

## **CDC's 25<sup>th</sup> ME/CFS Stakeholder Engagement and Communication (SEC) Call**

**September 18, 2026, CDC ME/CFS**

*Christine Pearson:* Good afternoon, everyone. Welcome to today's ME/CFS stakeholder engagement and communications call. I'm Christine Pearson; I lead communications in CDC's Division of High Consequence Pathogens and Pathology, where the ME/CFS program is located within CDC's organizational structure.

As you may know, CDC holds these SEC calls to provide information for people with ME/CFS, their loved ones, clinicians and anyone else interested in the disease as part of our outreach and communications activity. Today we'll hear program updates from Dr. Joanna Regan. She's a MD and is the team lead for our clinical research, epidemiology and outreach team in CDC's ME/CFS program. Then we'll turn it over to our guest speaker, well known ME/CFS researcher and clinician, Nancy Klimas from Nova Southeastern University in Florida. After Dr. Klimas' presentation, we'll move on to the Q&A section.

I'd like to start with a few housekeeping items before we begin. To turn on live captions in Teams, look for the more tab in the upper right-hand corner of your screen. Click on the three dots and then select language and speech from the drop-down menu and then click on the show live captions option. Captions are controlled individually, so each participant can choose whether to display them on your screen or not.

We will be using the Q&A function in teams to take questions today, so please submit all questions using the Q&A feature at the bottom of the, I guess actually at the top of, your screen. Select Q&A in the toolbar and then type your question and submit it. Questions will be addressed to the appropriate speaker whether you have one for Dr. Klimas or Dr. Regan. Also, attendee microphones and cameras will not be used during this webinar. Before we start, I'd like to remind everyone that the call is open to the public, so please use discretion in sharing personal information. We're recording this call, so please disconnect now if you have any concerns about that. We'll post a transcript and video as soon as possible after the call.

Now we'll turn it over to Dr. Regan to start the program. Welcome.

*Dr. Regan:* Thank you very much for that introduction and welcome everyone to our Stakeholder Engagement and Communication Call. We have many updates to provide you since the last S-E-C call. Next slide.

Since the last call we have said goodbye to a number of colleagues who contributed substantially to this work, including Beth Unger, Dana Brimmer, Sally Lin, Zachary McCann, Yang Chen, Mangalathu Rajeevan, Maung Khin, Val Poe and Jessica Maya.

Each of these colleagues contributed important expertise, institutional knowledge and dedication to the ME/CFS program, and we are grateful for their service. Next slide.

At the same time, I want to make sure you know who is here and continuing this work. I began shortly after the last S-E-C call and continue to serve as the ME/CFS team lead. Also on the team are Stephanie Weaver, Elizabeth Fall, Dane Benedict and Laura Eloyan is currently serving as the Acting Branch Chief.

I'd now like to share some of the accomplishments from the program. Before I move into our education and outreach activities, I want to highlight some of the scientific work this continued since our last S-E-C call. Next slide.

We have included slides summarizing publications from the program and our collaborators during this period. These publications reflect a broad effort to better understand ME/CFS and Long COVID - two complex infection associated chronic conditions that can have a major impact on people's health and daily lives. The research looks at these conditions from several different angles: what symptoms and health challenges people experience, how these experiences change over time, how we can better measure physical function and track these illnesses in the population, and what biological factors may help explain why some people become or remain ill? Next slide.

Just as importantly, this work recognizes that understanding these illnesses requires listening to the people who live with them. Several of these publications focus on patient experiences, barriers to participating in research, and ways to bring lived experience into healthcare and provider education. Taken together, these studies are helping build evidence needed to better recognize and understand ME/CFS, improve how we study and measure them, support healthcare providers and ultimately help improve care and quality of life for people affected by these conditions. Next slide.

I want to highlight a few areas of our current ME/CFS research. One is STOP ME/CFS, our surveillance project with a large healthcare system in Northern California. The project combines surveys about people's symptoms with information from their healthcare records to better understand how many people may have ME/CFS, what their experiences look like and how the illness changes over time. One important, and perhaps not surprising finding, is that ME/CFS may be substantially underrecognized in routine healthcare data. This work can help us better understand ME/CFS and identify opportunities to improve recognition and care.

We're also continuing our work with Medscape to help healthcare providers learn more about ME/CFS. The latest Medscape course just finished on September 6. Almost 21,000 healthcare professionals took part. Of those who filled out the survey, 94% said what they learned would help them or their team, and 79% said they plan to make at least one change in how they work. We're working with Medscape on a new course called "Untangling Complexities and Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Optimizing Outcomes in the Context of Comorbidities." The new course is

planned for release in 2026. It brings together clinicians with expertise in ME/CFS and related conditions and focuses on some of the challenges providers face when caring for people with ME/CFS, particularly when people are also dealing with overlapping conditions.

Another major effort is our work with family health centers of San Diego through Project ECHO. This program gives primary care providers opportunities to learn directly from experts through case discussions, telemeasuring, webinars and continuing education. People with lived experience are also included in the educational approach. In the past two years, the program has held 71 sessions, including 25 webinars. This work is especially important because many people with ME/CFS have difficulty finding clinicians who understand the illness and access to specialists can be challenging. Project ECHO is designed to provide training to primary care providers to improve access to high-quality ME/CFS care for patients in their own communities.

These are just a few parts of a larger ME/CFS portfolio underway at CDC. Our other work includes research and surveillance, sharing data and biospecimens with the broader research community, education for healthcare professionals, work involving children and school nurses and communication and engagement activities. Across these efforts, our focus is on using what we learned to improve understanding of ME/CFS, strengthen healthcare provider knowledge, and ultimately contribute to better recognition and care for people living with ME/CFS. Next slide.

It is now my pleasure to introduce our guest speaker, Dr. Nancy Klimas. Dr. Klimas is professor of medicine at the Dr. Kiran C. Patel College of Osteopathic Medicine at Nova Southeastern University, where she serves as Chair of the Department of Clinical Immunology and directs the Institute for Neuroimmune Medicine. She leads an interdisciplinary clinical and research group that includes clinical laboratory and computational research in addition to its missions in interdisciplinary clinical care and medical education. Dr. Klimas is also professor emerita at the University of Miami Miller School of Medicine and is a diplomat of the American Board of Internal Medicine, Diagnostic Laboratory, Immunology and Environmental Medicine. She has achieved national and international recognition for research in clinical efforts involving multi-system disorders, including ME/CFS, Long COVID and Gulf War illness. Her work in ME/CFS extends back more than three decades. Her first ME/CFS paper, published in 1991, was an early study examining viral reactivation, immune dysfunction, and chronic immune activation in ME/CFS. Dr. Klimas is a past president of the International Association for CFS and Myalgic Encephalomyelitis and has served on numerous national and international advisory groups including the HHS CFS Advisory Committee, the VA Gulf War Illness Research Advisory committee, several NIH working groups focused on ME/CFS, and the Institute of Medicine National Academy of Sciences Working group on ME/CFS.

Today, Dr. Klimas will speak with us about how progress and Long COVID is helping us understand ME/CFS. The relationship between emerging knowledge about Long COVID and decades of research on ME/CFS is an area of great interest to patients, clinicians

and researchers alike, and we're very pleased to have Dr. Klimas with us to discuss what we are learning. Dr. Klimas, thank you for joining us and I'll turn it over to you.

*Dr. Klimas:* Thank you, that was a lovely introduction and thank you for that. Thank you and thank you for having me here today, I really appreciate it. I've been in the field for a long time. Many of you heard me speak before, but this time it's kind of fun because many people, and I've given this talk myself about what ME has taught the Long COVID investigators and how to focus, but now that they've been doing Long COVID research and we have too for quite some time, what is Long COVID research actually helping us understand in the ME/CFS world that might translate to clinical care?

That would be great talk to give to patients and their people who love them and people who care for them today. So, thank you so much for having me and I'll do my best to see how this comes out. It's first time I've given this talk, so bear with me.

