The Mysterious Link Between COVID-19 and Sleep

By: James Hamblin, The Atlantic

The coronavirus can cause insomnia and long-term changes in our nervous systems. But sleep could also be a key to ending the pandemic.

The newly discovered coronavirus had killed only a few dozen people when Feixiong Cheng started looking for a treatment. He knew time was of the essence: Cheng, a data analyst at the Cleveland Clinic, had seen similar coronaviruses tear through China and Saudi Arabia before, sickening thousands and shaking the global economy. So, in January, his lab used artificial intelligence to search for hidden clues in the structure of the virus to predict how it invaded human cells, and what might stop it. One observation stood out: The virus could potentially be blocked by melatonin.

Melatonin, best known as the sleep hormone, wasn't an obvious factor in halting a pandemic. Its most familiar role is in the regulation of our circadian rhythms. Each night, as darkness falls, it shoots out of our brain's pineal glands and into our blood, inducing sleep. Cheng took the finding as a curiosity. "It was very preliminary," he told me recently—a small study in the early days before COVID-19 even had a name, when anything that might help was deemed worth sharing.

After he published his research, though, Cheng heard from scientists around the world who thought there might be something to it. They noted that, in addition to melatonin's well-known effects on sleep, it plays a part in calibrating the immune system. Essentially, it acts as a

moderator to help keep our self-protective responses from going haywire—which happens to be the basic problem that can quickly turn a mild case of COVID-19 into a life-threatening scenario.

Cheng decided to dig deeper. For months, he and colleagues pieced together the data from thousands of patients who were seen at his medical center. In results published last month, melatonin continued to stand out. People taking it had significantly lower odds of developing COVID-19, much less dying of it. Other researchers noticed similar patterns. In October, a study at Columbia University found that intubated patients had better rates of survival if they received melatonin. When President Donald Trump was flown to Walter Reed National Military Medical Center for COVID-19 treatment, his doctors prescribed—in addition to a plethora of other experimental therapies—melatonin.

Eight clinical trials are currently ongoing, around the world, to see if these melatonin correlations bear out. Few other treatments are receiving so much research attention. If melatonin actually proves to help people, it would be the cheapest and most readily accessible medicine to counter COVID-19. Unlike experimental drugs such as remdesivir and antibody cocktails, melatonin is widely available in the United States as an over-the-counter dietary supplement. People could start taking it immediately.

Yet Cheng emphasizes that he's not recommending that. Like any substance capable of slowing the central nervous system, melatonin is not a trifling addition to the body's chemistry. Its apparent benefit to COVID-19 patients could simply be a spurious correlation—or, perhaps, a signal alerting us to something else that is actually improving people's outcomes. Cheng thinks that might be the case. He and others suggest that the real issue at play may not be melatonin at all, but the function it most famously controls: sleep.

In fact, several mysteries of how COVID-19 works converge on the question of how the disease affects our sleep, and how our sleep affects the disease. The virus is capable of altering the delicate processes within our nervous system, in many cases in unpredictable ways, sometimes creating long-term symptoms. Better appreciating the ties between immunity and the nervous system could be central to understanding COVID-19—and to preventing it.

Throughout the pandemic, the department of neurology at Johns Hopkins University has been flooded with consultation requests for people suffering from insomnia. Rachel Salas, one of the team's neurologists, says she initially thought this surge in sleep disorders was merely the result of all the anxieties that come with a devastating global crisis: worries about health, the economic impact, and isolation. Indeed, patterns of sleep disruption have played out around the world. Roughly three-quarters of people in the United Kingdom have had a change in their sleep during the pandemic, according to the British Sleep Society, and less than half are getting refreshing sleep. "In the summer, we were calling it 'COVID-somnia,'" Salas says.

In recent months, however, Salas has watched a more curious pattern emerge. Many people's sleep continues to be disrupted by predictable pandemic anxieties. But more perplexing symptoms have been arising specifically among people who have recovered from COVID-19.

“We’re seeing referrals from doctors because the disease itself affects the nervous system,” she says. After recovering, people report changes in attention, debilitating headaches, brain fog, muscular weakness, and, perhaps most commonly, insomnia. Many don’t seem anxious or preoccupied with pandemic-related concerns—at least not to a degree that could itself explain their newfound inability to sleep. Rather it is sometimes part of what the medical community has begun to refer to as “long COVID,” where symptoms persist indefinitely after the virus has left a person. When it comes to sleep disturbances, Salas worries, “I expect this is just the beginning of long-term effects we’re going to see for years to come.”

