switches to IgG [Immunoglobulin G], and you really have a week to 10 days almost between those two responses. Here it almost came up at the same time, like the same day. You also have a lot more IgA [Immunoglobulin A] responses.

Barr: Are you surprised by that?

Laeyendecker: I was. There were also a lot of differences in the amount of antibodies that different people made. A lot of it was depending on how sick they got. For people who didn't get very sick or didn't notice at all that they were infected, there was a good 10 percent of those individuals who never made an antibody response at all, and now we've got samples from vaccinated individuals who all really all make fantastic responses. I mean really just maxed-out, what we can read on our instruments. The naturally infected folks, even the really sick ones, maybe 10 percent of those folks, make antibody responses, which are equivalent to the vaccinated folks.

Barr: Is it like that with other diseases or is it unknown because I feel with COVID people are really testing everybody and every part, every increment, of the illness? I know there's more testing going on. You're testing the antibodies more, but do other diseases have the same variance?

Laeyendecker: With HIV, having someone not seroconvert is very rare. In the decades that I've been studying the disease, I can tell you of one clinical case where it occurred, right, so [it's] rare. It's actually going to be more common now because you've got medicines, pre-exposure prophylaxis, and that can actually decrease the antibody response, but even in people who become elite suppressors, individuals who don't have a lot of virus, they all will seroconvert.

Hepatitis C when you have the people who clear, they also all seroconvert. It's harder to know with herpes infections simply because being able to know this person got infected versus that. It's harder to get information on everybody who's been infected to know did everybody seroconvert. People can serorevert, which means you go from antibody positive to antibody negative, and we've seen that certainly with herpes. We haven't really seen that with HIV. There are people who can be indeterminate with HIV who stay indeterminate, and we're now seeing for SARS-CoV-2 definitely seroreversion. In terms of people who were exposed a year ago who were antibody positive who are now becoming antibody negative, that also depends on the type of test you're using, and were they vaccinated, how sick they were. There's actually a really nice paper. I believe a group from San Francisco who just did a nice study on that.

All of these things affect studies that are either ongoing or data that needs to be interpreted, and that's a lot of what we assist in. I have an epidemiology degree, but I'm more of a lab person so I don't really design trials. I've worked as a laboratory technician and then as a lab manager. Then I got my Ph.D. while I was working full-time here, and that degree also allows me to communicate really effectively between the virologists and the biostatisticians because there're a lot of times where they're confusing each other. I just know enough of each that I can often translate, and that helps. Particularly working with SARS-CoV-2, that was also important in terms of how we best fit in, our ability to respond as effectively as we could to this pandemic.

Barr: You've been a part of more than 25 COVID-19 initiatives to date. You've spoken a little bit about your overall role, but can you talk about some specific projects that stand out for you that you've been a part of?

Laeyendecker: Sure.

Barr: And they've varied, like you said, from antibodies to testing commercial COVID-19 tests.

Oliver: Yes, and that is in terms of figuring out a different avidity modified samples, being able to test the blood of samples coming from the coroner's office. So we did a study where essentially, we get these cups of blood, which are six months old, and could we test that blood to determine who of the people died of an overdose…

Barr: How did you guys receive that?

Laeyendecker: Oh it's pretty easy. They delivered it, and they basically they looked like little Jello cups because the blood had congealed in most of them. Yeah, it was kind of scary.

Antibodies are generally pretty tough. You can boil samples and still get decent antibody data. We've actually developed a protocol where we test discarded cookers, which injection drug users use to make their heroin liquid so they can inject [it], and then they discard those on the streets, and people reuse them and sometimes you can you find remnants of blood. We can test for antibodies to HIV and HCV in those–so that's how tough antibodies are. So yes, getting a cup of congealed blood, there was still plenty there in terms of being able to get antibody tests to work.

Then how do you prove to yourself that you think the assay is working? You need to do a lot of tests where you look at what's the limit of detection. If you're spiking the known positive samples into that congealed material, well, there was liquid on it, but they were honestly pretty frightening. We've tested, I think, 1500 of those or something like that. You're working with the coroner's office who we don't really work with that often and then also with our colleagues at the School of Public Health who we have worked with in the past, but there's a different feel. Everybody essentially sort of knows what their jobs are, and it's very collegial, and it's very–you get this sense of "Let's get this done."