So the first comment that I wanted to make is that people, you know, there's always sort of like this sense that there's one pie and if you get more than I get less. And I want people to understand that in the case of Long COVID, even though that Long COVID has seen a ridiculously much higher amount of money from the point of view of research than ME/CFS ever had. It's not ridiculous they needed every nickel, but it's ridiculous that ME/CFS didn't get that much to begin with. You can appreciate that.

But Long COVID has had a major investment and what you see as a result is a tremendous flush of new people into the field - very talented people, great big names and passionate young investigators - a lot of good people flushing into the field, bringing new skills and skill sets. The other thing you see in the Long COVID literature that's a consequence of having enough money to do the work is that the studies are...it's called power. There's enough subjects in this study to say something definitively instead of calling it a pilot or a suggestion. We have these papers now published with thousands of patients in them that really give a lot of insight.

So the way we have been describing ME and the way we've been describing Long COVID is from the point of view, what's called a phenotype, a clinical phenotype. That's when symptoms cluster, like all the autonomic symptoms, might be a phenotype, or a pain or sleep or something like that might be a phenotype. But what I'm going to talk about today is something called endotypes. Endotypes is when the underlying biology is investigated and there is a mediator or some biologic part that can be defined and defined illness by its biology, rather than simply its symptoms. So then I want to talk about that today, because in the end that's what brings us interventions that are meaningful.

So I see this as a central opportunity. ME, because we've been around a long time doing this work, a lot of patients, a lot of advocacy, a lot of really good science has gone on for a lot of years and we have been able to move the field to understand how important first the post exertional relapse and the inability to exert without consequence. Let's just call it that is a defining component of the illness and it makes it unique. There are some

other illnesses that do this that aren't ME or Long COVID, like for instance multiple sclerosis or myasthenia gravis, that the illnesses that are neuroinflammatory and have a lot of neuromuscular connection. So that's a theme, neuromuscular connections.

Also, ME brought people to the field and primed the field so that when Long COVID hit, there were already experts that had worked out a lot of the issues that have to do with what's the right method? Do we all agree on a method? The entire common data elements project, which was put on as a CDC and NIH collaboration with all the experts on the planet trying to decide what's the best way to measure dysautonomia? What should we use to measure cognition? Measure sleep? So that we're not always comparing apples to oranges, even when we're in the same domain of illness we're looking at sleep. If you look at it one way and I look at another, we never compare our results. So there was a lot of work over the last 10 years or so to come up with a consensus on what we would use as the tools that we use to measure illness and its severity and the way it presents.

Then we had some pretty big clues from the ME world. What was going on that the immune system was overactivated, the autonomic nervous system was on a trigger and very sympathetically driven, that there was vascular problems, there were mitochondrial problems. All these things were already proposed as mechanisms with some data to support all of that.

Then Long COVID came along and sort of had a running start. You didn't have to start from scratch and it had some real benefits. You knew the day it started. With ME, sometimes you do, sometimes you don't. You have a patient [that] comes in and says on October 12, 1995, my life changed forever, and this is what that day was. Other patients say on and around the fall of 1995, I got sick, and I don't know what was there. So it's a little harder with the retrospect-o-scope to understand exactly what was going on and then we defined an illness that you had to be sick six months before we even defined it. So you really missed that window of time right after the acute illness to know what was going on that made people go from an acute illness to a chronic illness.

So with Long COVID we had the opportunity because it was recognized so early in Long COVID, or in the pandemic, it was recognized like by 2021 we knew it was happening, that there were already some studies trying to grab index cases, people that had acute COVID and follow them through. So there is some data and some biology and a data repository that's been developed at the NIH to help scientists that are trying to understand why did this happen to begin with? But people who are already ill want to know, even perhaps even more so, why does it persist? Why am I still sick? It's one thing to have gotten sick and not gotten better right away, but why now? A year, 2-3 years later, or in the case of ME/CFS, 10, 15, 20 years later, am I still sick? That's a really important research question that has to be answered to give us evidence-based guidelines in how we treat people, we need to understand that. To do that, we really need to understand the biology. So Long COVID gives us the opportunity to understand the early phases of the illness, but also as it's going on, what the duration.

*Dr. Regan:* Nancy, I'm sorry to interrupt. This is Joanna. Are you advancing your slides because we're still on the 1st slide?

*Dr. Klimas:* Are you an essential opportunity?

*Dr. Regan:* No, we're on your first.

*Dr. Klimas:* I am advancing OK. Can you guys switch to your sides and our next slides?

*Dr. Regan:* Yes, everyone, hold on one moment.

*Dr. Klimas:* I don't know why. Thank you very much. I'll stop sharing if I can or you can stop me sharing. Thank you for saying that as I could have gone on the whole talk. I wasn't very far. I was on the third slide or maybe the 4th? I was on the 4th slide. If you want, I can do it again and see if I can't share. That's weird because we practiced and it worked. I just pushed share, but then you guys unshared me. So I'll just wait.

Anyway, I'll talk while we wait. Oh, there we go. Thank you. I see it. Do you see it?

*Kristen Nordlund:* We do. Would you mind trying it one more time, Nancy?

*Dr. Klimas:* Yeah, that's working. Do you see a whole screen or a notes screen?

*Dr. Regan:* No, we see it now.

*Dr. Klimas:* Ok, the whole screen OK. All right. So that was the first slide, ME and this second slide research accelerator, I spoke to that for a moment that it's something that's really going to not replace ME/CFS but help us accelerate what we understand about ME/CFS. And then let's see if the third slide. I need to make this bigger for me. There we go. I can see it OK. I was on this slide that ME has contributed all this knowledge that we got up to the data in 2020 and since and then Long COVID contributed by giving us this contribution of catching the illness at its very starting point and then being able to see over time what the duration effects are and how things change over time, but also it's showing us a very heterogeneous, very complicated population of people and trying to understand how to group people into meaningful groups that we could treat in a logical way is very important.

So, and that's on full screen for you guys. Because I'm seeing a very small thumbprint.

*Kristen Nordlund:* Yes it is.

*Dr. Klimas:* OK, good thing I printed them out. So together between these two fields ME/CFS we can use the earlier knowledge of ME/CFS and then newer cohort of Long COVID to do comparator studies. Now we can replicate and refine what we already

thought we knew about ME/CFS now with much larger cohorts to see if it's something that matters in Long COVID as well and define these biologically linked subgroups that we can test. Importantly, the focus of this talk today, whether or not they're underlying mediators, that could potentially be targets for therapy.

So I've heard so many people say are they the same? You know, early on I might oppose this question myself. In fact, I probably did. Now I'm saying that's not the right question. The question is where are they the same? What can we learn from where they are the same? Because there's going to be differences, and why do we know this? Because science, you know...Long COVID, there's a part of Long COVID that our group is testing right now with a really exciting clinical trial, because there is a subgroup of Long COVID that still has spike protein leftover from the COVID infection. And it's our hypothesis that that spike protein matters. That it's affecting the way the blood vessels, it's inflaming the blood vessels that it's causing the immune system to stay overactive, that it's pushing the on button on the autonomic nervous system. So we're trying to mop out of the patient using a monoclonal antibody, the spike protein to see if we can get a clinical response and improve greater outcomes in people who have COVID.

Well, that's a very good Long COVID study, but what would it teach us about ME/CFS? Antigens matter. Antigens that are touching the blood vessels matter. Are there other antigens that are driving inflammation in the blood vessels or systemically that matter? Could we potentially mop them protectively than we have been? So even in a study that seems so targeted to COVID, it has consequences with ME/CFS population.

So the right question is not, are they the same? The right question is they're going to be the same in areas and even where they diverge, there might be a common underlying mechanism, perhaps triggered by different things, but the mechanism's common and therefore a treatable space or at least space that needs to be treated.

