Dr. Daniel Chertow

Behind the Mask: April 19, 2021

Barr: Good afternoon. Today is April 19th, 2021. My name is Gabrielle Barr. I am the archivist for the Office of NIH History and Stetten Museum, and today I have the pleasure of speaking with Dr. Daniel Chertow. Dr Daniel Chertow is the Head of the Emerging Pathogens Section at the NIH Clinical Center. He is also a tenure track investigator in the Critical Care Medicine Department at the Clinical Center and a tenure track investigator in the Laboratory of Immunoregulation at the National Institute of Allergy and Infectious Diseases. Today he is going to speak about some of his experiences treating COVID patients at the Clinical Center, as well as some of his COVID research.

So, thank you for being with me.

Chertow: Thank you so much for having me today, appreciate it.

Barr: Absolutely. So, we are going to start off with you as a clinician. Do you mind describing your experience caring for COVID-19 patients at the Clinical Center?

Chertow: Yes, so, we first started preparing to care for patients early on in the pandemic, I think it was in March, April of 2020, when, like other hospitals and ICUs around the country, we went into a preparation mode, and that involved interdisciplinary coordination among multiple groups within the NIH Clinical Center community, as well as across the intramural institutes. We had to put together a plan to adjust our normal practices to number one, be able to care for these individuals safely; two, keep staff safe but then also make an effort of not compromising our care. So, as a Critical Care Medicine Department, our group had an important role in that, and I and a number of other physicians in the Critical Care Medicine Department were put out in a leadership role, where we worked with the Critical Care Nursing Department, Hospital Epidemiology, the NIH Clinical Center Administration, and the Facilities folks. We had a whole series of meetings about figuring out and planning, about logistics and supplies, and that type of stuff. So, that process took a little bit of time.

We had the benefit of prior experience caring for patients with Ebola. That sort of helped with some of that, but we also understood that, you know, [COVID had a] new pathogen, different route of transmission, respiratory versus contact, and the sort of unknown about this pathogen. Ebola has been around since the 1970s and this [pathogen] was pretty new. There were certain uncertainties there. I was on one of the early clinical teams. Part of our planning process was to come up with the schedule, and myself and a couple of the other younger attendings in the department put ourselves out front as far as being some of the first attendings to care for these patients. Actually, I think I was either the [first or] I was the second week. Jeff Strich, who is another one of the attendings in the department did the first week, and I worked with him, and then, I did the second week.

Needless to say, that was an uncertain time because we had a number of individuals with COVID. Many of them were sick; a number of them were critically ill. We were working on our processes; we did not know what worked with this disease and what did not work, and it was tough.

Barr: Was it confusing and demoralizing, or you did not even have time for that, you just were trying to get through it?

Chertow: I have to tell you, there was one particular patient, who, I think, was the third patient that we cared for here at the Clinical Center, who had some of the risk factors for severe disease, and he was relatively early on in his disease course, and, unfortunately, he was—I mean that we have had a couple individuals who have died here at the Clinical Center—but he was our first death from COVID, and I was caring for him at that time, and I just remember it was demoralizing. I mean, we were at his bedside and he had become critically ill, he had a cardiac arrest, and we were caring for him with the nursing team, and [this was] one of the things that stuck with me because we had all of our processes in safety, but there was still uncertainty and a number of the team members, you know, because we were doing CPR and everything else, had concerns about their own safety, and even though we had all the protective equipment. And so, he did pass, but in the wake of that, I can tell you, we had a number of conversations about, well, these are the things that we have in place to try to maintain safety. Those are uncertain times, and reasonably, staff had concerns, and there were unknowns so, it was challenging.

Barr: How has the care that you have provided evolved since the spring of last year?

Chertow: So, we have been fortunate that as the pandemic progressed, we gained more insight into the natural history of this disease, what the progression is, what organ systems were involved, what to expect, sort of, at different time points in the illness. All those things began to reveal themselves a little bit. And then also what tools are at our disposal, so that we can begin to mitigate some of the more severe features of the illness.

Barr: Right.

Chertow: And so, it went from a lot of uncertainty and perhaps, certainly, like a higher stress involvement situation, to a more predictable and more manageable over time. There is no doubt that the care meaningfully evolved to become more, I do not want to say routine because it is never routine, but it became, it did become more routine, and more predictable, and less of a stressful kind of environment.

Barr: Yes, that is really good. So, what have been some issues in treating COVID-19 patients that you think still need to be resolved, and is there a particular area that you and others at the Clinical Center are focusing on? I know that they have learned a lot like not putting people on ventilators, or how to turn people, so many different things you guys have learned?

