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Long-Haul COVID

Real, Complex and Challenging

By Leroy Hood, MD, PhD

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Shortly after the COVID-19 pandemic took hold, doctors began seeing puzzling symptoms in patients that lasted well beyond the initial infection period. These COVID long-haulers suffered from distressing or debilitating problems months after supposedly recovering from the disease.

On a Facebook support page for long haulers, one person who had developed extreme fatigue said: "It was like I was chained to my bed. It seemed impossible to even think about getting up." Another with brain fog shared: "I was cleaning my gutters and forgot where I was and what I was doing on the roof."

Between 40% and 75% of long haulers describe a complex neurological constellation of symptoms and conditions. These include fatigue, intense headaches, muscle weakness, difficulty sleeping, anxiety, poor concentration, memory loss and changes to the sense of taste and smell. Most have three or more symptoms, which indicates that long-haul COVID likely affects multiple parts of the brain or multiple organ systems at once.

Just as puzzling, many long haulers never experienced severe COVID or needed hospitalization. Comorbidities, such as obesity, diabetes and heart disease, do not appear to be causal factors. Seventy percent of long haulers are women, although this may be because they are more likely than men to report symptoms. The young are also susceptible, another reason everyone should gain immunity by vaccination, not by infection. A study in China found that 75% of hospitalized COVID patients after 6 months reported at least one long-haul symptom. The conservative estimate from many sources is that at least 10% of COVID-infected individuals experience long-haul symptoms.

We do not yet know what causes long-haul COVID and why it differs from acute COVID. The virus may continue to infect internal organs even after it is no longer detectable in the blood, or it may trigger a long-term abnormal immune response that affects different organ systems in an ongoing manner.

Understanding and managing this complex disease requires new approaches, built on data and genetic analysis. In March 2020, the Institute for Systems Biology joined forces with Swedish Hospital in Seattle to launch a clinical study with 200 hospitalized COVID-19 patients.

Our aim was to assess the body's immune response to the coronavirus through the course of the disease. We studied the patients' blood at the time of hospital admission, 10 days later (near the peak of the typical COVID immune response) and at three months, when immune responses should have typically returned to normal.

From each blood draw, we analyzed 5,000 white blood cells and quantified each cell's complete gene expression patterns while also analyzing 250 cell-surface proteins and 40 secreted proteins. We categorized the white blood cells by type (T-cell, B-cell or natural killer cell) and determined each cell's state of activation. We used these data to describe each person's immune-response state at these three different stages of the disease.

We saw a number of different immune response trajectories in our patient population. For example, the immune systems of only one third of patients returned to normal after three months. We are now starting another long-haul COVID clinical trial with 100 long-haul patients to assess whether different immune system abnormalities may cause different kinds of long-haul symptoms.

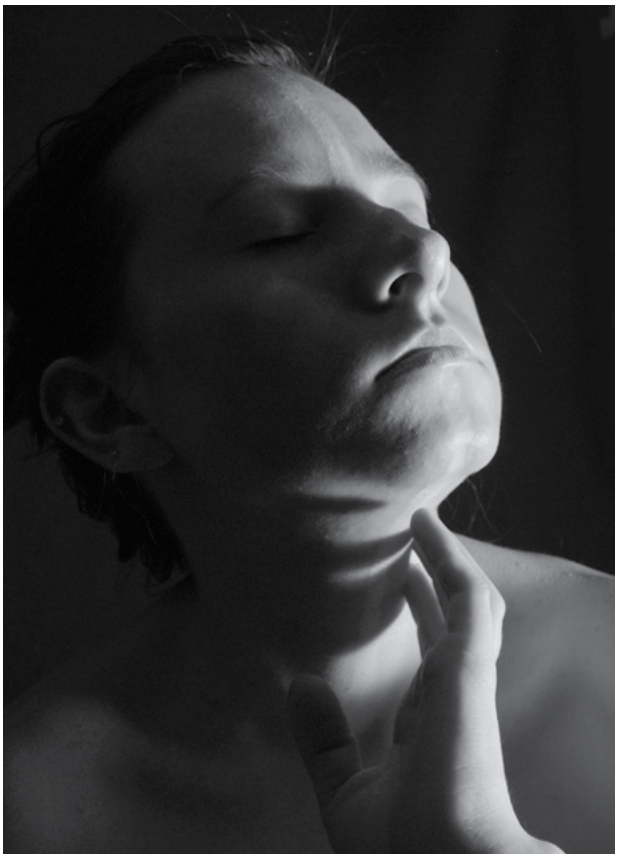
This kind of comprehensive immune analyses at the individual patient level may help answer fundamental questions, such as what are the mechanisms of COVID disease, both acute and long haul? What kinds of new medicines or therapies are needed? Is it possible to predict who is susceptible and provide treatment before severe symptoms develop?