That's one of the studies. Another study would be pulling the waste blood samples from emergency room patients. The emergency room stays open, and they keep on seeing people. This was actually a protocol that started here in the mid-1980s, early 1980s, where every three to five years for about a month we collect samples from the emergency room. Most of the people who come the emergency room get a blood test to see what their level of their white cells and so forth are, and after they get tested, they [the samples] get held on for a couple of days to see if we need to do re-testing on those samples or did the clinician want another test done? They've got the sample ready to go, but when they're done, they're going to get thrown away, and so when they're done, we come in, and we gather [the samples], and we coordinate that with the Pathology Department. We get at least 150 samples a day. We collect those, and then they do some chart abstraction and then cut all the information to

them. Then we can get a sense of how many people have antibodies to {SARS-CoV-2]. In the past, this would be to HIV to hepatitis C. What's the different levels of that? So we could do the same thing for COVID-19. That was another instance of where we were ready to work with where we had done similar studies in the past, which we could then adapt to COVID-19.

In the past, we've also worked with clinicians who do transplants, and when an individual has a transplant, they are put on medication to impede their own body's reaction to that new organ. With that group, it's also a question of how is their antibody reactivity? How's that different than in individuals who were not on immunosuppressants if they got infected? How's that different? I mean some of these things actually turn into projects which would turn into papers, and some of it you're just essentially helping on the side and communicating with them [collaborators].

Another part is how do these tests work in developing countries? That's actually where we have also a strong background because we have a laboratory that is based in Uganda and actually a very rural part of Uganda, and that's part of the Rakai Health Sciences program. and it's our International Center for Excellence and Research [ICER]. Our ICER laboratory is there. There are a number of ICERs in NIAID. We're one of them, and so we actually have a person of our lab group, our staff clinician Steve Reynolds, who is physically based in Uganda. That's where he lives. And now we've got Andrew Redd, who is actually also based in South Africa. That's something new. We know that assays, particularly ones that are developed in Western Europe and the United States, sometimes have trouble working in Africa, particularly in Eastern Africa, and what we believe is that individuals in those countries are exposed to a lot more different types of pathogens, infectious viruses, and bacteria and so forth, that are circulating there and [the people] just have adapted to have very cross-reactive antibodies in them. It helps them fend those off, and therefore our antibody tests often have a false positive. Hepatitis C was really bad in terms of false positive results, and certainly herpes testing is also difficult. So in terms of helping them and being able to help with getting the reagents there in place, helping to set up the studies, helping analyze the data–those are things [that] I can help out with, and our group helps out with.

Barr: You've done other studies too. You looked at populations who are most likely to have COVID in the Baltimore area, and you also looked at one that I thought was very interesting about blood groups that are most susceptible.

Laeyendecker: Well, so right. The blood group, that is clearly a study which was really more directed by Aaron Tobian and his group in the Pathology Department, and they actually were part of the group that set up a convalescent plasma trial here at Johns Hopkins. He also works with the blood bank there and blood donations and so understanding which groups of individuals are most prone to both infection and pathogenic, how sick they get from infection, is certainly of great interest to him in particular and us in general. In terms of helping with the antibody testing there, that's what we did. In terms of the figuring out which groups of individuals, that [work] was actually with the Health Department. What we found was that folks who had died in traffic accidents had a much higher prevalence of antibodies at that time to SARS-CoV-2 than individuals who died for other reasons, and that makes sense because they were out and about because they needed to go to work. They were mixing far more than folks who weren't

driving. What was surprising was folks who died from IV drug overdoses, they were at that time, less likely to have antibodies to SARS-CoV-2. People don't mix randomly; you generally are interacting with a particular set of groups of individuals. It's that you do have a good deal of segregation of different populations where you don't have a lot of equivalent mixing, and a lot of the infectious disease models, that part actually gets to be kind of tricky because a lot of times you're thinking about what's the risk of getting infected. Well then, you're making assumptions about how well people are mixed and how much they're interacting with one another to get that exposure equivalent over to it, and that doesn't happen.