So it's very exciting to look at the illnesses together side by side. In ME/CFS, you know, we were able to follow 30 plus years, almost 40 years of research to contribute before the Long COVID work needed to be done, and here we were able to find all these critical areas post exertional cognition, autonomic sleep and pain energy. I should put immunology in there because it's underneath all of that and that allowed us to generate a lot of hypothesis that could be tested, but in an inadequate scale because mostly because of there were years that the whole country only had \$3,000,000 of research going on and it was mostly almost all at the CDC. So there was very limited federal funding for long periods of time and to say that that's all better. It's not all better. It's just a little bit better because now we have some centers and we have, you know, we have new studies being funded which are exciting, but we still need a lot more ME/CFS research funding and work.

What did ME/CFS teach us then about that? Under recognition produces under research. You just heard that the CDC is doing an awful lot on provider education and that is trying to answer this under recognition problem and that is that it takes the average patient even in this day and age at least a year to be recognized if they

themselves recognize they have a problem. So two to five years in the early studies was the common bed and in my own clinical experience, it can be a lot more than that. People could be pursuing answers - they knew they were sick - but not get the answer they needed it to start down the right, sometimes for a decade. A really, really difficult situation. So there was a surveillance gap became a funding, an interventional gap in the ME/CFS world.

Part of this is that, I'm going to give some evidence for this in a minute with some data, that patients themselves, people, compensate when they think there's something wrong. So, I can't do all that I could do because I'm getting older because I'm dependent because this because that and instead of pursuing a medical diagnosis, instead you scaled it back and essentially start pacing and not test your reserve. Give up exercise altogether, because if you do, you get sick. But then you're like, wow, I can't give up exercise cause because whatever, but it doesn't mean that you pursued a medical diagnosis.

And so this idea that patients also are part of the problem not to point at patients because it's really the system. But patients also are part of the problem because they're like, eh, I'll just, I'll just adapt. I'll just scale back my life until you can't anymore. Until you can't work. Until you're not fulfilling your obligations until the consequence is such that you can't ignore it any further, and so in patient surveys this is been picked up that the patients themselves waited more than a year before they started pursuing interventions or treatments, or even a diagnosis.

So we talk about, you know, ME/CFS and talk about Long COVID and what do we learn from each from these. The CDC put out a call for proposals. It's been about five years ago now and we answered and it resulted in this study COVID-UPP, COVID Understanding the Post Viral Phase. That's UPP. In that we proposed to do a study that mirrored the MCAM study that CDC had completed just before the pandemic. It was 7 centers pulling in well characterized ME/CFS patients and doing a huge cohort of patients on-site evaluations and then a second wave of that where the same group came in the second time for exercise physiology and whatnot. So we had all that data with the CDC team had had contracted out to this group to pull in all that and my group was one of those. Our site was a such study site.

So when this call for proposals came out, our site proposed to be a Center for this COVID-UPP study where we would bring in a very large number of non COVID patients and then essentially do the same kind of assessments and follow them and see what became of them. So we had more than 1,000 people participating in an online survey. They all came from South Florida. We were trying to get a population study that reflected the population of South Florida. So we use the local healthcare systems to send out emails and text messages to people that had had COVID and said would you participate? Literally, I don't remember the numbers, but it's close to 100,000 emails went out to get these 1,000 patients. It's amazing how hard it is to recruit these things, but they were representative. We have 55% Hispanic, which is very South Florida, 10% African American, very close to what our actual demographic is down here and we're

really proud of that. That's an extremely...it's an excellent accomplishment, and in these more than 1,000 people filled out the baseline and then they're supposed to come in every quarter for several years and continue to follow it. So we can look at trajectory and change over time, and that's the kind of data we're currently analyzing. And then we have the incident data to compare to so that's very exciting. So we're hoping that this cohort is going to really help us understand where they overlap and where they differ.

There's a very large biorepository component to this that lets us dig into the endotype - into the biology of the illness. So this is one of the most important things that came out so far from this group. Out of these groups we had we enriched for being sick. So there's 639 sick people there in the red circle and 174 control group recovered people. But the people in the yellow circle were supposed to be in the green circle. They were people who perceived themselves as recovered. But when you really looked at their symptom burden, they had significant symptoms that did not exist prior to COVID. These are people who were calling this boundary group and they're very similar to the study the CDC did back in Wichita, where they were also longitudinally following people, and they came up with this group they called *insufficient* - people that had chronic fatigue syndrome like symptoms, but they either weren't severe enough or have enough of the symptoms on the checklist to make the case definition - and they follow them longitudinally and they saw in that ME/CFS data in that study that some people moved into the sick group and some people from the sick group would move into the boundary group where the insufficient symptom group over time. Essentially good day, bad day. Those of you with this illness know there are days where you are profoundly ill and if you're lucky, there are days when you're much less profoundly ill.

So this lucky group perhaps is the yellow group, but we're also proposing it might not be that. It might be people that are in that little space of time between the time when they are symptomatic but living in their reserves that they have just enough reserve that they can power through so they're not perceiving themselves as being very ill because they haven't hit a wall yet. But are they going to hit a wall? Because there's something going there.

There's another study by Doug Frazier up in Canada who looked at the epigenetics of this illness. He looked at the metabolome. I'm sorry I don't remember if it's the proteome or the metabolome, but it was an -omic study, and what he showed was in the healthy controls. He had a group of people that were pre-pandemic plasma samples in the freezer from before there was COVID and they had a group of people that were sick and they had a group of people who were recovered like we did study and in the recovery group he saw the signature of Long COVID. It just wasn't very severe, so he saw the proteome showing inflammation and mitochondrial reserve issues and this kind of thing. But below the threshold of symptomatic suggesting that having had COVID, at least in a portion of the recovered people, they were left with this below the threshold of symptoms, but changed. So a little worrisome, a lot worrisome. But we're wondering if this yellow group that we're picking up on here might be that group. So we're discussing what we should have to do to try to figure that out.

So the other thing, if you look green, yellow, red here is that to have the Long COVID case definition, you don't have to be post exertional so you can see that but not all of them did. They all had to have fatigue, but they didn't have to necessarily have post exertional relapse. And you can see the sick people split and this 42% would fit the case definition for ME/CFS because it requires post-exertional relapse. But in this boundary group you had post exertional folks, just not as many. Even in the recovered group you had some people that were acknowledging that type of symptom.

So when you're looking at this comparator zone, are we looking at function masking a reduced reserve that people can still do? But what well, are they drawing from? And I would suggest to you that preserved performance is not exactly the same thing as normalizing their biology. That's one of the things we explore in this study.

So I talked before about the difference between phenotype and endotype; phenotype being the clinical presentation the symptoms, and then endotype being the biology underneath that. The other thing we want to do in this Long COVID study and in ME/CFS as well is better define people by mechanistically what's underneath everything. Honestly that's the most exciting thing you can think of in this field is if you can put your finger on the biology then you can target that biology for treatment. That's the big goal. And are we there? We know a lot about the biology of ME/CFS and we know a lot about the biology of Long COVID and it takes time and money to do that and time and money has been spent. So it's exciting to see the kind of data that's coming out from studies at this time.

So what do we know? Well, one of the things we know, what does it mean to learn about the biology is that there's a much stronger understanding of what the underlying mediators might be. I didn't put it on this slide, but one of the things that we care a lot about, at least me as a clinician because I see it, is what does it mean to have this illness for a year or three years or 10 years or 20 years. Because things happen in a 20-year trajectory. For instance, autoimmune things can happen. The immune system's overactivated it's in hyperdrive all the time and all you have to do is get one clone of cells going that's against self and now you've got a whole another thing going on, another comorbidity and and those things could accumulate over time. They don't all have to present the day that you got sick. So, duration matters as much as what's going on early what goes on as you progress. So that makes an important target for understanding this illness.