Chertow: Yes, those are really good questions, and you highlight a couple of important pieces that at the beginning of the outbreak, because there was so much uncertainty about how to handle these individuals, and then also added uncertainty about, as providers, "When we have to put all the gear on, are we going to be able to get to the bedside in time to provide adequate care?" and those types of things. And you do. You highlight an important piece that probably others, perhaps others, have spoken about which is that we have learned that we can manage the respiratory failure aspects of this for a reasonably long period of time, sometimes avoiding invasive mechanical ventilation with some of the things that you talked about—use of high flow oxygen therapy. There is an approach that has not been rigorously studied but appears to be helpful at the bedside, which is this idea of self-proning, where a person can turn themselves over in bed and, perhaps, improve the matching of blood flow and oxygenation to the lung avoiding invasive mechanical ventilation.

But you asked about areas that still need improvement, and particularly areas that we might be interested in studying in the lab. Our interest in the lab is understanding the underlying mechanisms or the pathogenesis of organ injury and dysfunctions, you know, critical illness, and so it is very relevant because with all the improvements that we have made, with the various trials that have been done, and one of those trials has shown that systemic steroids appear to reduce mortality that, in the sickest of the sick, we still have fairly limited tools [for]. So, understanding what are the features that are contributing to organ dysfunction and failure, and ultimately death, in those sickest of the sick such that we can target additional pieces above and beyond the use of steroids, or above and beyond the use of Remdesivir, which is an antiviral that might bring mortality down. That is our primary interest of our lab.

The other piece that I would say that we are interested in, and we are pursuing, and as the NIH has invested a lot of money, they put a little over a billion dollars towards funding to understand what folks are calling Long COVID, or Post-Acute COVID syndrome, which is this whole phenomenon that we still do not really understand, this whole idea that you may have had mild to severe illness, but despite that you may still be not right, experiencing symptoms up to significant time out and what is driving that? We are interested in that piece as well and trying to better understand it.

Barr: At the Clinical Center, do you only really see the sickest of the sick or do you observe patients that exhibit the spectrum of the disease?

Chertow: We have seen the spectrum of the disease, and I will say that the primary mission of the Clinical Center is to support biomedical research, such that under normal circumstances, all the individuals that are cared for here, that are patients here, are enrolled in some sort of protocol, in some sort of trial, and for the most part that remained true through COVID with an exception. The COVID patients that we saw fell into three different categories: one, individuals that were on other protocols

for their cancer or whatever that became ill and had COVID, and we cared for those individuals; a second category of patients were individuals that were enrolled for COVID-specific studies that were being carried out, here. Some of those studies, one that we are involved with, is just a natural history study, that brings mild to severely infected individuals here; others of those studies were randomized trials that were testing efficacy, and sometimes safety, of various potential therapies. The third category of patients that we ended up seeing here at the Clinical Center were those individuals with COVID that were cared for at hospitals in the community where those hospitals were overrun, so there was a statewide initiative to help facilitate care for those critically ill patients, and we received a number of individuals through that system, just to help the community.

Barr: Yes, that is very interesting. So, what was your role in standing up the ICU at the Clinical Center to support critically ill patients? I know that you had put a lot of time into that.

Chertow: That is true. I was charged by the head of our department, Henry Masur, to lead, or to represent our department, in working with the interdisciplinary group to set up and establish essentially the COVID ICU. We have about 24 ICU beds here at the Clinical Center under normal circumstances. Twelve of those ICU beds are used truly for ICU purposes, and the other 12 are used for our procedure service and for overflow. But what happened is early on, when we realized that there was going to be an influx of patients with COVID, we converted that whole second 12 beds into a COVID ICU, and that had to do with working with Facilities, and with Nursing, and hospital Epi[demiology]. All those individuals had to walk through that unit and say, "What is it that we need to do to this place to make it safe, to make us accomplish our goals so staff does not get infected in this location, number one and number two, that we can continue to provide high quality, top-notch, care for these folks?" I was involved in that process right from the beginning, and I had certain insights.

I have understanding of the Critical Care piece, I have understanding of the pathogen piece, and so, I was able to help with the decisions: you can enter the unit here, this is what the workflow would be, you would go from here to here and then when you are done with your work, you would go to here and you would do this with your personal protective equipment as far as removing it. So, I was very much involved. I was, certainly, by no means, [the only one]. This is a very large interdisciplinary team, but I was involved in all those conversations early on planning, preparing, and then, ultimately, launching that ICU for COVID care.

Barr: How long did it take to organize? It sounds like it was quite a feat, and can you use that process once COVID is over now that you have converted the space into other kinds of a space?