Her colleague Arun Venkatesan has been trying to get to the bottom of how a virus could cause insomnia. He focuses specifically on autoimmune and inflammatory diseases that affect the nervous system. Initially, Venkatesan says, the common assumption among doctors was that many post-COVID-19 symptoms were due to an autoimmune reaction—a misguided, targeted attack on cells of one’s own body. This can happen in the nervous system after infections by various viruses, in predictable patterns, such as that of Guillain-Barré syndrome. In the days after an infection, as new antibodies mistakenly attack nerves, weakness and numbness spread from the tips of the extremities inward. Disconcerting as it can be, this type of pattern is at least identifiable and predictable; doctors can tell patients what they’re dealing with and what to expect.

By contrast, the post-COVID-19 patterns are sporadic, not clearly autoimmune in nature, says Venkatesan. The symptoms can appear even after a mild case of COVID-19, and timescales vary. “We’ve seen a number of patients who were not even hospitalized, and felt much better for weeks, before worsening,” Venkatesan says. And the findings aren’t limited to the brain. At Northwestern University, the radiologist Swati Deshmukh has been fielding a steady stream of cases in which people experience nerve damage throughout the body. She has been looking for evidence that the virus itself might be killing nerve cells. Hepatitis C and herpes viruses are known to do so, and autopsies have found SARS-CoV-2 inside nerves in the brain.

Still, she believes, symptoms are most likely due to inflammation. Indeed, the leading theory to explain how a virus can cause such a wide variety of neurologic symptoms over a variety of timescales comes down to haphazard inflammation—less a targeted attack than an indiscriminate brawl. This effect is seen in a condition known as myalgic encephalomyelitis, sometimes called chronic fatigue syndrome. The diagnosis encompasses myriad potential symptoms, and likely involves multiple types of cellular injury or miscommunication. In some cases, damage comes from prolonged, low-level oxygen deprivation (as after severe pneumonia). In others, the damage to nerve-cell communication could come by way of inflammatory processes that directly tweak the functioning of our neural grids.

The unpredictability of this disease process—how, and how widely, it will play out in the longer term, and what to do about it—poses unique challenges in this already-uncertain pandemic. Myalgic encephalomyelitis is poorly understood, stigmatized, and widely misrepresented. Medical treatments and diagnostic approaches are unreliable. General inflammatory states rarely respond to a single prescription or procedure, but demand more holistic, ongoing interventions to bring the immune system back to equilibrium and keep it there. The medical system is not geared toward such approaches.

But this understanding of what is happening may also offer some hope. Although the technical details are clearly thorny, there is some reassurance in what the doctors are *not* seeing. When nerves are invaded and killed, the damage can be permanent. When nerves are miscommunicating—in ways that come and go—that process can be treated, modulated, prevented, and quite possibly cured. Although sleep cycles can be disturbed and damaged by the post-infectious inflammatory process, radiologists and neurologists aren't seeing evidence that this is irreversible. And among the arsenal of ways to attempt to reverse it are basic measures such as sleep itself. Adequate sleep also plays a part in minimizing the likelihood of ever entering into this whole nasty, uncertain process.

A central function of sleep is maintaining proper channels of cellular communication in the brain. Sleep is sometimes likened to a sort of anti-inflammatory cleansing process; it removes waste products that accumulate during a day of firing. Without sleep, those by-products accumulate and impair communication (just as seems to be happening in some people with post-COVID-19 encephalomyelitis). "In the early stages of COVID-19, you feel extremely tired," says Michelle Miller, a sleep-medicine professor at the University of Warwick in the U.K. Essentially, your body is telling you it needs sleep. But as the infection goes on, Miller explains, people find that they often can't sleep, and the problems with communication compound one another.

The goal, then, is breaking out of this cycle, or preventing it altogether. Here the benefits of sleep extend throughout the body. "Sleep is important for effective immune function, and it also helps to regulate metabolism, including glucose and mechanisms controlling appetite and weight gain," Miller says. All of these bear directly on COVID-19, as risk factors for severe cases include diabetes, obesity, and sleep apnea. Even in the short term, getting enough deep, slow-wave sleep will optimize your metabolism and make you maximally prepared should you fall ill. These effects may even bear on vaccination. Flu shots appear to be more effective among people who have slept well in the days preceding getting one.

All of this leads back to the basic question: Is one of the most glaring omissions in public-health guidelines right now simply to tell people to get more sleep?

The only health advice more banal than being told to wash your hands is being told to sleep more. But it's a cliché for a reason. Sleep fortifies and prepares us for any given crisis, but especially when the days are short and cold, and people have little else they might do to empower and protect themselves. Monotonous days can slip people into depression, alcohol abuse, and all manner of suboptimal health. It may well turn out that standard pandemic advice should be to wear a mask, keep distances, and get sleep.