So immunology, I always have to start with immunology because, you know, I'm immunologist. Let me start there, it's still up front and center. But it's more complicated than you think. Because immunology's not a single button. There's a lot of aspects to immunology and so one thing, for instance, is we talk about natural killer cells. One thing the Institute of Medicine could agree on is that there was sufficient data to consider NK cell dysfunction as a real thing, a real biomarker in in ME/CFS. What would that mean if you had impaired NK cell function? Well, I like to refer to it maybe over simplistically as a backup system because you have this more sophisticated, more evolved system to try to take care of things that come along, the cytotoxic T cells are

supposed to take out viral reactivated cells and then if they fail to do that, NK cells would come along and do that. NK Cells though, have a really important role to play in oncology and watching out for cancer cells, as do cytotoxic T cells. You have this other part of your immunity, the B cell immunity, that which is your antibody production and we don't talk a lot about it, but it's also a thing and there's a lot of papers that have been showing immunoglobulin sub class deficiencies in ME/CFS and now in Long COVID. That matters because the subclasses that tend to be impaired are the ones that tend to be holding your antiviral memory - IgG1 and IgG3. All this taken together means a backup system that's broken does matter because your front system, the more efficient effective jump on its systems, the T cells and the B cells, they're not working all that well. They're not broken to the point of, you know, opportunistic infections, but they're broken enough to let old viruses reactivate and perhaps have surveillance down.

There's another really important part of the immune system, and that is one that recognizes autoimmunity and takes those cells out before they get out of hand and that too is an issue to be considered because there is evidence of autoimmunity is an important player in both Long COVID and in ME/CFS. The impaired immune containment as an underlying endotype is an important one. It gives us a target for treatment.

From immune containment failure to things that now become persistent loops, you fail to contain it, it reactivated. Take Epstein Barr virus, one of the most famous ones or SARS Co V2 antigen. What if these things are activated, going and then what they do is turn the immune system on. This immune system on is already over activated. The very first thing the 1st paper we wrote in 1991 talked about over activated numbers of T cells circulating that the immune system's overactivated and later on is the language changed we started talking about chronic immune activation leading to immune senescence and aging immune system, or if you would, an immune system in hibernation. A quieter, less reactive immune system because it can't keep in this hyperdrive forever. But when it's less effective then more viruses reactivate. Viruses reactivate they keep driving the chronic persistent overactivated state and so on this constant circle.

The other thing that contributes to a constant circle is any autoimmunity, because that is another immune system activator. And so the system consequence is inflammation everywhere, including in the blood vessel wall, the endothelium, the autonomic nervous system being affected because there's an interplay between the autonomic and the immune system inflammation in the brain, subtle, but enough to interrupt the fine tuning, the triggering of the hypothalamic pituitary axis. And then the role of oxidative stress in mitochondria and in driving both the abnormality and function, as well as some of the inflammation involved in these conditions.

So that's one target, the immune system. Can we fix it? Another target is the endothelium and the microcirculation. This is incredibly important and you know how things come sort of in waves of new knowledge? This was a wave of new knowledge, and it started with David Systrom's really elegant study that looked at profusion by

doing an elaborate study on hundreds of people - a definitive study in ME/CFS and then again, he did it in Long COVID. A very definitive study that showed a number of different problems with just delivering oxygen to the tissues. It was later looked at through a different window by the group in the Netherlands, Dr. Foust and Dr. Appleman - I think I have their slide here - that looked at the ability of oxygen to be extracted in the tissues and what the effect was in their tissues. So they're cross validating studies and they're important because you can imagine if you don't get oxygen to the tissue then how's it supposed to work? And so that is one big player, but also how do we deliver oxygen to the tissue through the microvasculature, through the capillary beds, through the arterials and that's the other thing they saw here was a two-step kind of problem where the drive of the sympathetic nervous system, the adrenaline clamps it down so it can't perfuse that well. But there's also inflammation on the wall of the vessel itself and so. And so there's a sort of a double hit there that causes the capillary beds to be really affected and not be able to maintain perfusion.

So using exercise as a way to demonstrate that the elegant experiment would be this exercise is like I described with Dr. Systrom and again with Dr. Bruce's work that they use put people on a bike and measure them before, during, and after challenge, and then demonstrated that despite a demand for more, the body gave less oxygen and glucose to the tissue, and failed to extract oxygen so that the blood leaving the heart and going out to the muscles, which normally would reduce grab all the oxygen - go from red to blue - come back to the heart red with very little oxygen extraction because it never got pulled out as it passed through the tissues. So it's an extremely important concept because it's a treatable concept, a place to go to try to fix things.

In this slide, this is describing Dr. Systrom's work. He showed not only this inability to perfuse the tissues, the oxygen on the left, on the red part of the slide, but also not enough blood coming back to the heart, the preload they call that...how much is the heart filling before it beats? And it wasn't filling all the way before. It would be, which would make it much more, much less able to maintain circulation correctly.

So this comes back to treatable points. Part one - cardiac output. How do you get enough blood to come back to the heart? A paper that we published for Dr. Hurwitz about 10 years ago showed this pre-loaded reduction showed this inability to totally fill the heart before it went to beat. We also were able to demonstrate that that was attached to a total blood volume reduction of almost a liter of blood. So that's why you'll find your physicians just pounding on you to get enough electrolytes and fluids on board because that's a demonstrable fact, that there's a reduced blood volume and that alone will cause vasoconstriction. I mean, if you don't have enough to fill it up, you got to constrict it. So that's part of it. But it also means you're not getting enough back to the heart to push it out and give you enough of a pump to get it all through all the tissues.

Then the part two is vascular regulation, another treatable point, and you'll see some trials on right now looking at vascular regulation. Can you open up the arteries without opening the veins so much that they pool the blood and make everything less efficient,

way to preferentially get it through the artery side and then let it return normally through the venous side. And there are a number of studies, but we commonly use a drug called *Midodrine* in clinic that does that...that vasoconstricts the veins rather than vasoconstricting the arteries. But you still need a way to keep those arteries open. Then things that would improve micro circulation at the capillary level, how do you make that one by one by ones blood vessel trickle through those tiny little capillaries instead of being completely constricted? Again, vasoconstriction being one of the problems, but the endothelial wall itself being damaged is another and can we work on repair making those walls slippery again, opening up that vasculature, and there's some very reasonable clinical trials either underway or about to be underway going down that path

Then step four you got the blood there. Now it needs to get into the cell and be extracted and drive that mitochondria. There's been a lot of studies that are focused on mitochondria and they should continue to be so. The mitochondria are definitely a problem; they don't work unless you perfuse them, and so the idea that perfusion first mitochondria second in my mind, my clinical brain, says don't make them work harder if they're not working with anything that they don't have oxygen and glucose, they're just going to make a lot of oxidative stress and perhaps make me more damaging. And so trying to make the circulation work and then get the mitochondria to do their job that makes sense. And then there's some very beautiful work, Dr. Fares work and others on the actual mitochondrial dysfunction going on in ME/CFS.

What do they have in common now? You've got David Systrom's doing studies Long COVID and ME/CFS that showed essentially the same thing, and you have Dr. Bruce and Appleman's group doing the muscle biopsies before and after exercise challenge and showing essentially the same thing.

Here we have a shared pathophysiology where anything we learn on Long COVID is going to really benefit the ME/CFS patients and wouldn't it be nice to have them both in all those trials? Let's hope that we can get there, but, it's very exciting that the sophistication of this work, and that they were done in large numbers, you can't quibble about the findings. This is really important discoveries that have moved the field in the last few years.

Just actually talked about this one, but let's see what did I leave out? I talked about the metabolic changes and the exercise is bad for muscles, but I didn't mention the amount of inflammation that's being driven in the muscle itself as a result of this hypoxic state and the other thing that David Systrom postulates, we don't know this because there's two theories on the sensory...the pain...the fibromyalgia pain, that patients so frequently have and the concept of small fiber neuropathy, which is when the sensory fibers are damaged and cause pain because they're inflamed and damaged. Dr. Systrom postulated, and it's not a bad one, if this is one of those what came first, you know...what came first? Did the ischemic damage? Did the inability to see oxygen and glucose delivered to the tip tippy, tippy tip tips of your capillary beds with a sensory fibers are cause ischemic damage to the nerve ending? That is what caused the nerve

endings to diminish and be more inflamed. Is that the cause, and perhaps as a part of that breaking down and showing themselves the immune system, setting up an auto immune downstream event? Or did auto immunity happen first and they're being damaged by auto antibodies because the German group Commons Group in Germany has shown very clearly auto antibodies, both to the vascular and to the small fiber neuropathy and in [just block the person in Harvard that did it] anyways, there's a number of groups that have looked at autoimmunity at the level of the small fiber and at the blood vessels that are feeding the small fibers and found autoimmune changes.