Chertow: Yes. The short answer is, I think it took about three weeks or so, and what I will tell you is that as that space was being prepared, in those 12 beds we were actually seeing patients here with COVID at the Clinical Center, but they were being cared for up in what is called the SCSU, the Special Clinical Studies Unit, on the fifth floor, which, okay, as you probably know, that that unit was designed, that is

where we took care of the Ebola patients, but that unit has a limited capacity as far as the number of patients and it is really not designed to be an ICU, where we need the flow, the space for equipment and meds, and all this other stuff. So, we were doing two things at once, we were caring for four or five patients up in the SCSU with COVID, while at the same time saying: “Wait, we have got to get all this stuff ready so that we can have our regular workflows.” And that took about three to four weeks.

Barr: That must have been a hard on everyone trying to transition.

Chertow: It was! You are making me have flashbacks, but you know it was a challenging time. We have very good people here, and I, [was] one of the younger folks in the department. Lindsay Bush is a Critical Care Infectious Disease doctor, who was one of our recent graduates in our program from the Critical Care Medicine program, who was a young attending. Lindsay played a huge role in this and she was so enthusiastic and so proactive. And another individual, Jeff Strich, was also Critical Care and I.D. trained, and Jeff was so motivated; Jeff, I told you, took the first week of attending, caring for the patients in the SCSU. So, there were people that stepped forward, that were ready to take on the task, and, of course, our Nursing staff, and we have such a capable and competent excellent Hospital Epidemiology service. So, yes, we were busy, and we were tired, which is good that it did not last for forever, but it was those challenging times.

Barr: Do you all still get assigned like a week? Is that how it goes?

Chertow: So, interestingly enough, and this gets back to the question that you were asking before about how things have changed over time. Initially, we kind of doubled or tripled our ICU time, and by that, I mean we continued to run a routine non-COVID ICU with our normal team structure, meaning, in our normal team structure with the attending, ICU doctors, and our fellows. But while that was running, we set up a parallel team to just work on the COVID side so that, immediately, was a doubling of your clinical time because you would still have duties over here and then now you have an equal number of weeks over there for us, for the fellows, and for others. What it evolved into over time, as the care became more predictable in a more controlled setting and the COVID ICU was really set up, we ultimately rotated back to our single team structure, where we have one ICU team of attendings, fellows, etc., that covers both sides, and that has allowed us to go back into our normal rotations. But yes, when we are on attending duty, it is a one-week block, it is one week at a time.

Barr: Okay, it is very interesting. So, I think now I am going to move on to your research. One of the first studies that you did was an autopsy study of fatal COVID-19 cases. Can you expand on the goal of this study, which is to characterize viral distribution, persistence, and host response to the virus across the body in the brain?

Chertow: Yes, that is exactly right. So, I, as you mentioned, am a tenure track investigator which means that I have got a laboratory staff and we have research funds and run a research program. So as COVID was arriving, and given that we are an emerging pathogens lab, we had to say, “Okay, where are we going to focus our attention?” Then, based upon my prior experiences, I realized and valued the strength of autopsy studies to give insight into pathogenesis, and the pathogenesis that we are particularly interested in, which is the critical illness and the most lethal cases.

So, long and short, we set up a system where we collaborated with a number of hospitals from the University of Maryland Medical System, a number of hospitals around the state all the way to the Eastern Shore, to both downtown Baltimore and a number of other regions, where if there were COVID deaths, we would hear about them. And that if families or next of kin were interested in participating in our research study, we would recruit them [and arrange the] transfer of the remains here to the NIH Clinical Center. We worked with the pathologist from the National Cancer Institute, the NCI pathologist. My lab team and the pathologist were integrated where we would do these very detailed autopsies. We have done 44 autopsies to date, and we collect and preserve specimens across the whole body and brain, and that means that it is a hundred or so different sites across the whole body. We preserve those tissues to really ask two questions: “Where is the virus across all the body?” and subsets of that question are: “What tissues?”, and then specifically “What cells within those tissues?” Above and beyond that, we don’t just look for RNA, but we try to determine “Is the virus that is in those cells replicating or not?” “Is it viable or not?” Those have implications for questions about persistence in different sites, so that was one of our questions. And then the second question was: “In all those places that you found virus, how did the body respond?

Barr: Are you looking for more autopsies if you could get them?

Chertow: Well, that is a good question. For right now, we have closed the cohort because we are in the process of all the downstream analyses and because we are sort of a small team, and now we are trying to dig into the data to answer some questions. One of those really important questions is: “In all those places that you find the virus, what does the body's response to the virus look like? Is there a massive infiltration of immune cells, or not?” Interestingly enough, in a way that is a little counterintuitive, in many of those locations where you might have virus—in the heart or the liver or the kidney—there appears to be largely an absence of immune cells going in and recognizing the presence of the virus, which you would expect to be there.