That's easier said than done. Asim Shah, a psychiatry and behavioral-sciences professor at Baylor College of Medicine, believes sleep is at the core of many of the mental-health issues that have spiked over the course of the year. "There's a complete lack of structure. That has caused a huge disturbance in the sleep cycles," he says. "Usually everyone has a schedule. They get sunlight and they generate melatonin and it puts them to sleep. Right now we're seeing people

losing interest in things, isolating, not exercising, and then not getting sleep." Depression and anxiety make insomnia worse, and the cycle degenerates.

This may be where melatonin—or other approaches to enhancing the potent effects of sleep—could be consequential. Russel Reiter, a cell-biology professor at the University of Texas at San Antonio, is convinced that widespread treatment of COVID-19 with melatonin should already be standard practice. In May, Reiter and colleagues published a plea for melatonin to be immediately given to everyone with COVID-19.

If the world of melatonin research had a molten core, it would be Reiter. He has been studying the hormone's potential health benefits since the 1960s, and tells me he takes 70 milligrams daily. (Most bottles at the pharmacy recommend from 1 to 10 milligrams.) After we spoke, he sent me some of the many journal articles he has published on melatonin and COVID-19, at least four of which appeared in *Melatonin Research*. He blithely referred to them as "propaganda" and noted that he has been studying melatonin since before I was born (without asking when that was). "I know melatonin sideways and backwards," Reiter said, "and I'm very confident recommending it."

The majority of sleep scientists, though, seem to agree that the most crucial interventions that facilitate sleep will not be medicinal, or even supplemental. The general recommendation is that getting your body's melatonin cycles to work regularly is preferable to simply taking a supplement and continuing to binge Netflix and stare at your phone in bed. Now that so many people's days lack structure, Shah believes a key to healthy pandemic sleep is to deliberately build routines. On weekends, wake up and go to bed at the same time as you do other days. Take scheduled walks. Get sunlight early in the day. Reduce blue light for an hour before bed. Stay connected with other people in meaningful ways, despite being physically distant.

Even small daily rituals can help, says Tricia Hersey, the founder of a nap-advocacy organization called the Nap Ministry. Light a candle. Have a cup of tea in a specific place at a certain time. "Repetitive rituals are part of what makes us human and ground ourselves," she told me. They're also perhaps the most attainable intervention there is. Wherever you are, Hersey says, "you can daydream. You can slow down. You can find small ways to stop and remember who you are."

To her, feeling in control over sleep is important precisely because order is lacking in so many other parts of life for so many people. Year over year, there are significant sleep disparities across the U.S. population. The amount and quality of sleep we get depend on our environment as much as, if not more than, our personal behavior. Socioeconomic status and quality sleep chart on parallel lines. The most effective way to improve sleep is to ensure that people have a calm and quiet place to rest each night, free of concerns about basic needs such as food security. The pandemic has brought the opposite assurances, exacerbating the uncertainties at the root of already-stark disparities.

As the quest for sleep falls only more to individuals, many are left to think outside the box. That has included, for some, dabbling in hypnosis. Not the kind of hypnosis where you're onstage and told to act like a chicken, but a process slightly more refined. Christopher Fitton is one of a number of hypnotherapists who have spent the pandemic creating YouTube videos and podcasts

meant to help put people to sleep. Fitton's sessions involve 30 minutes of him saying empowering things to listeners in his pleasant, semi-whispered voice. He tells me he is now getting more than 1 million listens a month.

Hypnotherapy is meant to slow down the rapid firing of our nerves. Similar to guided meditation or deep breathing, the intent is to stop people from overthinking and allow sleep to happen naturally. As you listen to Fitton saying banal things about the muscles in your back or asking you to envision a specific tree in a specific place, "the aim is to get into a relaxed, trancelike state, where your subconscious is open to more suggestion," he says. Then, when he tells you to sleep, your brain is less likely to argue with him about how you're too busy, or how you need to worry more about why someone read your text message but didn't reply.

Hypnotherapists such as Fitton provide tools to ground yourself, ultimately in pursuit of being able to do it unassisted, sans the internet. (It's better not to bring your phone into your bedroom anyway.) Focusing involves practice; the trancelike state rarely happens easily, and no single way works for everyone. Some experimentation is usually needed. Apparently it still is for me. While listening to one of Fitton's recordings, I couldn't fully escape the image of him in his home office speaking softly into his microphone, reading an ad for Spotify, just as alone as everyone else.

But regardless of whom you trust to help relieve you of consciousness, now seems like an ideal time to get serious about the practice. Draw boundaries for yourself, and sleep like your life depends on it. Hopefully it won't.

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