In terms of how we helped, one of the earliest papers was on what's the frequency of false negative PCR results? When somebody gets infected, for the first couple days they will not have a positive response by PCR. Then there's this sweet spot from like three to ten days after they get infected, which is really a couple days after they start having symptoms, where they're most likely to be positive. And certainly of the initial strain which was circulating, it may have been like an 85 percent chance of having a positive result. And so that all went to how frequently are we missing people who have actually been infected and how big is the spread? That was understanding more of the nuts and bolts of the laboratory assays and what they can do and what they can't do in helping to inform the infectious disease modelers. It's also what we do. It's in terms of trying to be helpful and providing that information in a way that they can understand it and they can use it in their models to best do predictions is where we also come into play.

Barr: What are some current projects that you are part of, or something that you hope to get to do with COVID?

Laeyendecker: We're still working on essentially doing surveys. We are both in the emergency room; we'll probably do another study with samples from autopsies. I hope we can do some more broad studies in Uganda, but honestly, I just hope it gets controlled sooner. I mean…

Barr: It's sad. What devastation it has brought to the world.

Laeyendecker: Exactly. I mean the key thing is we've got a vaccine that works really well. We're getting to the place where we can have pills that can help treat, but those are if you give them early. That's actually the difference [with] what we see with HIV versus what we have with SARS-CoV-2. With HIV, we do not have a vaccine network, but we do have great, wonderful medications, which makes your life expectancy essentially almost the same. If you got infected [with HIV] and you started taking those medicines pretty early in your infection, basically you almost have no change of life outcome. While with SARS, we've got a great vaccine, but we don't really have the medicines. We also don't really know a lot of what the long-term outcomes are going to be. We do know that a lot of people have what's called long COVID, and the number of different types of debilitating impacts from lung to brain function are really quite broad. To be able to get where we can have better treatment for those, I think that's still coming. I'm actually pretty certain that's going to be soon.

But it's not like the HIV pandemic went away. That's actually another thing which we're looking at: there were a lot of factors during the SARS pandemic which shut down a lot of your easy ability to ship goods, which means medicines. Did the people who were on all the {HIV] treatments, were they able to stay on their HIV medicines, and if not, how bad is that impact in terms of people who could then transmit to other people? That's another thing which we're going to be working on. It's not like the work went away; there's still plenty to do.

Barr: What was the most challenging aspects of your COVID work so far, and what has been the most rewarding?

Laeyendecker: The challenging aspect actually has been the logistical issues. We are still, in terms of getting pipette tips for being able to do testing, they're on backorder for six months. We're finally getting plastics that we need for the lab that were ordered months ago, early in the pandemic for doing the viral load testing. I mean here physically at Hopkins what they did is they had the space telescope group actually make the swabs because they had the manufacturing capacity to make the swabs. They have the cancer research people make the buffer which you put the swabs in because you couldn't buy them. I mean that was just amazing. It's interesting because the most difficult part and the best part are kind of interrelated, because the best part has been the way that everybody's worked together, the way that you have the surprising collaborations happen, the way that people have really helped out; and the most frustrating has been not being able to get the things quickly. I think time is a funny thing with COVID work.
All these pre-reviewed articles are very influential and get a lot of press. That never happened before. I mean it's almost makes me worried the next step is that they're going to be reading what I type.

Barr: Right, then like a social media post something could be seen as something official.

Laeyendecker: Right. Like how quickly is that information going to get out? The very frustrating part is the misinformation. It's also shown that we in the scientific world can do, need to do, a better job of communicating our findings and also understand the difference in terms of how folks who aren't very well trained in science, how they perceive [science]. Even particular words have very different meaning and can get misinterpreted. Even the same sentence can be stated by both parties and completely differently perceived, and so there needs to be a lot of work on better communication of scientific findings.

Barr: How difficult is that for you and others in diagnostics because you guys deal a lot with nuance–not that others don't–but a lot with nuance and percentages and comparisons to one thing versus the other that can sometimes get misconstrued in the media’s, and then public’s, understanding of something either working or not in terms of a test or an assay?