Barr: Yes.

Chertow: So, we are trying to understand. Well okay, we found the virus, we have got the map of the virus, and now we are understanding what the body is doing. Why is it acting that way, and in certain locations it is causing damage and [in] others it is not? So in that study we are starting to get little pieces of insight that are informed.

Barr: Did you find the virus in certain places that you were not expecting to find the virus?

Chertow: Yes, so that is a good question. That data is beginning to be filled in, and we are in the process of putting together the first manuscript that describes all of that, but one of the places that we are able to look in the last 11 autopsies that we have done is the brain. So up until now, there have been a number of studies where investigators have found a little bit of virus here and there in different parts of the brain, but using the approach that we have used, we have been able to locate significant amounts of virus in multiple regions of the brain, and we are beginning to drill down into what cell types that virus is infecting, and whether or not there is an associated pathology and inflammation, etc., in each of those areas. So, the brain is one particular area that we are focusing some of our attentions on.

Barr: That is very interesting. Can you speak a little bit about your role in this study?

Chertow: Well, with regard to that study, I am the principal investigator. The concept behind the study was conceived in my lab and we have implemented it in collaboration with our intra and extramural partners.

Barr: In the beginning of the pandemic or was it a couple of months until you got your idea together?

Chertow: Yes, great question. We were out of the gate really early. I just recently put together a talk in which one of our slides has a map of the epidemiology curve of cases and deaths in Maryland over the last, you know, from really, it was from April of 2020 till April of 2021 so, literally over the last one year.

Barr: Wow!

Chertow: And what we have on that Epi Curve are little tick marks where we have done autopsies dating all the way back to April of 2020, so my group was on the ground like this, yes, starting with this stuff.

Barr: So, you were saying that you are a P.I. and some of your responsibilities…, I cut you off.

Chertow: No, no, that is fine. We conceived of it and, as you asked, we implemented it early. It was interesting because again, I will get back to, I mentioned some of the younger folks in the clinical setting, but we also have a number of young trainees and investigators in the lab, and needless to say, many or

most of them have never done a human autopsy before, so, I can remember distinctly, it was again very early on, I mean this was like March beginning of April and this is before they sent everybody home, before they had nobody on campus, and I had everybody in my lab in my office, and I remember sitting down with them, and I said, "We are an emerging pathogens lab. This year, we are going to be very, very busy. Each and every one of you is going to be engaged and you are going to be busy, and now whether that engagement is here in person or if you are more comfortable with that engagement being at home and teleworking, either is okay, and that is a personal choice, and you are going all have to tell me that, and when you tell me we are going to discuss it, and I am going to be okay with it, but you are going to be busy one way or the other."

What I can tell you is that when it became clear that we were going to be doing these autopsies, we had a number of conversations, that we had individuals that were volunteering to come and to do these studies and to feel comfortable. It was on 24-hour, seven days a week on-call schedule, where I might hear about a case at 2:00 am, and send a text message out and my team would be ready for an autopsy next morning at like 9 am. These are young trainees that have done an amazing job. It is easy for me to say, but what I am telling you is that the people on the ground, the trainees, and the dedicated folks, the pathologists, the fellows, and the techs, the people in the NIH Clinical Center Admissions Department (you should interview them), they would get calls from me at like 3 am, and I know them all by name, by now. I said: "Muhammad, there is another autopsy." And he is like, "Oh, I know, doctor. Sure, no problem." And they, because we would want to get them [the bodies] here in a very short interval because it mattered for the study, they would facilitate the paperwork and the contact funeral home, going out and bringing the bodies, and really a remarkable teamwork to get these things done.

Barr: What was, out of curiosity, the demographics of the autopsies that you got?

Chertow: Yes.

Barr: In terms of the split between men and women, different ethnicities, and races and I think that must be very interesting for you or has that not made as much of a difference?

Chertow: No, it does make a difference and it is a really good question, and we have a relatively diverse cohort. I would have to go back and cheat and look at my slides to tell you the exact numbers, but let me say this, for example, that we have diversity across a number of variables. One is the time from symptom onset to death, and that ranges from as short as less than one week to as long as 200 and some days so, months. We have a spectrum across really acute illness to chronic, kind of chronic COVID, we have a fairly even split. I think, we have a slightly more male versus female predominance, but we have a relatively even split. We have, I believe, about 40 percent black, 20 percent Hispanic, and only about 2 percent Asian. The rest is white non-Hispanic. We have an age diversity from as young as six years old, which is very sad.

Barr: That is very sad.

Chertow: Very, very sad. To as old as individuals in their 90s, and we have a number of individuals in their 20s that also are part of the cohort. So, we have a very nice diversity, and what I will tell you is, across this cohort, we have collected over 10,000 specimens that are all carefully collected and preserved for all the downstream work that we are working on now.