So, there's endotype very targetable things. If this is an auto antibody condition, then we know what to do with autoantibodies. There's endless studies in autoimmune diseases and the whole armamentarium of things you can push at it. And there are people doing those trials already in ME/CFS and in Long COVID to approach this illness through the auto antibody hypothesis.

But if it's ischemia, there's far less being done to try to figure out how to get those blood vessels to see enough blood flow. But if you put this all together, this idea that you got to profuse it to have metabolism to make mitochondria work, mitochondria stop working, you get less energy, less energy fatigue, a great vicious cycle of activities there that get you into a perfusion metabolism loop of chronicity and chronic illness.

So where does this give us some things to treat endothelial dysfunction? We know that the endothelium is inflamed, that it's overactivated, that it's killing cells off...there's a dead endothelial cells circulating that we can measure as a measure of what's going on, and they're a targetable place. And so that's exciting. If we find the problem and it looks like there's a lot of work now going on to discover these problems, Dr. Pretorius's work in South Africa has been just extraordinary there. There's a Dr. Shehada at the University of Miami too, I got to give her a shout out, but the endothelial activation and chronic activation and cell death and turnover has a vascular consequence and a clinical consequence, and these are targetable points, treatable spaces.

Autonomic dysfunction. How am I doing on time? Autonomic and vascular worked hand in hand, right? So the, blood flow is also being completely regulated by the autonomic nervous system, as is your intestinal peristalsis, your rate of your intestines going the fullness and the bloating and all those kinds of symptoms is a part of this illness, that postprandial eating something and getting much worse, very autonomic in its way of doing. So, the autonomic nervous system is there playing with the blood vessels and now again we're down to is what we're seeing strictly motility issues? Is there actual dysfunction? Is their actual ischemia driving some of these symptoms? Because they are severe symptoms and they need to be thought in a very serious way. We're not talking about things that are just to be glanced over and go ho hum, that's interesting. These are major drivers of serious health issues, and so this autonomic vascular space is important and relies on the ability to deliver oxygen and glucose to the tissues so that they make energy. When they fail to do that, they fill up into something called anaerobic energy that's much more inflammatory, much more oxidative stress

generating a lot, a lot of free radicals going on and less efficient. And so it's the reason why we have blood flow and oxygen and glucose. We need it.

What does it mean to the brain though? We talk a lot about the muscle, but the brain is then the muscle uses more energy than anything, but the brain is second in line. The brain uses more energy right after muscle, and so the ability to deliver oxygen and glucose to the brain really matters and you'll see that there's also been some great work by a lot of different groups. Mickey Tao's recent work in the Maestro study stands out, but there have been people before her in ME/CFS that show the same thing. Blood flow to the brain is diminished, particularly after you sit up in the people that are the most autonomically affected. The POTS patients and the folks with a lot of autonomic overlay, which is most of them. And so, if your brain's not getting enough glucose and oxygen, it has to switch to anaerobic. It's going to make a lot more oxidative stress, even in a young person. Measurably, you can see oxidative stress in the brain and that matters 'cause then the brain...what is brain fog? You know, is it inflammation? Is it oxidative stress? Is it a lack of perfusion or is it all three? It's all three in my mind. It's you couldn't say you can't have the one without the other two popping in. But the brain and the skeletal muscle have a lot in common, and it's easier to look at muscle. And so you're going to see a lot of muscle studies that will matter.

Our group does a lot of systems biology. We're not the only group that does. I know Cornell's doing a lot of this work and others, but this is the idea that when you have all this data across an exercise challenge, it's called dynamic data. You're looking at people at rest, and they look pretty decent. You only see a few things wrong and ME/CFS patients at best. You put them under an exercise challenge, now you see a whole lot wrong and then you follow them for the next 24 or 48 hours and you see all these downstream things that then go wrong. And you can put them in order and using computational modeling you can figure out what happened first, second, third and try to figure out what to fix this first to try to prevent all this downstream stuff that you can measure later. And so our group and others has been doing this type of work and predicting clinical therapies. Our group would say very clearly that pushing one button never makes everyone all better...that if the immune system and the endocrine system and the autonomic nervous system, it's all engaged in all of this, that you're going to have to fix at least two things to try to realign things back into a normal balance. And so you'll see that studies that are trying to do things in combinations and in the right order of go...like I said, perfusion probably matters before you try to fix the mitochondria because they need oxygen. So trying to think about how do you fix these things in a logical sequence with things that you can fix.

So, shifting balance than the mediator focus management. I know what you really care a lot about is what does this mean to you as a patient as you've got this terrible illness? Is there something to be gleaned from this lecture of mine that might matter to how you're being or if you're a physician, how do you align your treatment to what you understand about the illness? This is what I was trying to hopefully make it my major points on here. There is this idea of mediator-focused management. So when you look at clinical patterns, you know they can give you the place that these treatment.

The obvious one is autonomic. When they've orthostatic intolerance in POTS and tachycardia and hypotension, ravenous pooling. Is there a treatable space to fix and their management targets that are there. When you see people with [um] you can define it more and more even in a clinical in your patient, rather than waiting for research to happen, you know, can you measure things like blood volume or changes in blood pressure and pulse standing and sitting? And yes, you can and more and more there's like devices like watches and bands and things that give us, you know, in real time our patients what's going on in a patient. This little Lumia device you can put in your ear that measures blood flow to your head it gives the patient immediate feedback. When I stand up, do I get a drop of my blood flow. When I drink a liter of fluid, does it still happen? You know, those are kinds of things give them really immediate feedback that they can...actionable points. So, as we better understand and actually have devices that can help measure things for our patients, I think we're giving them better and better advice.

For me, the autonomic loop, this loop is maybe the most transparently easy one to manage and I don't mean that, it's easy to get them all better. It's easy to know that you're doing the right thing. You're not working in a vacuum of knowledge. If they have a low blood volume, you can fill it. If they have a tachycardia with a normal blood volume and their echo says everything's OK in their heart, then you can, you know, beta block them or you can do things that control their heart rate so they don't go so high that their heart is less efficient. If they have a lot of vasoconstriction be careful about using things that cause more vasoconstriction. You can look at your drug list and make sure you're not a part of the problem. Those types of things are...you know...typical management tools and because we have a long history of POTS before COVID and ME/CFS, there are already guidelines to help you manage these types of things.

From the patient's perspective they often groan and moan when I talk about compression, but there's great data that compression garments keep you from venous pulling in your lower extremities and in your abdomen. And this recent CDC webcast that we just filmed [inaudible] been shown yet, we had the pleasure of being with one of the world's authorities, Dr. Singh, and he showed us data that showed that the abdomen and the thighs were the most important. If you can't get them to wear toe to belly, at least get them to wear shorts with belly-belly. And now, because all the athletes are wearing these things, you know, it's kind of handsome and sexy to be wearing compression garments and they're all pretty. So it's not quite so hard to sell. Down here in South Florida, where it's really, really hot, it's still a hard sell, but I push it.

So compression garments, volume measuring, making sure with an echo that you're not dealing with something else, or that your preload is corrected. All these things are things we can do just in normal routine clinical care. But we do need studies and we need studies to try with, you know, more directive and more targeted therapy.

