

THE FUTURE OF **PSYCHOBIOLOGICS**

Evidence is mounting that microorganisms
in the gut influence mental health—
but designing a healthy microbiome won't be easy

BY KIRSTEN WEIR

A DECADE AGO, the notion that the bacteria in your gut could guide your behavior and mental health was seen as “very fringe and kind of kooky,” says Faith Dickerson, PhD, MPH, a clinical psychologist at the Sheppard Pratt Health System in Baltimore who studies the role of infectious and immune factors in serious mental illness. ¶ Today, it’s well established that the trillions of microbes in the gastrointestinal tract—collectively known as the microbiome—influence health in countless ways. Inside the gut, those microscopic puppet masters program the developing immune system, help us make nutrients, defend against infection and produce neurochemicals important for brain function. ¶ In the past several years, researchers have compiled convincing evidence that suggests the gut and its resident microorganisms influence mental health and cognition as well. “We refer to this as the microbiome-gut-brain axis, and that axis

is bidirectional,” says Christopher Lowry, PhD, an associate professor of integrative physiology at the University of Colorado Boulder who studies the neural mechanisms that underlie stress-related physiology and emotional behavior. “The microbiome and gut are communicating with the brain, and conversely the brain is communicating with the gut and the microbiome.” ¶ But when it comes to understanding how those players communicate, researchers have a lot to sort out. Indeed, scientists who set out to explore this axis often find themselves “in awe of the complexity of the system,” says Emeran Mayer, MD, a gastroenterologist and neuroscientist at the David Geffen School of Medicine at the University of California, Los Angeles. Fortunately, researchers in fields including psychology, microbiology and neurobiology are undeterred by that complexity. Research has already uncovered digestive and immune benefits of probiotics, live microorganisms in foods or supplements that benefit the health of their host. As scientists learn more about the gut-brain connection,

they are moving closer to the prospect of treating psychiatric and behavioral disorders with dietary changes or “psychobiotic” supplements filled with brain-benefiting microbes. “I think we have every reason to be optimistic that these psychobiotics are coming,” Lowry says.

MULTIPLE MECHANISMS

For many decades, scientists have observed links between the gut and the nervous system. Researchers have described an important “second brain” in the gut, a complex network of neurons and neurotransmitters known as the enteric nervous system. Meanwhile, scientists have noted that gut problems and mental health disorders often coincide. “There are a number of different kinds of evidence for this gut-brain

connection,” says Dickerson.

People with gastrointestinal disorders have higher-than-average rates of neuropsychiatric problems such as bipolar disorder and depression, she notes, while people with schizophrenia often have blood markers suggestive of gastrointestinal inflammation. People with autism spectrum disorder, too, have higher rates of gastrointestinal problems than the general population.

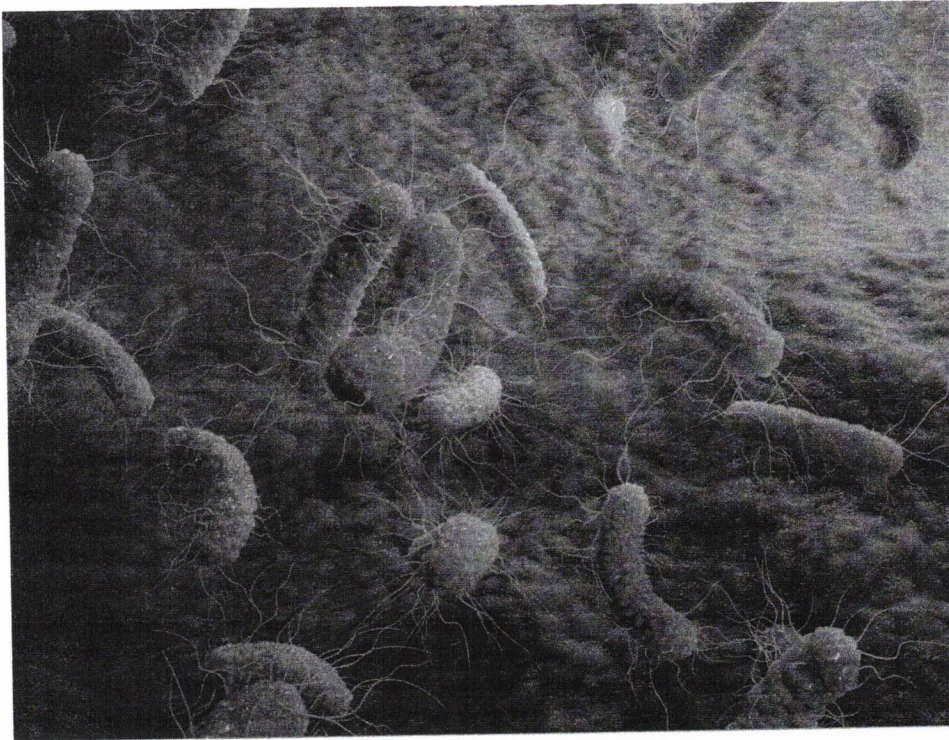
Researchers have identified a suite of potential mechanisms to explain those patterns, which probably work in parallel, Lowry says. Messages travel from the digestive tract to the brain along the vagus nerve, which forms a direct highway from gut to brainstem. There’s also evidence that bacteria in the gut can generate metabolites that