Barr: Are you all doing a lot of the analysis or are you outsourcing any of the [data]?

Chertow: A combination. We can only do so much. We have, relatively, limited areas of expertise. We have done the quantification of RNA across all the tissues; all that processing has been done in-house. Obviously, all the standard histopathologic analysis that is being done by the pathologists. We have collaborators who are helping us who have access to the containment labs that will do some of the live viral culture we want to know about; viable virus that has to be done in the BSL3 labs. We have friends and colleagues also within NIAID that have expertise in sequencing, and so one of the things that they are doing is sequencing virus that was collected from different compartments to see if there is any difference in viral species across compartments. So, we have folks that are collaborating on the sequencing, and we have multiple collaborators both within NIAID but also across multiple institutes: the Dental Institute, the NIDDK, the Neurologic Institute, the Musculoskeletal. [All] asking specific questions that relate to either a particular compartment, a particular organ, a particular component of pathogenesis.

I will give you an example. We are collaborating with Mariana Kaplan from Musculoskeletal, and Mariana has an expertise in the role of NETs or neutrophil extracellular traps. This is kind of a web that a neutrophil will release that is thought to have a kind of a protective physiologic role of trapping pathogens, but also is known to contribute to some injury to the host. And so we are working with Mariana to characterize the presence of NETs in tissues across different areas of the body, in the lungs, obviously, but also in the kidneys, in the liver, in the brain, etc. We are working with collaborators across NIH, and then also a number of extramural collaborators as well.

Barr: It is really interesting. I think we will move on to another one of the studies that you are doing. You have done many. This is a newer one: your biomarker study. Will you, please, speak about the premise of your study that is looking for a biomarker that may indicate whether a person who is sick with COVID-19 may be at risk for long-term symptoms?

Chertow: Yes, so, my role in this study is as an Associate Investigator. This is a study that is led by Anthony Suffredini, who is here in the Critical Care Medicine Department. We worked with Anthony a little bit on the concept, but also with some of the plans, for sample handling and then ultimately on some of these downstream analyses. The premise behind this study, which is a natural history study, is

that individuals with COVID across the range of illness from mild to severe, who are brought here and evaluated at the Clinical Center, are deeply characterized at three different stages of their illness. The first stage is during acute illness, within the first couple weeks. Then the second is within a couple of months, and then the third is up to six months to a year out. One of the aspects of this study that is unique is that we are performing bronchoscopy with a bronchoalveolar lavage. This is a procedure where you can actually wash or sample the lower airways so you will get a sense of what run-of-the-mill in those airways is. One of the key questions here is: If you can catch somebody early in their disease course and you either sample this lung lining fluid, the lavage, or perhaps the blood, can you identify a marker in that blood or in that fluid that predicts long-term organ injury? The most obvious one is scarring of the lungs, or fibrosis of the lungs, and the idea here is that if you had a marker that you can detect early in the illness that predicts scarring in the long run, there are a number of potential therapies that target fibrosis in the lungs.

So you can imagine if you were to design a clinical trial to test one of those therapies, you would want to have a marker that says, "Okay, this marker predicts that you are likely to get long-term lung injury", and then do a trial to say, "With this drug, it either does or does not prevent" [long-term injury]. One of the goals, aside from just understanding the natural history of COVID, when you study the lungs, and the brain, and the heart, in a detailed way over time is, "Are there things that we can pick out that are going to predict a problem in those places that might help guide therapeutic interventions early?"

Barr: That would be wonderful. What challenges have you all experienced with this study today?

Chertow: So, I think the greatest challenge with these studies (which is a challenge and a strength), is that we do have limited capacity. These types of studies, because they do such a deep dive, because there is such in-depth evaluation of a single individual with imaging of their lungs and their heart and their brain, and this invasive bronchoscopy, and the blood work, and there are some functional studies, by the nature of it, you cannot enroll a thousand people. So, these are really sort of smaller cohorts. We have about 80 or so. We have a target of enrolling about 150, so we are about halfway through to our target, but the challenge with these smaller studies is, unless you have a really, really strong signal among one of these biomarkers, that really stands out, the challenge of identifying one that really sort of says, "This is what is going to happen in the future," is a bigger challenge. It is less of a challenge if you do obviously a lot larger [study], so that is probably our greatest challenge.

Barr: Yes. What do you find especially interesting about the long-hauler condition and how have you applied your knowledge of other infectious diseases you have worked with—such as measles, Influenza, Zika, and Ebola—to this particular COVID study, but also to some of your other COVID studies?

