

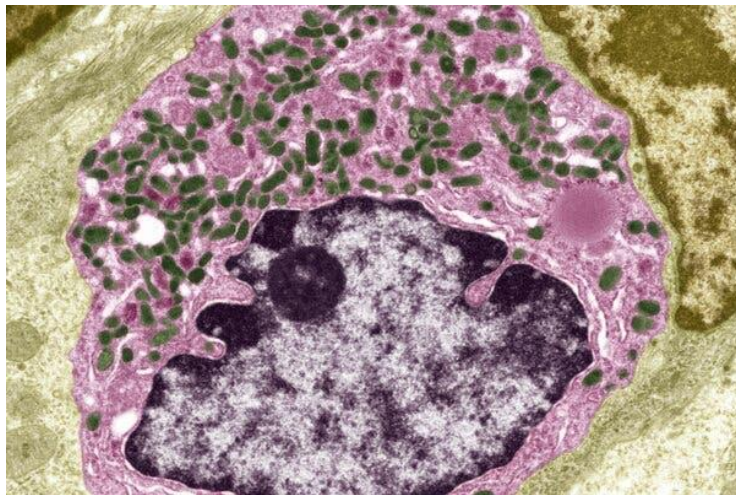
# The New York Times

## Scientists Offer a New Explanation for Long Covid

By [Pam Belluck](#) Oct. 16, 2023

A team of scientists is proposing a new explanation for some cases of long Covid, based on their findings that serotonin levels were lower in people with the complex condition.

In their study published on Monday in the journal *Cell*, researchers at the University of Pennsylvania suggest that serotonin reduction is triggered by remnants of the virus lingering in the gut. Depleted serotonin could especially explain memory problems and some neurological and cognitive symptoms of long Covid, they say.



A colored transmission electron micrograph showing an intestinal endocrine cell, with granules containing serotonin in green.

### **Why It Matters: New ways to diagnose and treat long Covid.**

This is one of several new studies documenting distinct biological changes in the bodies of people with long Covid — offering important discoveries for a condition that takes many forms and often does not register on standard diagnostic tools like X-rays.

The research could point the way toward possible treatments, including medications that boost serotonin. And the authors said the biological pathway that their research outlines could unite many of the major theories of what causes long Covid: lingering

remnants of the virus, inflammation, increased blood clotting and dysfunction of the autonomic nervous system.

“All these different hypotheses might be connected through the serotonin pathway,” said Christoph Thaiss, a lead author of the study and an assistant professor of microbiology at the Perelman School of Medicine at the University of Pennsylvania.

“Second of all, even if not everybody experiences difficulties in the serotonin pathway, at least a subset might respond to therapies that activate this pathway,” he said.

“This is an excellent study that identifies lower levels of circulating serotonin as a mechanism for long Covid,” said Akiko Iwasaki, an immunologist at Yale University. Her team and colleagues at the Icahn School of Medicine at Mount Sinai recently published [a study](#) that identified other biological changes linked to some cases of long Covid, including levels of the hormone cortisol. These studies could point to specific subtypes of long Covid or different biological indicators at different points in the condition.

## **The Back Story: A series of disruptions set off by bits of virus in the gut.**

Researchers analyzed the blood of 58 patients who had been experiencing long Covid for between three months and 22 months since their infection. Those results were compared to blood analysis of 30 people with no post-Covid symptoms and 60 patients who were in the early, acute stage of coronavirus infection.

Maayan Levy, a lead author and assistant professor of microbiology at the Perelman School of Medicine, said levels of serotonin and other metabolites were altered right after a coronavirus infection, something that also happens immediately after other viral infections.

But in people with long Covid, serotonin was the only significant molecule that did not recover to pre-infection levels, she said.

The team analyzed stool samples from some of the long Covid patients and found that they contained remaining viral particles. Putting the findings in patients together with research on mice and miniature models of the human gut, where most serotonin is produced, the team identified a pathway that could underlie some cases of long Covid.

Here’s the idea: Viral remnants prompt the immune system to produce infection-fighting proteins called interferons. Interferons cause inflammation that reduces the body’s ability to absorb tryptophan, an amino acid that helps produce serotonin in the gut. Blood clots that can form after a coronavirus infection may impair the body’s ability to circulate serotonin.

Depleted serotonin disrupts the vagus nerve system, which transmits signals between the body and the brain, the researchers said. Serotonin plays a role in short-term memory, and the researchers proposed that depleted serotonin could lead to memory problems and other cognitive issues that many people with long Covid experience.

“They showed that one-two-three punch to the serotonin pathway then leads to vagal nerve dysfunction and memory impairment,” Dr. Iwasaki said.

There are caveats. The study was not large, so the findings need to be confirmed with other research. Participants in some other long Covid studies, in which some patients had milder symptoms, did not always show depleted serotonin, a result that Dr. Levy said might indicate that depletion happened only in people whose long Covid involves multiple serious symptoms.

## **What’s Next: A clinical trial of Prozac.**

Scientists want to find biomarkers for long Covid — biological changes that can be measured to help diagnose the condition. Dr. Thaiss said the new study suggested three: the presence of viral remnants in stool, low serotonin and high levels of interferons.

Most experts believe that there will not be a single biomarker for the condition, but that several indicators will emerge and might vary, based on the type of symptoms and other factors.

There is tremendous need for effective ways to treat long Covid, and clinical trials of several treatments are underway. Dr. Levy and Dr. Thaiss said they would be starting a clinical trial to test fluoxetine, a selective serotonin reuptake inhibitor often marketed as Prozac, and possibly also tryptophan.

“If we supplement serotonin or prevent the degradation of serotonin, maybe we can restore some of the vagal signals and improve memory and cognition and so on,” Dr. Levy said.