can circulate through the blood into the brain. Inflammation is another probable connection, as immune-signaling molecules and even immune cells can move from other parts of the body into the brain and affect neural function, Lowry adds. “It seems that there are many potential mechanisms, but we really need more clarity on how they actually work,” he says.

As scientists continue to elucidate those pathways, many researchers are moving ahead with experiments to understand how specific microorganisms might influence mental health, for better or worse. Much of the evidence so far comes from animal studies.

Lowry and his colleagues have studied whether beneficial bacteria can help tamp down stress-related pathology in mice. They used an established model for triggering psychosocial stress by housing the mice in colonies with a dominant aggressor mouse. Normally, subordinate mice in this situation show signs of anxiety and develop colitis, an inflammation of the colon. In this study, the researchers injected some of the rodents with heat-killed *Mycobacterium vaccae*, a bacterium shown in previous research to reduce inflammation throughout the body. (Like heat-killed viruses used to create vaccines, some strains of heat-killed bacteria have been shown to trigger a positive immune response.)

A week after the treatment, the treated mice showed lower levels of inflammation, Lowry says. Compared with control mice, the treated mice showed



fewer submissive behaviors when they later encountered the dominant mouse, as well as less anxiety and fear when navigating a stress-provoking maze. What's more, the treatment appeared to prevent stress-induced colitis in the mice (*Proceedings of the National Academy of Sciences*, Vol. 113, No. 22, 2016). In separate studies, Lowry and his colleagues showed that injecting *M. vaccae* reduced inflammation in the brains of rats and prevented stress-induced anxiety. "Just injecting the bacterium had

a major impact on the brain," he says (*Brain, Behavior, and Immunity*, Vol. 73, No. 1, 2018).

In a similar animal study, Lowry's team explored whether *M. vaccae* could prevent post-operative cognitive dysfunction (POCD), a common problem for older adults after surgery. POCD is associated with inflammation and is often a serious problem for adults over 60, causing marked declines in memory, concentration and information processing. Older rats, too, experience symptoms of POCD.

Bacteria such as *Escherichia coli* are commonly found in the lower intestine.

To explore possible protective effects of *M. vaccae*, Lowry and colleagues treated aged rats with the bacterium or with a saline solution for three weeks. Then the rats each received a surgical incision to the abdomen. The treated rats showed reduced inflammation in the brain, with memory benefits to match (*Neurobiology of Aging*, Vol. 71, No. 1, 2018).

"When we immunized with the anti-inflammatory bacteria, it completely prevented the surgery-induced memory impairment," Lowry says. More work is needed to bridge the gap from mice to people, but the findings raise the possibility that beneficial bacteria could help people with cognitive and mental health problems. Now, Lowry is testing whether anti-inflammatory probiotics might reduce symptoms of post-traumatic stress disorder in people.