Chertow: I think there are two questions for the long-haulers that do apply because we have looked at this in Ebola. The number of people that recover from Ebola, all often have ongoing symptoms, and so the first question is how do you differentiate which of those findings, which of those symptoms, which

of those clinical manifestations, are directly attributable to the prior infection versus “Man, it has been a really hard year and we are all having some stuff that maybe we did not have”? This gets into doing actually large project prospective studies with the right control group to really decipher what can be attributed to long-hauler.

And then the second, which ties into your prior set of questions, is, okay, this piece we are attributing to long-hauler, what is driving it? That is the second question. What is the mechanism?

The way that I think about these things—and perhaps it is overly simplistic, but you got to start somewhere—you know that any given manifestation, any given finding, whether it is the brain or whatever it is, has got to fall into one of two categories: it is either driven by the virus, or it is driven by the host response to the virus, or some combination of the two. This is where this issue that we mentioned previously, at least in the most severe cases, these fatal cases where were we created a map of where the virus goes across the body and in individuals that are more than 200 and some days into their infection. Well, at least in a subset of folks, I can tell you where the virus is. In a way that we cannot query that in a healthy person, I cannot go in and sampling, you understand? So these different pieces give us insight to say, “Okay, you have got a problem with your breathing”, or maybe certain things we call brain fog; you know how much of that is attributable to persistence of all virus, of all RNA in the brain, versus just a single hit? These are the types of things that we have to decipher.

Barr: Yes, that is very interesting. So, another study that you were involved with is the high-throughput single-copy sequencing of SARS-CoV-2 to spike variants. Can you briefly introduce this study as well as your role?

Chertow: So, this was a study that was led by Eli Boritz. Eli Boritz is an infectious disease doctor and physician investigator who is also a tenure track in NIAID. The concept here is a relatively straightforward one, which is that if you do serial sampling of the virus in a single person, over time, because this is an RNA virus, there is the possibility that that virus may be changing within that person over time. One way to look at that is to serially sequence the virus from respiratory samples over time so that is what Eli did, and what he found was that in the number of patients that we looked at where we took this longitudinal serial sequencing approach, is that in one of those patients at certain time-points later in the disease, there were small populations of the virus that became more prevalent, more common. These viruses always exist in quasi-species but there was a point where a number of these, where a number of variants, became more prevalent when he sequenced the RNA. And so the thought there is, well, if you find that, then theoretically there is a possibility that what happened was that you had what is called an “escape variant.” In other words your body was building up immunity to the primary variant, putting pressure on that virus, so that virus would change over time and change just enough to avoid the immune response. And we saw a hint that that was what was going on in one person over time and so, that was what was reported in that paper.

Barr: It is very interesting. What do you think are some concrete ramifications that can come out of this study's findings?

Chertow: Well, I think that one ramification is that—and there have been others that have shown the same thing—is that there can be what is called "intra-host viral evolution." The idea there is that under certain circumstances, for example, individuals who are immunosuppressed because they have cancer, or perhaps they are on long-term steroid therapy, that that immunosuppression can allow the virus to continue to replicate. And what we then know is that the virus can change over time, and now we have already seen, for example, certain variants of the virus they call the UK variant, or the South African variant, and whatever, and some of those variants have different properties. So it highlights that this these types of things can happen within a single individual over time and that we need to be cognizant of it, and we need to continue to surveil for those changes that might have implications for the transmissibility of the virus, the pathogenicity of the virus, etc., etc. Those are the implications.

Barr: Does it happen, these different variants within a single person, within particular kinds of patients? Because I was seeing on the news that a lot of people who have had the virus for very long periods of time are those who already have immunosuppression issues, they seem to be the ones who may have this condition more than other people?

Chertow: Well, I can tell you that from our experience it is absolutely true that certain individuals that are on—I'll give you an example. As you are aware, steroid therapy was found to be one of the therapeutic therapies that was shown to be effective in reducing mortality in some of the sickest patients with COVID. Now that those steroids are routinely prescribed, but for a short period of time, and some of those patients get better, what can happen is that they can get better and that there are a subset of them that then have a re-flare of the respiratory illness where they get worse. And even though the trials have not shown that there is benefit of re-adding steroids in clinical practice, where we have very little to offer, oftentimes those people end up back on steroids. But the catch-22 is, and the idea is, that they are back on steroids to reduce the inflammatory response, but the catch-22 is that that re-addition of steroids allows the virus to continue to replicate, so the underlying problem can remain. It is in those individuals, certainly, that there would be a higher likelihood of viral evolution over time.

Barr: That is very interesting. You have been involved in many, many other COVID initiatives. If you wanted to speak about your role and some of the other studies that you have been involved with—one was looking at oral SARS-CoV-2 infection and transmission, another was a Fostamatinib study —I did not know if you wanted to speak a little bit about those.

