A-Bacterial-Vaccine-Could-One-Day-Help-Treat-Mental-Health-Issues_HF

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Health

The Vaccine That Could Prevent Stress, Anxiety, and Depression

As mental health disorders run rampant, scientists are trying to make an immunization from bacteria that could help.

By Shayla Love

In 1989, University of Cambridge psychiatrist Ed Bullmore, then a physician-in-training, examined a woman unable to walk from destroyed collagen and bone in her knees. That, plus painfully swollen joints in her hands, indicated rheumatoid arthritis—an inflammatory disease. After Bullmore asked the usual questions to reach the diagnosis, he inquired about something else: how she was feeling emotionally.

"Over the course of the next 10 minutes or so, she quietly but clearly told me that she had very low levels of energy, nothing gave her pleasure anymore, her sleep was disturbed, and she was preoccupied by pessimistic and guilty thoughts," he wrote in a 2018 Medium essay.

When he told his supervisor, the senior doctor didn't find it very exciting. Having a chronic inflammatory disease would likely make anyone depressed, he said. "It did not occur to either of us that it might originate in the body," Bullmore wrote. "That Mrs. P might be depressed, not because she knew she was inflamed, but simply because she *was* inflamed."

Inflammation is a natural and necessary function of the immune system. It's what happens when your body activates an army of different molecules to protect itself from an outside threat—say, to fend off a virus or heal a wound. But when inflammation persists, it can wreak havoc. Autoimmune and inflammatory disorders like arthritis, asthma, inflammatory bowel disease, Type 1 diabetes, and allergies happen when the body's immune system doesn't know when to call back the troops.

These disorders of chronic inflammation are steadily increasing. This is troubling not only because they are a leading cause of death, but because, as in the case of Mrs. P, there's an association between these disorders and mental health issues, which are also on the rise.

In the past two decades, scientists have begun to realize that the link isn't merely a byproduct of living with a difficult disease. Researchers—like Bullmore, who wrote a book called *The Inflamed Mind*—have been uncovering a more meaningful and sinister connection between inflammation and mental health. Inflammation seems to directly cause mental health issues, while at the same time, stress and mental health issues themselves provoke inflammation—creating a dangerous feedback loop.

One single risk factor will never explain the entirety of psychiatric problems, wrote Chuck Raison, a psychiatrist at the University of Wisconsin-Madison, in a special report on the topic in *Psychiatric Times*. But "inflammation turned out to be a common denominator and likely risk factor for every manner of psychiatric disturbance, from schizophrenia to obsessive compulsive disorder, from mania to depression," he wrote.

Christopher Lowry, a behavioral neuro-endocrinologist at University of Colorado Boulder, envisions a future where an immunization could be given to protect against inflammation-caused mental health disturbances. In a series of studies over the past decade, Lowry and his collaborators have shown in animal models that a particular soil bacteria, *Mycobacterium vaccae* (or *M. vaccae*), can reduce inflammation and the troubling behavioral symptoms that come with it.

> Inflammation seems to cause mental health issues, and mental health issues themselves provoke inflammation, creating a dangerous feedback loop.

One reason runaway inflammation happens is that the immune system has lost its way. A surprising potential explanation for why this can happen is emerging: Our immune systems could be missing exposure to some crucial things that aid in its healthy development: bacteria and viruses, and parasitic worms—the very things it is designed to ward off. The loss of exposure to these microbial organisms due to our modern diets, medications, and lifestyles could be producing naive and untrained immune systems that have a tendency to go haywire.

The immune system can't fire off like a loose cannon at every foreign cell, it has to decide when something is a threat and when it's not. That's why humans and other mammals have both an innate and an adaptive immune system, said Graham Rook, a professor of medical microbiology and immunology at University College London. The latter learns what to target and when, but to do so, it needs data.

"It's is like a computer," Rook said. "The question is, where does the data come from? It comes in part from the microbiota, or the organisms in the gut. It also comes from outside infection and other microbes we are exposed to, especially in early life."

As humans moved to live in urban environments, they've lost exposure to a wide variety of microorganism that Rook calls "old friends." Our diminishing interaction with certain bacteria could be creating an immune system that's a bit trigger-happy.

This concept is more widely known as the "hygiene hypothesis," which suggests that the sterility of modern life is leading to health issues. Rook doesn't like this term. He thinks it's not expansive enough to include all the ways we're missing microbial interactions. (And that it glosses over how we need hygiene to prevent spreading pathogenic diseases, especially in tightly packed urban environments.) The actual problem is on a larger societal scale, Rook said. It does stem from cleaner living conditions and food, but also an overuse of antibiotics, cesarean sections, the radical changes in the foods we eat, the loss of old infections (like TB, hepatitis A, helicobacter pylori, and parasitic worms), and from not coming into contact with organisms that live off dead and decaying matter found in the mud and soil.