Endothelial and microvascular dysfunction that Long COVID people have a lot more literature than the ME patients on this, and it would help the ME patients to keep an eye on what's going on in Long COVID because this is so clearly a problem from very early

on and in Long COVID. But the endothelium is affected, the micro clotting, the endothelial markers turning over the vasoconstriction, the capillary bed perfusion problems. These are all very well documented and better and better understood. And it's also, I'm curious to see what's going to happen over time, because I think clinically I'm seeing quite a very big problem early on. But still the vascular dysfunction is a player as it is an ME/CFS.

So that gives us management targets, how to reduce endothelial injuries, or ways to reduce this with anti-inflammatory... if there's micro clotting, do they need anticoagulation? What kind of anticoagulation? There are trials underway to better give us guidelines on that.

Optimizing the autonomic vasoconstriction is a part of the problem in microcirculation, then that's something you can wrap your head around and try to find ways to quiet the cholinergic drive. We spend a lot of time on our practice working on the parasympathetics. Be that in non-drug ways...meditation, vagal breathing, vagal nerve, vagal nerve exercises. But now there's also vagal nerve stimulators that need to be tested in trials....but they're readily available now...that can also improve parasympathetic counterbalance and drive down the cholinergic drive. These are all things that are doable and have tools that we have in our hands.

There are other trials underway to try to repair the endothelium. Then there's some natural things that are anti-inflammatory that benefit, like Omega 3s, that type of thing are just natural nutrients that make things more slippery so that cells can get through but also are anti-inflammatory, quiet down TNF and other mediators, and these things are all safe to use. And what we need to do is if I need to see what the right way to use them might be. You'll see a lot of patients already on there.

How to quiet immune activation? I think this is probably the place where I spend a lot of my energy because I'm an immunologist, so I care about this stuff a lot. But what is driving it? What is autoimmune? You can define that. You know, there's a lot of different types of assays to look at different types of autoantibodies, but the ones that are specifically directed at the blood vessels, the A1 adrenergic receptors and then just general review of autoantibodies is important.

We still survey and I think you should survey for viral reactivation. It matters. One of the problems we have with viral reactivation is that we don't have the perfect tools that most of our antivirals are either not strong enough or too toxic to use if in long term. And so, we've been limited in everything we can do with them. But they still, you know, most clinicians see that they have a place in their clinical repertoire of things that they have.

The other problem with viruses is that...two big problems. One is that if you're only looking in the blood and there somewhere else, then you're missing it. And Dr. Chia did a lot of early work on Coxsackie viruses in the gut wall and found with very large end studies, 300 and more subjects, a high instance of Coxsackie virus reactivation in the gut wall but at the same time you look and maybe found that. So this idea that the

immune surveillance is down, and whatever you happen to be carrying around with you is what's going to reactivate...that's a player.

But I think one of the things that shocked us with COVID was the SARS 2 antigen would be there a year, two years, three years later because it's a coronavirus. That's like a common cold virus that mutated and you never think of cold viruses being able to hang out past the cold. They're not latent viruses. We don't hold on to them forever. And yet here is this spike protein that came from coronavirus that we're measuring years after coronavirus. So either that virus persisted or there was so much antigen laid down at the time of the infection and you never cleared it, there's a reservoir of old antigen. Those are the two hypothesis, and we do not know and there's that research is going on, but finding the end is the trick [Inaudible] and requires immune activation.

I can't underscore this slide enough. Mast cells. Mast cells are the really important mediators of a lot of nasty. Just a tremendous amount of nasty and you do not have to have urticaria which is hives. You don't have to have, you know, classics, allergy things to have your mast cells go crazy. Because if they're low-grade smoldering and just releasing, releasing, releasing and not suddenly bursting out and causing hives and all the misery, but just little smoldering leading its mediators out, which is what seems to be happening in non-COVID and ME/CFS patients. They release dozens of mediators that are not good for you, not just histamine and tryptases and things. And they're a player in why pots is so bad, because they actually can break down collagen.

So the [Airlord] downloads patients that were doing fine and now they're horrible, or the POTS patients that were getting along and now they're horrible. In our ME patients that got COVID, you know they're much, much neglected group that already had something, and then I got sick on top of my something.

What does it mean to have had an infection that seemed to drive mast cells into, back out into, be an active player in there in their overall illness? And so, there's things to do for mast cells. And that's the good news. Again, it's something we can do something about now and then things we need to learn a lot more about to do better.

So there are things that mop up antihistamines. We use antihistamines, H1 and H2's work together synergistically. That means you're using drugs like, pick antihistamine and then you're using drugs that are typically used for stomach acid, like Famotidine. And you use them together and you clean up more of the mediator, but even better than cleaning up the things that are released is to not release them to begin with. And those are called mast cell stabilizers, things that quiet the mast cells or getting rid of the triggers that are driving the mast cells. So again, get rid of the triggers. If you knew what the trigger was...it's mold in your house, it's foods that you eat, that kind of thing.

But there's another important trigger in mast cells. They have receptors for adrenaline, for cholinergic drive, and so the super sympathetic drive that so many patients are the tachycardia's into the hundreds with just minor inducement, release mast cell mediators.

So, quieting sympathetic drive just like all that parasympathetic meditation and all that kind of stuff I was talking about before, that's good for your mast cells. But so is getting rid of the things that trigger. And then there's a host of mast cell stabilizers that are used, and there's some guidelines in their use. We're lucky enough in our group to work with Dr. Thea Hereditis, he's one of the world's most amazing mast cell experts. And he speaks a lot about this and there's a lot of webcasts and things you can go, including on our website. But the flavonoids are really good for fighting mast cells, and so luteal and quercetin, there's drugs, there's nutraceuticals like that. And then chromolin, not the world's best thing because it doesn't absorb, but if you take it before you eat it quiets the gut. If you spray it up your nose, it quiets your nose. But a long-standing mast cell stabilizer. I know Harris is not a fan, but it's commonly used and like I say, the antihistamines.

So what Long COVID is teaching us as we go along here is allowing us some great big stuff that you see in, I like this. There's a GLP-1 study right now going on and scripts just winding down, that the Schmidt initiative for Long COVID funding, who by the way funded our monoclonal study, shout out to silk. Shout out to the state of Florida for funding it too. But, shout out to Scripts for doing a study, a completely virtual study of GLP-1s, fully recruited in six weeks with 1000 patients. That's crazy! That is not in my lifetime (laughter). I've never seen a study recruit in six weeks, and get 1000 patients on board, and design a trial that was entirely virtual. To answer that question, whether or not GLP-1s are going to be good. They should be analyzing their data. And we'll hear a whole lot more, I hope by the end of the year. That's exciting! That's what you mean by doing a study the right way. Answering the question. That's really exciting. So shout out to the folks that are doing these amazing Long COVID studies with sufficient resources to recruit big numbers of people to answer the question in a major way, and understand that the subgroups and all the things that come out of them.

So what is it teaching us about more effective treatment? What ME sort of told us where to look. Long COVID was urgently looking for ways to treat and initiated trials using government and private sources, using very large cohorts and being able to go after these mechanisms and then because the basic science is moving along so nicely, brand new targets like the ones you're seeing from Dr. Systrom's work and Dr. Weston Appleman's work in the field. It's very exciting stuff.

So I'm doing well. Good conclusion.

So from persistent symptoms to treatable mediators, that's the basic idea that we learned from ME/CFS and from looking at the patient and hearing them and listening well to get to the point of understanding what the mechanism might be underneath them. And then going after that.

So much gratitude for the volunteer for studies, you've never been more important. Thank you for everything you do. When you volunteer for a study, you're helping everybody.

Thank you everybody that's funding this work and that is believing in all those of us that are trying so hard to find the answers for you. And a great big shout out to the CDC and to the Institute for New Immune Medicine, Nova Southeastern University's team of investigators that gave you all that lovely COVID update. Hopefully you'll hear a lot more about that in coming months.

Also, our Long COVID study on using monoclonals will be at the unblinding point we hope in January, so we should be able to tell you in February or March what's going on there.

So, thank you everyone and I will stand for questions.

*Christine Pearson:* All right. Thank you Dr. Klimas, again everybody. My name is Christine Pearson. I help with communications for this group, so I'm going to take us through the questions.