Chertow: Well, I will just say briefly that we again have been fortunate to work with a number of collaborators across NIH and sort of have synergistic efforts at trying to unravel what the underlying drivers of illness are and illness transmission, and how we can perhaps mitigate it, [in] individuals with the SARS-CoV-2, and in the oral axis. We worked with Blake Warner in the Dental Institute. Blake is an Assistant Clinical Investigator who is early in his career, and is a very intelligent, dynamic individual, and

he reached out to us. He knew that we were doing these autopsies, and he had this observation that cells that produce saliva, the salivary glands, that those cells were, he believed, were able to support viral replication, that he was able to detect virus in saliva. And we actually were able to provide him tissues from fatal cases where he could actually prove the presence of virus in those cells by having access to some of our specimens. So, we contributed to that study which I think is an important study and emphasizes the role of saliva in transmission.

Fostamatinib actually is a drug. This trial was run by—it was a phase-two trial, so this is just showing safety of a drug that was repurposed. The idea behind this drug is that it acts at certain cells that are thought to contribute to the negative or the immunopathologic inflammatory response, and some of those cells are neutrophils, platelets, and monocytes. So, we worked with Jeff on doing some in vitro studies with that drug and in fact showed that by adding that drug to neutrophils that were stimulated with COVID plasma, that in the absence of that drug these neutrophils would NET and contribute to this inflammatory process. But when you put that drug in that milieu, it would reduce the amount of NETs that were formed, so it is sort of proof of principle. I can tell you that in the meantime Jeff has now run a phase-two clinical trial and hold your breath, because those results are coming out soon, and we are excited about it.

Barr: Yes. Has your lab helped a number of scientists across NIH proving whatever they were looking for?

Chertow: Well, we have been involved in a number of studies. This is, I think, you asked me beforehand. You said, “Oh, you guys have done so much in this past year,” and looking back, I guess we have done a lot. I guess the issue is that there is so much to do.

Barr: Yes.

Chertow: You know, it feels like there is so much more to do so when we have an opportunity to work with folks and to try to contribute to move this forward, then we try to contribute.

Barr: Yes, so, can you talk just briefly about the surviving sepsis campaign which was an international effort that sought to provide guidelines on how to manage critically ill adults with COVID-19? What was your role? Yes. We will start with that. I have subsequent questions.

Chertow: Okay, no problem. The surviving sepsis campaign is an initiative that is put forth by the American Society of Critical Care Medicine but also the European Society of Critical Care Medicine, and as you likely know there were a number of societies that came out that iteratively tried to provide guidelines on care of patients with COVID. This particular set of guidelines was focused on just the

sickest of the sick, the critically ill individuals. Early on there was a group of people that were pulled together, international folks that have expertise in this, I think it is up to 40-some individuals or so across the globe that have expertise in this, that are charged with reviewing, assimilating, and then interpreting the existing literature as it evolves, to provide evidence-based guidelines for the management of critically ill patients with COVID. I was fortunate enough to be invited to participate in that effort, and participated in the initial effort, and have participated in the subsequent efforts to update those guidelines.

Barr: Yes, that was going to be my second question. Have the recommendations been revised since it was published in June of last year?

Chertow: There has been one published revision which integrated mostly the updated data from the steroid trials that showed that steroids help with survival. That was not in the first iteration of the guidelines and now we are on our second update. We are, actually, actively reviewing some of those studies and getting ready to put that second update forward. One of the key trials that is included in that update, are trials around the use of Tocilizumab, which targets the role of the IL-6 and inflammatory cytokine in COVID, and Tocilizumab counteracts the role of that cytokine, and so there are upcoming recommendations that take into account. There are actually quite a few trials now that try to simulate that data and give some concrete recommendations on when to or not to use that drug in critically ill patients with COVID.

Barr: That is really interesting. Are you involved in any other COVID study? Well, I know you are involved in a lot of different studies but also any other initiatives on campus or off campus?

Chertow: Gosh! I think we have covered, let me just think, I think we have covered the majority of activities. It is mostly around clinical research and, you know, the other of my job is as we have emphasized, aside from the clinical care, and the research, is the training piece. I have alluded to it a little bit, so, I would like to highlight that we have a really great group of trainees in the lab that range from post-docs (postdoctoral) to doctoral candidates, to post-bacs. Part of my efforts are to inspire in that group the value of doing this kind of research, and to kind of walk them through it. So if you were to ask me what my third initiative would be, it would be to motivate that group to be able to pick up the mantle when those of us are ready to step aside and hand it off to the next generation.