> A surprising potential explanation for runaway inflammation: Our immune systems could be missing exposure to enough bacteria, viruses, and parasitic worms.

Soil bacteria's effects on inflammation are easily seen in a phenomenon called the "farm effect." Studies show that interacting with the land and being around farm animals is protective against inflammatory conditions like asthma and allergies. For children who don't live on farms, simply having pets or coming into contact with cats and dogs can similarly lower the risk of allergies. Rook thinks the farm effect can be explained by the animals bringing in microbial life on dirty paws and bodies, which then helps to train the immune system.

A recent study led by Stefan Reber at the University of Ulm in Germany revealed a connection between good emotional health and growing up around dirt. Forty men were brought to the lab and put through a stress test, where they had to give a speech in front of steely-faced scientists in white coats. The ones from rural environments reported feeling stressed, but it was the ones who grew up in cities who had a massively exaggerated inflammatory response. Their inflammation lasted for the whole length of the study.

“There's something out there, something that we need to meet in the earth," Rook said.

I n the 1970s, Rook and an immunologist, John Stanford, pulled M. *vaccae* out from the mud near Lake Kyoga in Uganda. They were trying to figure out why vaccinations for leprosy were more effective in certain countries when they came across *M. vaccae*—a bacteria closely related to leprosy that was possibly boosting the effect of the vaccine.

“Later, because John was a good immunologist, he realized that this bacterium had the ability to induce something that we call immuno-regulation,” Lowry said.

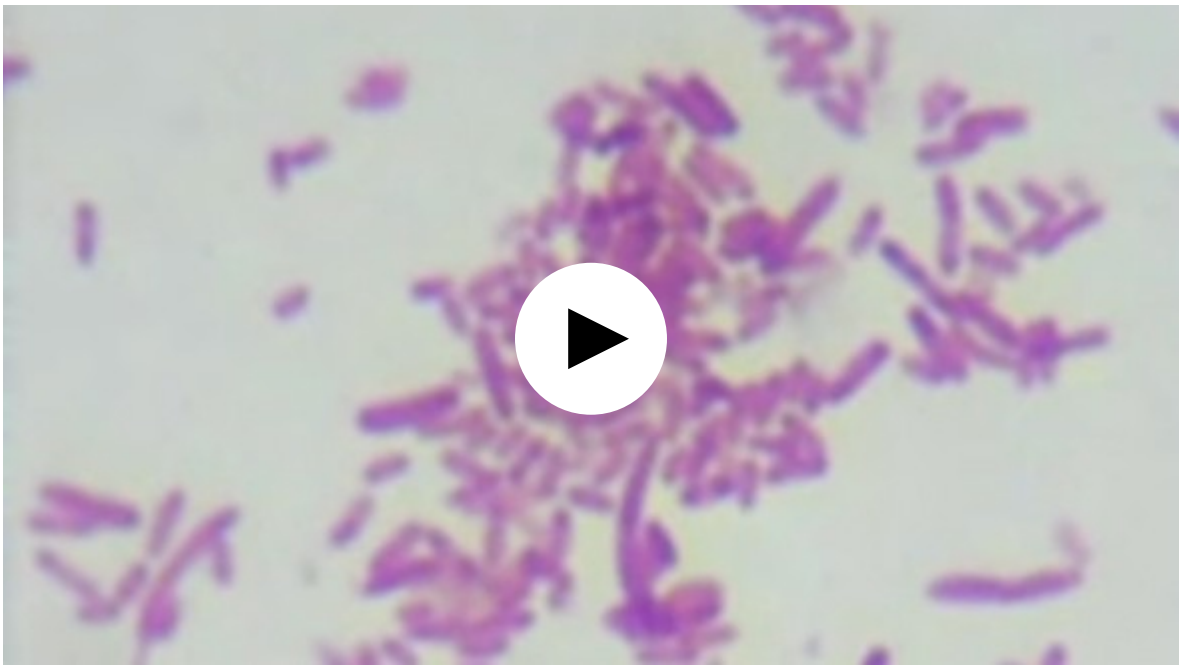
Other researchers tried to see if *M. vaccae*'s effects on the immune system could be harnessed. In 2004, an oncologist in the U.K. tried giving patients with inoperable lung cancer *M. vaccae* alongside chemotherapy to see if it would improve survival rates. The bacteria didn’t help people live longer, but intriguingly, it improved their quality of life. They had increased levels of emotional health, cognitive functions, and decreased pain.