THERAPEUTIC POTENTIAL

Other researchers are also beginning to explore the microbiome-gut-brain axis in humans. In one study, Peng Xie, MD, at Chongqing Medical University in China, and colleagues found that the gut microbes of patients with major depressive disorder differed significantly from those of healthy controls. The researchers transplanted fecal matter from the human participants into bacteria-free mice. The mice that received fecal-microbial transplants from people with depression showed more depression and anxiety behaviors compared with mice that

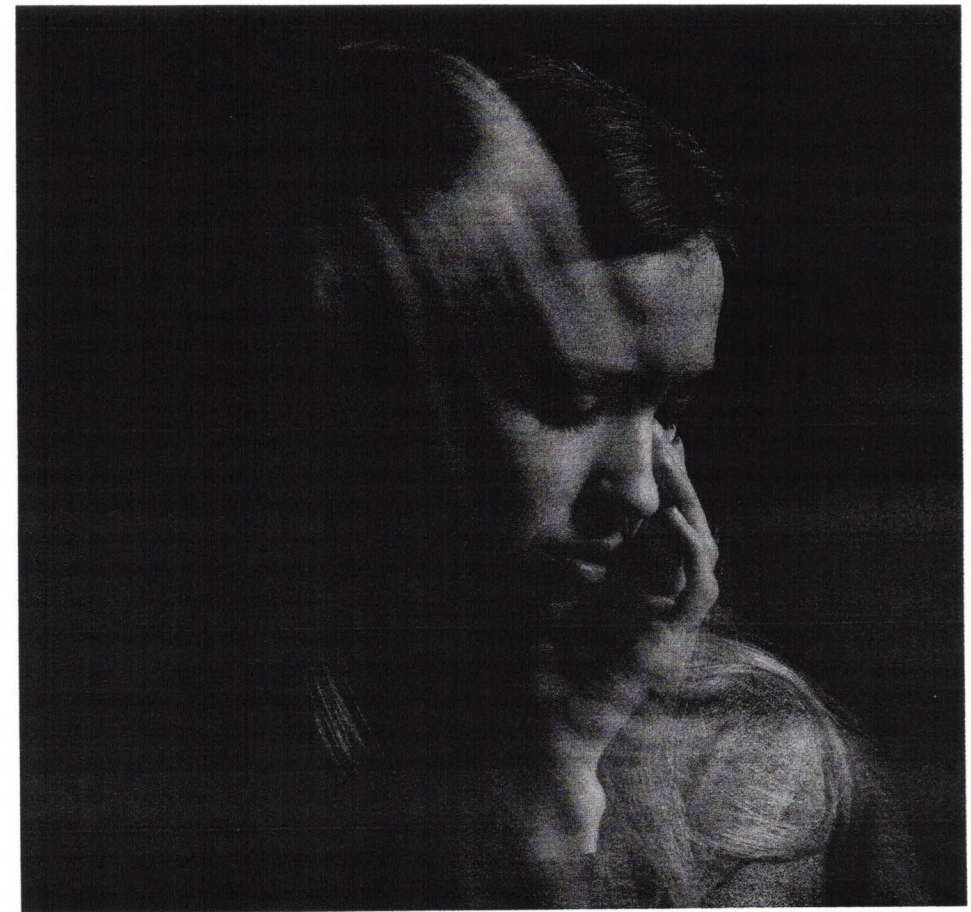
RESEARCHERS HAVE FOUND THAT PEOPLE WITH GASTROINTESTINAL DISORDERS HAVE HIGHER-THAN-AVERAGE RATES OF NEUROPSYCHIATRIC PROBLEMS SUCH AS BIPOLAR DISORDER AND DEPRESSION.

received transplants from healthy human participants (*Molecular Psychiatry*, Vol. 21, No. 6, 2016).