One interesting effect recently observed is that some long haulers who got vaccinated experienced rapid and complete remission of their symptoms. The percentage of those who respond positively to vaccination and the length of remission is unknown, but reports suggest that vaccination will be an important long-hauler treatment as well as a defense against COVID-19.

Understanding the immune system's response to COVID may even help us understand, diagnose and treat other complex chronic immune-related conditions. This could be particularly true with illnesses with neurological symptoms common to long-haul COVID.

For example, Lyme disease, caused by a bacterium, resolves in most patients after antibiotic treatment. But a fraction of patients will suffer long-term Lyme disease symptoms, which are similar to long-haul COVID — pain, fatigue, or difficulty thinking that lasts for many months after treatment and for some people, years and perhaps a lifetime. Why some patients experience these symptoms post-treatment is not known and there is no treatment for such continuing symptoms.

Today, millions of people struggle with chronic conditions that may also be triggered by immune system abnormalities, whose origins are often unknown — including rheumatoid arthritis, multiple sclerosis, lupus, Lyme disease, chronic fatigue syndrome, Guillain-Barre syndrome and inflammatory bowel disease. Comprehensive immune analyses will almost certainly provide fundamental new insights to many of these diseases.



Unfortunately, most people with long-haul symptoms share at least one prominent experience: the difficulty in getting their conditions recognized, diagnosed and effectively treated. Physicians and insurers often deny patients' reality and experiences when they present complex and seemingly unrelated symptoms and treat their conditions as psychosomatic. Not only does this demean the patient, but it exacerbates the worry, confusion and stress of patients and families dealing with significant mental and physical health challenges. This also delays treatment, adds to overall costs and diminishes productivity and quality of life.

Until now, we've lacked the science, resources and focus to make significant headway with these disparate diseases. This time is different. COVID-19 has already led to breakthroughs in vaccine development, forced greater healthcare coordination, encouraged widespread adoption of telemedicine and other digital tools and propelled the development of new techniques such as comprehensive immune-system analyses.

This new kind of analysis has the potential to advance an understanding of disease mechanisms and accelerate holistic therapies for millions of long haulers and perhaps for people suffering from other chronic diseases as well.

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AUTHOR

Leroy Hood, a world-renowned scientist and recipient of the National Medal of Science in 2011, Dr. Leroy Hood co-founded the Institute for Systems Biology (ISB) in 2000 and served as its first President from 2000-2017. In 2016, ISB affiliated with Providence St. Joseph Health (PSJH) and Dr. Hood became PSJH's Senior Vice President and Chief Science Officer. He is also Chief Strategy Officer and Professor at ISB.

He is a member of the National Academy of Sciences, the National Academy of Engineering, and the National Academy of Medicine. Of the more than 6,000 scientists worldwide who belong to one or more of these academies, Dr. Hood is one of only 20 people elected to all three.

He received his MD from Johns Hopkins University School of Medicine and his PhD in biochemistry from Caltech. Dr. Hood was a faculty member at Caltech from 1967-1992, serving for 10 years as the Chair of Biology. During this period, he and his colleagues developed four sequencer and synthesizer instruments that paved the way for the Human Genome Project's successful mapping and understanding of the human genome. He and his students also deciphered many of the complex mechanisms of antibody diversification. In 1992, Dr. Hood founded and chaired the Department of Molecular Biotechnology at the University of Washington, the first academic department devoted to cross-disciplinary biology.

Dr. Hood is currently carrying out studies in Alzheimer's Disease, cancer, and wellness. He is pioneering a 1 million patient genome/phenome project for Providence St. Joseph Health and is bringing scientific (quantitative) wellness to the contemporary U.S. health care system.

Dr. Hood has played a role in founding 15 biotechnology companies including Amgen, Applied Biosystems, Arivale, and Nanostring. He has co-authored textbooks in biochemistry, immunology, molecular biology, genetics, and systems biology.

In addition to having received 18 honorary degrees from prestigious universities in the U.S. and abroad, Dr. Hood has published more than 850 peer-reviewed articles and currently holds 36 patents.

Dr. Hood is the recipient of numerous national and international awards, including the Lasker Award for Studies of Immune Diversity (1987), the Kyoto Prize in advanced technology (2002), the Heinz Award for pioneering work in Systems Biology (2006), the National Academy of Engineering Fritz J. and Delores H. Russ Prize for developing automated DNA sequencing (2011), and the National Academy of Science Award for Chemistry in Service to Society (2017).