> People who had higher levels of inflammation were more likely to be depressed about 12 years later.

Lowry first injected mice with *M. vaccae* shortly after, in 2007. He saw increases in serotonin metabolism in the prefrontal cortex, a neurotransmitter and part of the brain linked with mood and personality. Another study in mice found that when the animals were put with a large aggressive male, the ones injected with *M. vaccae* behaved less anxiously, and were less likely to develop inflammatory issues like colitis. In a more recent study in rats, Lowry and his colleagues found that animals that had been given *M. vaccae* had faster fear extinction—they were able to get over something they had been conditioned to be afraid of more quickly.

"That's what individuals with anxiety or PTSD can't do, is extinguish fear," Lowry said. "Even in safe environments."

With more research, Lowry could see *M. vaccae* being put to use in early life, along with the other routine immunizations, as an injection. It could teach the immune systems to regulate itself, or reduce inflammation in those at high risk for depression or PTSD. It could even be given as a booster shortly after someone experiences a trauma—after going through something disturbing or violent, someone could be treated with *M. vaccae* to prevent PTSD.



L owry had been cautious about his lab's findings, especially since the team had mostly done experiments in animals. But simultaneously, evidence continued to mount in humans that matched their findings—that inflammation wasn't just associated with mental health disorders, but was *causing* them.

By measuring levels of inflammatory molecules in blood, researchers were finding they could predict mental health issues later. In 2010, people working in U.K. government offices who had higher levels of inflammation were more likely to be depressed about 12 years later. In 2014,

another U.K. study looked at 15,000 children around 9 years old and found that those who were not depressed but showed raised inflammation were more likely to be depressed a decade later. And a study from 2014 done by the U.S. Marines found the percentage of soldiers who got PTSD was greater in those who had raised levels of inflammatory molecules in their blood before they went to combat.

> Cancer patients given the soil bacteria *M. vaccae* had increased levels of emotional health, cognitive functions, and decreased pain.

"In other words, if you have a propensity for high inflammatory function, then that in fact is the deciding factor on whether or not the individual goes on to develop these anxiety and depressive-like syndromes," Lowry said.

Chronic inflammation affects our whole bodies, including the brain. Inflammation can interfere with the way the brain functions, altering neurotransmitters to the behavior of synapses, the connections between neurons. The brain also has its own immune system which, when overly active, can lead to persistent neuro-inflammation. *M. vaccae* could stop the neuro-inflammatory response of the brain's immune cells in rats, and the associated negative behavioral changes that came along with it.

In May of this year, Lowry, Rook and others found a single molecule from *M. vaccae* that has anti-inflammatory effects in human and mouse cells. It's a lipid—a fat molecule—with a very specific chemical shape. Mammals can't make it.

In mice, the molecule binds to a receptor that triggers a shutting off of various inflammatory processes. This likely evolved so that a disease-causing bacteria could turn off a host's immune system and take over. But in non-threatening bacteria, it's actually a form of ecological

service, Lowry said, helping our immune system learn how to [illegible] instead of running on overdrive all the time.

Currently, Lowry is doing a clinical trial in humans, but not with *M. vaccae,* because he hasn't yet gotten FDA permission to do that. He's using another commercially available probiotic that has been shown to have immuno-regulatory effects. His team is also working towards a trial with *M. vaccae*, but in the meantime, they're seeing if any other bacteria could work just as well.

John Cryan, a neuroscientist at the University College Cork in Ireland, said that this is just one way our futures will likely involve microbes as medicine for mental health. Bacteria help regulate our immune system, but also produce important molecules that have more direct interactions with our brain. A study of more than 1,000 people from February found that people with depression had reductions in specific bacteria that were producing key chemicals. Knowing who has what microbial deficit—like a vitamin deficiency—could help people for whom other drugs aren't working.

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Not every case of depression is caused by inflammation. But figuring out the cases where inflammation *is* playing an overwhelming role can bring us closer to understanding the best treatment options, said Jane Foster, a neuroscientist at McMaster University who studies the immune system.

Regardless of what happens next, the causal role of inflammation and mental health issues forces us to rethink the underlying cause of mental health disorders. The changing environments in which we live could be altering the ways our bodies function and dramatically affecting the way we feel. This brings us a long way from what used to be a prevailing dogma: that the mind and body are separate, and so are their illnesses.

To Cryan, these kinds of microbial approaches are reason for optimism. "Unlike our genomes, which we can't do much about except blame our parents and grandparents, our microbiomes are potentially modifiable," he said. "That gives us a little bit more, and also gives the individual more agency over their own health."

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