Simon Evans, PhD, now at the Institute for Systems Biology in Seattle, investigated the microbiome in people with bipolar disorder in his previous post at the University of Michigan. In a comparison of the microbes found in stool samples from people with and without bipolar disorder, he found notably lower levels of the microbe *Faecalibacterium* in those with the disorder. He also found that among the people with bipolar disorder, those who had higher levels of *Faecalibacterium* had better self-reported health outcomes, including lower anxiety and depression, as well as better sleep (*Journal of Psychiatric Research*, Vol. 87, No. 1, 2017).

Dickerson, too, has been investigating microbes in people with bipolar disorder and other serious mental illnesses. She and her colleagues discovered that among people with bipolar disorder who had been hospitalized for mania, those with increased levels of inflammation were more likely to be readmitted to the hospital within six months. That finding prompted her colleagues to design a trial to target that inflammation.

Dickerson and her colleagues tested the intervention in 66 patients hospitalized for mania. Half of the participants received a placebo, while the other half took supplements containing two commercially available bacteria strains shown to have anti-inflammatory properties in humans and animals: *Lactobacillus rhamnosus*



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(strain GG) and *Bifidobacterium animalis lactis* (strain BB-12). After hospital discharge, the participants took either the supplements or the placebo for 24 weeks, along with their usual medications. During that time, just eight of the people taking the probiotics were rehospitalized, compared with 24 of those who took the placebo

(*Bipolar Disorders*, online first publication, 2018).

This study didn't directly examine the gut bacteria of the participants, Dickerson notes. But she hypothesizes that the probiotics improved outcomes by modulating the patients' immune systems—possibly, she adds, by acting on their microbiomes. Another research team is

KATARZYNA BIALASIEWICZ/GETTY IMAGES

now collecting gastrointestinal microbe samples from participants as part of a replication trial. "This is a beginning area of research, but it's exciting in many ways—one of which is the potential for therapeutics," Dickerson says.

Other psychologists are also conducting research with an eye toward identifying psychobiotics that could impart mental health benefits. Ted Dinan, PhD, at University College Cork in Ireland, and colleagues are testing possible psychobiotic interventions for stress. In one study, Dinan's group gave participants either a placebo or a supplement containing *Bifidobacterium longum* (strain 1714), a bacterium that has been shown to affect stress levels and cognitive performance in mice. Before and after the trial, participants underwent stress tests and cognitive assessments. The researchers found that compared with controls, the participants who took the probiotic had lower levels of cortisol and self-reported anxiety during a stress test in which they submerged their hands in an ice-water bath. In addition, they reported less daily stress and showed subtle but statistically significant improvements in visuospatial memory (*Translational Psychiatry*, Vol. 6, No. 11, 2016).

A CIRCULAR CONVERSATION

While much of the research thus far has investigated how changes to the microbiome might affect the brain, other researchers are looking at the question in

reverse: Can changing behavior alter the microbiome and improve gut health?

Mayer, with Jeffrey Lackner, PsyD, at the University of Buffalo, and colleagues recently finished a study of cognitive-behavioral therapy (CBT) aimed at reducing gastrointestinal symptoms and increasing coping skills in patients with irritable bowel syndrome (IBS). Mayer and colleagues presented the results at the 2018 Digestive Disease Week conference, showing that after a CBT intervention, participants with a certain pattern of gut microbes at the start of the study had reduced IBS symptoms after the intervention. In other words, the microbiome could predict who would respond best to the therapy. And among those responders, the intervention actually altered the composition of their microbiota.

"That suggests a top-down effect," Mayer says. "If you change autonomic nervous system activity by decreasing anxiety and increasing coping skills, the signals get from the brain down to the microbes in the gut. It's not just the microbes talking to the brain. The brain has a big part in this conversation as well."

Experts still need to sort out where that conversation begins, Mayer adds. "Are there brain changes first that signal to the gut and the microbes and alter their behavior? Or are the changes in the gut first? The model we have proposed is that it's really a circular system, so you can't say which is the chicken and which is the egg."