We have a whole lot of questions, so I will do my best to get to as many as we can. So many of these are for you Dr. Klimas. So the first one is, does the immune pathway that you've described apply to other triggers like bacterial environmental toxins etcetera, or only viral?

*Dr. Klimas:* Oh, it's just so interesting, because you know we study Gulf oil on this too, and that was clearly a toxic exposure. In fact, it was, you know, a organophosphate exposure very mixed up with some other stuff. But organophosphate was the big driver. And you know that's the trigger. The consequence is a chronic neuro inflammatory state that results in all the same downstream stuff you see in me and Long COVID. The same kind of things going on, except that we haven't studied endothelial dysfunction in our field, but all the immune dysfunction dysautonomia, all that is the same. Chronic Lyme, very similar. And in ME/CFS as you know, there's more than one trigger and yet we haven't been able to define any phenotype or endotype by what triggered it in ME. Unless this COVID group is also defined as ME is going to teach us something new there. So that's interesting. But yeah, it's a good question. Thank you.

*Christine Pearson:* Yes, sorry about that. We had technical problems for a second.

*Dr. Klimas:* OK. I just thought I might have gotten dropped because there's a thunderstorm out here.

*Christine Pearson:* Yeah. No, no, you're good. You're good. So, there was another question about is there is the potential for recovery greater if people are diagnosed earlier versus after decades?

*Dr. Klimas:* So the potential for recovery is always better early, just because some people spontaneously get better, you know, not necessarily because early intervention made that big difference. Though I wish we could say that...no one has looked...can't say yes or no to that, but there clearly are some people that just get better. All of our work would suggest that having it a long time does not mean you're going to have it forever, if we get the right buttons pushed. All of our systems biology is very encouraging and to give you a sense of that, we just engulf 4 illness which I just said is very similar. We designed the study based on putting people through the exercise challenge, reading out every single thing we could read out from what happened before, during, and after, giving it to the computational scientists...having them model the illness and what the statement point should be, and then ask and challenge them saying can you make it right again, not just better. And this concept is that when you're well, you're in a balance. When you're sick, but you're in a balance, you're not changing. But why can't I just move somebody in a straight line from sick back to well? And they said, well, that's because there's a mountain between them. They see two wells. This is a, well, a Wellness and a well of steady sickness. But I can mathematically model how to get up the mountain and then fall back into wellness. So we challenge them to do that and they did. And Gulf War Illness, they gave us this model and we had an animal model to test it in. We were able to cure the animals that had the equivalent of 10 years of illness, these were mice, but you know. But anyway, then we did a phase 1 study in Gulf War. The first study was promising, but didn't do it, didn't push them over the mountain. Second study, we changed the dose and the duration and we pushed 60% of the people in the cohort back over the mountain back into the well of, or at least clinically feeling like they were in the well of wellness. We're still doing the math to see whether or not we biologically got them there. But clinically there they got an improvement from pretty ill to in the range of normal and wellness.

So that was exciting.

We had the same data in ME/CFS. We haven't been able to find the funding yet.

We'll go after it again now that we have that data, I think maybe it will be seen more favorably by peer review. So we're going after it again in the next round of grant applications. So ask me about it again in a couple years. I hope so.

But for me, what that is, is promising. Those Gulf War guys have been sick since 1991. And so that was a human study. It was nice to get the mice better, but it was really great to see those guys get better. So pretty exciting stuff.

But again, we had to push more than one button. In our ME model we had to push three different buttons. We have to push the endocrine button in two places. We had to make the testosterone or estrogen levels correct before we make the inflammation go down and then we have to after the brain inflammation goes down, push a button that resets the hypothalamic and pituitary axis. So we're doing 3 steps in that in that proposed study. We don't have an animal model, so we're just going straight to human.

We're doing it with donation money right now, but it won't be enough subjects to do more than give us the pilot to support the bigger, bigger ask.

So still some time coming, and I know we've been talking about that study for a while,

but it's when you don't have money and it's really expensive. It's the drugs cost about \$40,000 a patient. So it's been a labor of love to get as far as we have.

*Christine Pearson:* Thank you for that. So I do have one question for Dr. Regan. So they mentioned that they noticed some of the articles on the slide that you presented, had Long COVID in the title and asked about do we consider the terms interchangeable?

*Dr. Regan:* Yeah, so there's various opinions on that and I'm happy to speak to that. So Long COVID is a long-lasting condition that can show up in many different ways. One of those ways is ME/CFS, which means some people with Long COVID also fit the criteria for ME/CFS. Both conditions can include post exertional malaise, debilitating fatigue, and cognitive impairment. And emerging research also points to biological similarities. So rather than viewing them as either completely separate or identical, the evidence does support kind of recognizing that ME/CFS can develop following COVID, acute COVID and can be a manifestation within the broader Long COVID spectrum. And too Nancy, I don't know if you want to give your take on the separation of those two terms.

*Dr. Klimas:* Because, you know, I think of it clinically. I am a very mediator focused person. If someone walks in, I'm going to figure out what's wrong with that person, and then the label's not going to matter too much to me. But clinic, designing a research study, it has been very challenging. Even the one that we're doing right now to compare to M Cam. There is a lot of nuances there. But I think it's fair to say people got COVID. Some people have damage to the heart and lungs. That's not the same thing, right? We know that. But luckily, it's a minority. But there are people that scarred their lungs, scarred their hearts, and that's different. And they might present in the same way. Then there are the people that have post exertional malaise, like we say in our cohort there, where this is a great study to say what percent of people with acute COVID go on to have Long COVID because I should say what percent of people with symptoms post COVID, have ME/CFS subtype of Long COVID. Because of the defining symptom is post exertional relapse. And so you know, a little less than half, but an important half in our study. Other studies it was more, it was like 60 or 70% in some other studies. So, so it matters. So what you want to make sure as you're doing all this, that you're leaving no one out. They that the ME patients get what they need. That the Long COVID patients who also have ME, get all that they're going to get because they have ME and we know a lot about that and therefore we can, you know, treat you the way we were treating ME. It's not perfect, but at least you got a head start on a lot of folks. But the group of people who don't have post exertional relapse and have a persistent symptoms after COVID, they need to be understood as well. And so luckily, there's that 17,000 people in the recovery initiative that they're following and I'm hopeful that the recovery initiative is going to give us a lot of endotype, meaning biology of these different types of subgroups.

*Christine Pearson:* Great, thank you so much. So one of the questions was asking how PEM happens in mechanically. I think that's how I pronounce it.

*Dr. Klimas:* So I'll try to grab that one the. I'm going to oversimplify it, but that's the way I think so sorry. If you fail to perfuse the tissue, so you you've pushed, you asked your muscles to do something. I'm going to say cognitive push matters too and that's a different kind of exertion. But let's just use muscle exertion as the example, because that's where all the science is coming from and you fail to perfuse it. That work from Dr. Ruth's group showed in a muscle biopsy before they did the exercise, that there was old damage, that the day-to-day effort of exertion was enough to show remodeling and old damage. Then they exercised and showed acute ischemia, like I did not get enough oxygen to this tissue. These are the changes that happen, right? And that and that to me was like, I remember those old ads when you say your brain, your brain on drugs and they fry an egg, you know you're like, ah, there's a fried egg analogy. Your muscle without oxygen can't do these things. But one of the things they can't do, and Dr. Wuss's group did this too, is they went down at the cellular level in the cell, looked at the mitochondria and showed that the mitochondria couldn't function under those conditions in a normal way. Ok and so then you say, well, that makes sense. The mitochondria require oxygen and glucose to do their work. If they had tried to function, they would have created so much oxidative stress it would have killed the cell. So a way to save the cell was to go into a low, low energy state in the cell, OK. So that's is, I'm calling it hibernation for the sake of making it simple. When you can't get oxygen and glucose, you have got to reduce the need for energy or the organism will die. So that's what's happened. Your body's adapted and said OK, well, then I just won't make enough energy because you're not giving me oxygen and glucose. So I think you know, it's an oversimplified way of looking because Dr Farris' work would say it's more complicated than that, but and it is. But let's just start with the obvious, get enough oxygen and glucose to the tissues.