Laeyendecker: Yes. What seems to be helpful or what has helped is that I've had friends and relatives and so forth keep on asking, “How does this work or that work?” and “How well?” And so to be able to put it in a way that folks understand [such as] “What is the chance of getting hit by lightning?” That's something that most people are aware of. That's a pretty rare event, and so to have an ill effect from a COVID vaccine be something which is equivalent to getting hit by lightning. There are a lot of people who understand percentages in sports, so what's the likelihood of this team winning against that team? Or even in terms of differences like the size of the sun and the moon. Putting the percentages and the values that the things that we know in relation to objects and concepts that are clearly understood by the general public, that's actually seemed to help a lot. That's a lot of times what I try to do. And then also keeping it short because we like to drone on and on and on like, “You know, well, but in this case, you might have this and, in this case, you might have that and a lot of these.” Really, it's like what can you say in two or three sentences that are the most important points that you want the individuals to understand and to be as clear as possible and making sure that even the word choice is that you're not using a lot of words that most people don't understand.

Barr: I think our last question will be along those lines. Do you think that the diagnostic expectations for COVID-19 were reasonable?

Laeyendecker: I mean that's kind of a hard question to answer. I think initially we had no idea. In terms of diagnostics, the diagnostics for HIV are among the best of any diagnostics in the medical community. I mean the performance of those antibody tests can outperform pretty much any test for any other condition in terms of what the viral load test can do, what a PCR test can do, and what an antibody test can do, what even a CT scan can do, and how there's been a lot of effort in terms of being able to miniaturize some of these assays, get it adapted to being able to use on saliva in terms of how can we get samples from individuals easier. I mean the thought with the PCR assays [is] you're trying to amplify a virus that's generally in the lungs by sticking a swab down somebody's nose as far as it'll go. It's certainly not going into the lungs, but I honestly think that they're good. The problem is you need to understand what they can and can't do, right, and I don't think that's been accurately communicated. There gets to be a lot of nuance, and that makes life difficult and particularly with no tests, right. We've come a long way I think. I don't know how much better they could get now, and it's also working out like potential other biomarkers to test. In terms of testing for the presence of the virus for antibodies through the viral infection, those are things that we know how to do. That's what we've been doing on a lot of different types of infections, but because we're going to have seroreversion, because we have a tough time actually getting to the area where the samples are, I think we'll also want to be able to detect the presence of the virus in the air. That would be wonderful especially if we could do it for three cents. Do something that's super accurate, cheap, easy to understand, easy to use. The point of care antigen assays, that's pretty good stuff. That's pretty high up there in terms of you're taking out a lot of complications to be able to do something that normally an RT PCR is a pretty complicated assay. You've got at least 13 steps or something like that in terms of all the processes that go into it, and on top of it, it's a quantitative assay and to essentially replace that with something where you can swab and stick it

and get a band yes/ no, is pretty remarkable. I think they're pretty good; I'm pretty sure they're going to get better.

Barr: Well, that's good.

Laeyendecker: Hopefully that answered that question.

Barr: Definitely. Is there anything else that you would like to share about your COVID-19 research or experiences both professionally and personally?

Laeyendecker: I think I've covered most of it. It's been a lot of work, but it's been very rewarding, and it's been particularly rewarding with my colleagues in terms of feeling this sense of community to respond to this pandemic, which has been very moving.

Barr: That's great. Do you feel like you've made more relationships with COVID-19 than you have with other or different kinds of relationships than you have with other diseases that you've worked on?

Laeyendecker: Different. I mean part of my job is making relationships. As an epidemiologist, you're always interacting with either different laboratory groups or different public health agencies so there's a lot of relationship building that goes into that. That's also something which I've definitely learned from my boss Tom Quinn. He's really remarkable at building networks of people and collaborators, but there's definitely been a number of people who I never had met before and have been very impressed with the work they've done. Andy Pekosz and Sabra Klein at the [Johns Hopkins] School of Public Health are really just amazing scientists and amazing people so that's been really great.

Barr: That's really wonderful. On that note, I will say thank you so much for all that you do, and I wish you and all that work with you continued success and continued health.

Laeyendecker: Well thank you very much. The same with you.