FURTHER READING

Current Evidence Linking Diet to Gut Microbiota and Brain Development and Function
Ceppa, F., et al.
International Journal of Food Sciences and Nutrition, 2018

A Psychology of the Human Brain-Gut-Microbiome Axis
Allen, A.P., et al.
Social and Personality Psychology Compass, 2017

Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals
Sarkar, A., et al.
Trends in Neurosciences, 2016

The Gut Microbiome and Mental Health: Implications for Anxiety- and Trauma-Related Disorders
Malan-Muller, S., et al.
Omics, 2018

The Mind-Gut Connection
Mayer, E.
HarperCollins, 2016

A PRESCRIPTION ON YOUR PLATE

While researchers have begun zeroing in on specific bacteria that may help us or harm us, they're a long way from describing what a healthy microbiome looks like. "Most likely, there are several healthy microbiomes," Mayer says. Just as a healthy ecosystem in the Amazon looks nothing like a healthy Arctic habitat, a healthy ecosystem in the human gut is likely to vary considerably from culture to culture and even from person to person, Lowry adds. "That's what's so hard about the microbiome. There are many different ways to come up with [a microbiome] that is stable and healthy and thriving," he says. "And likewise, there are many ways it can go south."

And there are signs of trouble in our stomachs, Mayer adds. Diversity is often an indicator of an ecosystem's health—and researchers have shown that the variety of species in Western microbiomes is typically much less than those of hunter-gatherers and people who consume rural agrarian diets. That could be due to Westerners' higher consumption of high-fat, low-fiber foods, as well as their use of antibiotics. Even among Westerners who don't report any health problems, microbial diversity has declined over the past half century, Mayer notes.

In one example that shows we are what we eat, Justin Sonnenburg, PhD, at Stanford University, and colleagues introduced human microbiota to the guts of mice. They found that microbial diversity dwindled from generation to generation

in mice fed a low-fiber diet (*Nature*, Vol. 529, No. 7585, 2016).

As tempting as it is to imagine psychobiotics that alleviate mental health problems, it isn't likely to be as easy as finding the right pill. Indeed, a study by Eran Elinav, PhD, MD, at the Weizmann Institute of Science in Israel, and colleagues found that many people's microbiomes expel the bacteria in standard probiotics, preventing the probiotic species from becoming established in their digestive tracts (*Cell*, Vol. 174, No. 6, 2018).

Rather than start out trying to change the micro-

biome, researchers might benefit from taking a step back, says Evans. "The question is, why are the bacteria out of balance in the first place? Instead of trying to find a quick fix, I think we need dietary approaches that will rebalance the system to have long-term effects."

Although dietary changes aren't glamorous, they are accessible—and something that clinicians can readily encourage without the need for more evidence. "Doctors that treat diabetes or heart disease have already come around to understanding that diet is an important factor," Evans says. "The brain is a

physical organ and it plays by a lot of the same rules, but rarely does a psychiatrist or a clinical psychologist talk to patients about what they eat."

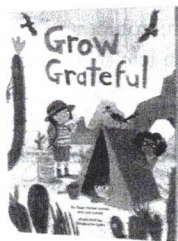
The tried-and-true advice of a high-fiber, low-sugar, mostly plant-based diet can benefit patients in body and in mind, he adds. "Diet alone isn't going to cure mental illness, but it can make other therapies work better. Clinical psychologists can take action just by getting patients to appreciate that what they're putting in their mouths can actually have an effect on their mental state."

Other researchers agree that diet is important, but

they aren't giving up on the idea of psychobiotics. "That really is the driving mission of researchers like us. We desperately need new therapeutics," says Dickerson. Though she cautions it will take time for potential psychobiotics to be developed and approved, she's optimistic that it will happen—and that psychologists will be key in bridging the gap between the laboratory scientists studying the gut-brain connection and people with psychiatric disorders and cognitive challenges. "This is such a fast-moving field, and psychologists can really help make that connection." ■

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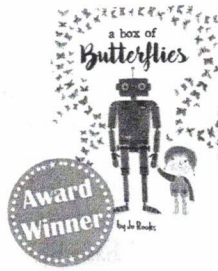
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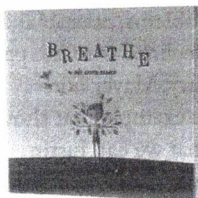
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—Mindful



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