*Christine Pearson:* All right, great. Thank you. So another question was asking whether for you to clarify, if you said that any patients are having endothelial dysfunction as well as Long COVID patients.

*Dr. Klimas:* I did say that because that's work that predates the pandemic. There was work like that in our field before, but now again because Dr Wüst's group and I guess mainly his group Dr. Systrom's group did it indirectly. He did it with ME first and he showed the inability to extract oxygen from the tissues in the patients that had the fibromyalgia type of symptoms. So he did that first, and he did that a while back. But Dr. Wüst's group did the Long COVID first, then last year they repeated all that work in ME and they presented now in several places, and I think they've published the paper now, that they saw that same kind of capillary, the damage to the capillaries that they were able to show in, you know, pathology sections visually, the damage to the cells.

*Christine Pearson:* OK, great. Thank you. So sort of staying with that, what we've talked about a little bit of the longer patients who've had it for longer, there was a question about whether or not you're looking at doing a cohort that are aging with ME/CFS?

*Dr. Klimas:* Oh, would I love to do this study. Would somebody help me find the funding to do this study? I would love to do this study! First, of course I've cared for patients

since 19, I'm going date myself, 1987 I think I saw my first patient, maybe 86. I mean, and I'm not going to date myself, but yes I will, I'm 71. I have patients I've taken care of, you know, for my whole career and we don't meet my criteria right now to get into a study. That's wrong, but I will say with ME/CFS and with Long COVID, aging matters. I've since seen some people, but thankfully not as many as I anticipated, that rapidly aged. I mean, I've seen some people who you look at them and you think, oh my God, this person's 85 and they're 62. You know, you're like, oh my God. What's with this patient? Happily, they're rare. Most of my older patients, maybe it's just survival skills, because they've learned to pace so well. They're doing OK. Not fabulous, not rollerblading, but they're doing OK. I hate that they're excluded from the study. I particularly hated it in our Long COVID study for the monoclonal study, because I think the patients that are older are sicker with Long COVID and they have more endothelial dysfunction. And we already know people with Long COVID developed accelerated atherosclerosis. People that already had but subclinical, you know Parkinson's, or mild cognitive impairment when they got COVID accelerated and developed Alzheimer's or developed Parkinson's that needed treatment. So there's something about the aging mechanism in this post COVID cohort that's well defined already, that we know there's a problem. But in ME/CFS, we haven't looked because more often than not they've been excluded from our studies because we weren't looking to the older group and they really need to be assessed. So I would be thrilled to do that study.

*Christine Pearson:* OK, thank you. I hope that happens.

So now a question for people who have had it for a short period of time, they were asking how important it is that a patient who was diagnosed with ME/CFS after 2020. But had no COVID positive antigen test, that they be tested for past COVID infections and if so, what kind of testing should they undergo? Like, is that useful?

*Dr. Klimas:* That's a great question. You know, because for me, one of the dilemmas is a clinician taking care of ME/CFS all this time and then trying to do research after COVID is that you're assuming everyone that's ME now had COVID, but they may or may not have. You know, we would have gotten new ME in the same, you know, six years as but of course we got a lot more of it because there was COVID. So first one of the research questions is who's got post COVID and how do I know? Versus who, you know, had mononucleosis or something else. So that's one thing, that's a really good question. But you asked about how to test. Right now the only test I know that you can get done, that's got a lasting good signature for antibody, is the one that's out of Oxford, a company called automaker, ATTOMAKER, Dr Shaw, Andrew Shaw. He did every single variant. And actually I used to, and we're going to be measuring in our in our COVID up study. We are doing this. No, I'm sorry, in the monoclonal study, we're doing this. He showed the people with Long COVID, 65% failed to maintain their antibody response to the variance they were exposed to that they might be there, but they're very low levels. 10% had hyper reactivity. Those were the vaccine reactors. The people that overreacted immunologically and had this hyper immune response, which left 25% that don't fit either group. But if it helps explain 65% of Long COVID, wouldn't that be something? So in our monoclonal study, we are doing his assay and also the spike protein assay, to see whether or not it predicted who responds or who doesn't respond to the monoclonal, because it makes sense that if you fail to maintain your immune response or ever make

a good one, that pounding it with more antibody might be a great idea...where it might not be a great idea to pound somebody that already has a ton of antibody on board and is overreacting with even more. So hopefully we'll understand that better with good science, which we're going to do. So yeah, but right now the only commercial use I see, I understand they just got a LabCorp contract. So you might need to wait a little bit and it'll be in LabCorp.

*Christine Pearson:* All right, great. Thank you. So I'm going combine a few questions because we had several that were along the same lines of if you have any advice for patients. So, the questions were who don't feel better with more hydration or electrolytes and if compression doesn't help.

*Dr. Klimas:* So I'm going to say about hydration versus electrolytes. OK, there is such a thing as over hydration and if you use water rather than electrolytes and you drink a gallon a day, there's this part of your kidney that concentrates your urine and you can wipe that out. So then it just pees out all that water and more and you're even more dehydrated than you were if you hadn't drunk water at all. It's amazing. So one of the things to be wary of is how you take your fluids because you can flush your kidneys to the point that they can't concentrate urine, and that's a bad thing. We can see that because your sodium falls, there's ways to look if the doctor can see it. But if you're just wondering, am I drinking the right stuff? You do need some electrolytes. You can't just rely on water all day long, so generally we tell people to get two or three 12-ounce bottles of something with electrolytes, and I usually use powders and things so that they don't have bunch of chemicals and colors in them. But no one brand, but electrolytes that aren't full of other stuff.

So, that's one thing. Be careful what you're calling hydration. And then when it doesn't work, compression doesn't work and hydration doesn't work then I'd need to know more, because if you're still tachycardic and your blood pressure's still all over the place when you stand up, then you still have, you know, a positive NASA lean test and all that's not working...then we would go to the next thing, we would add, you know a evasive constrictor like Mitogen to reduce the amount of venous pooling or we would go looking for other sources to see what it is. Some patients are really complicated, and the [airlo damless] loss patients are really very difficult to get squared away. So, it really, really depends on the patient.

*Christine Pearson:* All right, great. I see we've already gone over as I want to be mindful of the tax we're putting on some of the callers. So I think let's do one more call, or one more question, which is does mitochondrial dysfunction exacerbate ME/CFS? And if so, how?

*Dr. Klimas:* It's the other way around. And sort of, they're the same. I don't know how to say exacerbate. They're part of it. So yeah, mitochondrial dysfunction matters. And it matters. It happens for several different reasons. Like I said, perfusion is the simple reason but there's some other reasons, and there's approaches and studies underway to try to find ways to make that better. But in the end, the obvious thing that needs to be done is to clean up oxidative stress...because the mitochondrial dysfunction makes a

lot of that and that just is a vicious cycle of misery. So there's a number of antioxidant type of approaches to try to clean up oxidative stress. But yeah, no mitochondrial just functions a really important part of this. You can't make them do a better job though if you don't get oxygen and glucose to them. So profusion becomes step one, and then fix the mitochondria, step twp.

*Christine Pearson:* Great. Thank you so much.

*Dr. Klimas:* OK, sure.

*Christine Pearson:* So I wanted to thank everyone for joining us today. I hope that you found the call helpful. We do have our e-mail address right there and we would really like to hear from you, for you know, any input that you have about, you know, today's presentation or suggestions for future speakers or topics or how to make the call useful for you. This call is for you and so we'd love to hear from you. Thank you. So please use that e-mail address, and just FYI we are working on updating it to include the ME. This is an old e-mail box, but we will hopefully have that set up to route with the ME included soon. So on behalf of all of us here who work on ME/CFS at CDC, we wish you all the best moving forward. And we'll see you next time.

*Dr. Klimas:* Thanks everybody.