Barr: That is really nice. What has it been like, how you work with a variety of ages and expertise, what has it been like trying to help those, all those different groups navigate just the work environment that has been so changed?

Chertow: Well, it is very satisfying. It is challenging and to be honest with you, it is a two-way street. We try to have an environment where we all come to the table with humility and say these are the things we know, and we do not know. We are going to be honest about them and man, there is a lot of stuff that I do not know and oftentimes it is not about years of experience and whatever. I will be taught by any number of the young folks in the lab. They will dive into the literature; they will ask really challenging or thoughtful questions and it is an exchange.

Barr: It is so satisfying, energizing!

Chertow: Yes, that is part of the benefit. I mean that honestly. Like they say, "Oh, you choose a career" and you know everything has the good and the bad, and you add it all up, but there is no doubt, there is no doubt, that that is a very motivating and satisfying part of the job.

Barr: That is very nice. So now, we are going to transition quickly to you as a person living through the pandemic. What have been some personal opportunities for you and challenges that COVID has presented?

Chertow: Yes. You have got tough and good questions. You know, we are all human beings, right? When we have talked about the work hat, but there is a home hat too, and I have an equal at home. Her name is Jessica. She is my wife, and she is also a full-time working professional. She is the Deputy Scientific Director here at the National Heart, Lung, and Blood Institute so she wears a big hat, and she is very busy, and we have two wonderful little kids. They are not that little anymore, an eight-year-old boy and our 12-year-old girl. We are a working professional family, like so many others, that had to navigate COVID and man, it has been a long year! Well, I will tell you a funny anecdote.

So, my son is in second grade this year, and we are kind of type A parents, and it is like "Go to school!", "Do your homework!", "Study, study, study!" So, I think it was the second quarter of online schooling or whatever, [when] we met with his teacher, and we were going over [his work] and we were talking about room for improvement, and she told us that of, some ridiculous number, of the last 40 individual reading sessions, he was absent from 34 out of 40. My wife and I, we are on Zoom, right? The jaw drops and I am incredulous. I am like, "How could we be this far into it?" Could we have not noticed somewhere around like eight out of ten? You know something, but that was fairly emblematic of how the year was. And, you know? The funny thing is that when we talk to our friends it is like everybody is having these same experiences.

Barr: Yes.

Chertow: So, you know, it is never about the kid. We were like how could we have let him down? So, he is no worse off, he still knows how to read and write, and he is going to get through the year, but, you know, at the time it was a bit… you know.

Barr: Oh, my goodness!

Chertow: So, we have adjusted, we are working from home, we were largely sequestered. We are very careful. My wife is largely working from home. I have come in most days, I have participated in the clinic and running the lab, but we are also looking forward to normalization again, to slowly getting back to—you know, it will not be as it was before—but you know more normal stuff: travel, seeing friends, in those ways. We found novel ways. We turned our back porch into, I do not know how you would describe it, but it was sort of like an outdoor, a lovely outdoor dining environment where, periodically we would have other friends that would be at a table over there and we would be over here with the heat lamps, and some of that innovative stuff, just to kind of maintain your sanity.

Barr: Yes, really. We are going to end on a fun question: what has been the most rewarding part for you and taking part of NIH's COVID-19 endeavors?

Chertow: Man, I got to tell you, I reflect back, and you sort of say, "It has been hard, we have done all these things. I have asked these young people to take phone calls in the middle of the night, to go and do autopsies, or to take the first shift as the attending, or to coordinate the preparation for the COVID ICU, or whatever." Honestly, the most rewarding part is—no, it is no one thing. The most rewarding part is the realization of how fortunate we are to be part of this NIH intramural community, where we have an unbelievable, almost utopian, situation of trainees to world-renowned scientists who have largely, over a very short period of time, done a hundred percent refocus of their attention to try to understand what is driving this disease and how to figure it out, and for and the most rewarding part for me is to be one of the one of the pegs in that Venn diagram where we can have touch points. I have met so many different people! And again, to sit on the phone calls and they are talking to me about stuff, I am like "Whoa, whoa, I do not understand that!" But slowly, over time, I am understanding more and realizing how amazing it is for myself and my group to be able to be part of it.

Barr: to learn so much.

Chertow: Yes. So, that to me is the most rewarding piece.

Bar: That is really nice, but is there anything else that you would want to add that you did not have the chance to mention?

Chertow: You covered it. You are an amazing interviewer. You took me all the way from the beginning through a really amazing year, and I just want to thank you for taking the time to interview me, and also, for all your thoughtful and insightful questions.

Barr: Absolutely. Well, I wish you, and your group, and your family the best as unfortunately the pandemic continues, and I look forward to learning more about your studies, as they continue as well.

Chertow: Thank you so much.