Unlocking the Mysteries of Long COVID

A CONVERSATION WITH DR. JIM HEATH

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At the start of 2020, Dr. Jim Heath was looking forward to kicking off a yearlong celebration marking the 20th anniversary of the Institute for Systems Biology, a Providence-affiliated nonprofit biomedical research organization located in Seattle's South Lake Union neighborhood. Heath was named president of the institute in 2017 and was excited to share its research — and more about its researchers — with the public. The chemist-turned-biologist was also deep in his own research projects that included immunotherapies for cancer, among others.

Just three short months later, the lives of Heath, and indeed all of us, were turned upside down. COVID-19 had landed. "COVID-19 quickly went from nonexistent to the scientific challenge of our time," Heath said.

For the past two years, Heath has tirelessly worked to uncover COVID-19's secrets. He immediately refocused the institute's efforts, resulting in major scientific breakthroughs that shed light on COVID-19 and provided guidance for further research and clinical care. His most recent research focused on long COVID was published in the journal *Cell*, and has received a tremendous amount of news coverage.

At the request of *Health Progress*, I recently talked with Heath about his COVID-19 research, where he thinks we're headed with the disease, and much more.

Your long COVID research findings have certainly made the rounds. What led to that incredible amount of interest?

Long COVID — also known as post-acute sequelae of COVID-19, or PASC — has been a true mystery. In the early days of the pandemic, people who were reporting long-term COVID-19 effects weeks or longer after infection were simply dismissed and ignored. But as we all know, the long-term effects of COVID are quite real, and impact a significant number of people.

We have identified four factors, we call them "PASC factors," that can be measured at the point of COVID-19 diagnosis, and that greatly increase the risk of long COVID. These PASC factors are: the presence of certain autoantibodies; pre-existing Type 2 diabetes; SARS-CoV-2 RNA levels in the blood; and Epstein-Barr virus DNA levels in the blood.

In general, if a patient had one of these risk factors, their odds of having PASC with three or more symptoms (about 35% of our patients) were greater than 90%.

Was one of these PASC factors more likely to lead to long COVID over the others?

COVID-19 patients were twice as likely to have PASC if they had a presence of autoantibodies [antibodies produced by the immune system that are directed against one or more of an individual's own proteins].

High levels of some of these autoantibodies are often associated with autoimmune diseases

Dr. Jim Heath

Photo by Scott Eklund

like lupus, but even moderate levels increased the risk for certain PASC. We also found that higher levels of autoantibodies mean lower levels of protective SARS-CoV-2 antibodies, which suggests a relationship between long COVID, autoantibodies and patients at elevated risk of reinfections.

What do these findings mean for clinical care?

I think that there are several take-home messages. First, patients with autoantibodies should probably get boosted, perhaps more than once, to help elevate their antibodies against SARS-CoV-2. Second, two of the PASC factors are viral loads in the blood, suggesting that antivirals used very early in the infection might help ward off PASC. Third, we found some strong immunological similarities between certain patients that had high autoantibodies and long COVID, and patients with systemic lupus erythematosus [the most common type of lupus]. I think it is worthwhile to begin exploring whether drugs that are effective for lupus erythematosus might also have a role in treating patients with long COVID.

Who was involved in this study?

Our study looked at blood and swab samples from more than 300 COVID-19 patients at different time points, from initial diagnosis through to recovery. This allowed us to perform comprehensive phenotyping [or the process of determining one's phenotype, which is the broad set of observable characteristics — such as height, eye color and blood type — resulting from the interaction of your genotype with the environment], which we integrated with clinical data and patient-reported symptoms to help resolve these PASC factors. We are tremendously grateful to all of these patients that gave of their time and blood.

The research team that worked on this study is world-class and truly collaborative. The Institute for Systems Biology worked closely with peers from Swedish Health Services in Seattle, the Providence medical system, the University of Washington, Fred Hutchinson Cancer Research Center, Stanford, UCLA and UCSF.

Is there an accepted way to diagnose long COVID at this point? What should a patient do if they are struggling with a variety of symptoms and their clinician doesn't know if it is long COVID?

This is a tricky question. The fact that there are multiple PASC factors and such a wide variety of symptoms suggests that long COVID represents a range of conditions, so any single diagnosis will

likely be incomplete. I think that the default is if a patient is experiencing chronic health issues since COVID-19 that didn't exist before, then they are likely experiencing long COVID. We had several findings that physicians can look for in their patients. One example was that of repressed cortisol and cortisone levels in a subset of long COVID patients. Such low levels are also associated with a treatable condition known as Addison's disease.

Do we know how many patients have it, and can they fully recover from it? What are the most common symptoms?

While as many as 40% or even more of COVID-19 patients report long COVID symptoms, for most of these patients, most of the chronic ailments will disappear after a few months. But for perhaps 10% of patients, they can linger for much longer. The most common symptoms are chronic fatigue, while less common are gastrointestinal issues, such as diarrhea or nausea. Neurological issues, such as brain fog or trouble sleeping, are somewhere in between.

Is the array of potential symptoms and potential biological mechanisms involved in long COVID frustrating for medical professionals, or is there some kind of consensus emerging?

I think it is safe to say that it is still frustrating. However, these types of chronic "long" diseases — which include not just long COVID, but post-acute Lyme, chemo brain (for patients with cancer) and others — have long remained a frustrating mystery. I think that we and others are beginning to shed some light on these, so hopefully the future is brighter.

What are the next steps in terms of future long COVID research?

One major initiative currently underway is the NIH-funded RECOVER study, which stands for REsearching COVID to Enhance Recovery. The Institute for Systems Biology is leading a multi-site Pacific Northwest consortium of this nationwide effort. This national study will explore why some people have prolonged symptoms following acute COVID-19 diagnosis in a way that allows us to understand even the rare symptoms, which range from cardiac issues to hair loss, and to begin resolving strategies for treating these patients.

JOE MYXTER is director of communications for the Seattle-based Institute for Systems Biology.

QUESTIONS FOR DISCUSSION

Researchers at The Institute for Systems Biology, a Providence-affiliated nonprofit in Seattle, and their colleagues recently published some findings about Long COVID. These include four factors that can increase the risk of Long COVID: the presence of certain autoantibodies; pre-existing Type 2 diabetes; SARS-CoV-2 (coronavirus) RNA in the blood; and Epstein-Barr virus DNA levels in the blood.

1. How is your health care system currently monitoring for potential risk factors for long COVID, and how is it being diagnosed?

2. Patients with Long COVID say a real struggle for them is feeling heard. We know from media accounts that having Long COVID can include many challenges: the symptoms, the diagnosis, a clear clinical pathway. What are you as a care provider doing to support those who have Long COVID? How can diagnosis, treatment and referrals be better managed to ease the path forward for patients?

3. What kinds of emotional and spiritual support do these patients need? How is that being provided?

4. Can steps already in place to assist patients with chronic conditions be adapted to those with Long COVID? How so?

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