

A dark teal rectangular logo with white text. The text reads "ME AND EARL" on the first line, "AND THE DYING" on the second line, and "GIRL" on the third line.

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Can the Bacteria in Your Gut Explain Your Mood?

The rich array of microbiota in our intestines can tell us more than you might think.

By **PETER ANDREY SMITH** JUNE 23, 2015

Eighteen vials were rocking back and forth on a squeaky mechanical device the shape of a butcher scale, and Mark Lyte was beside himself with excitement. “We actually got some fresh yesterday — freshly frozen,” Lyte said to a lab technician. Each vial contained a tiny nugget of monkey feces that were collected at the Harlow primate lab near Madison, Wis., the day before and shipped to Lyte’s lab on the Texas Tech University Health Sciences Center campus in Abilene, Tex.

Lyte’s interest was not in the feces per se but in the hidden form of life they harbor. The digestive tube of a monkey, like that of all vertebrates, contains vast quantities of what biologists call gut microbiota. The genetic material of these trillions of microbes, as well as others living elsewhere in and on the body, is collectively known as the microbiome. Taken together, these bacteria can weigh as much as six pounds, and they make up a sort of organ whose functions have only begun to reveal themselves to science. Lyte has spent his career trying to prove that gut microbes communicate with the nervous system using some of the same neurochemicals that relay messages in the brain.

Inside a closet-size room at his lab that afternoon, Lyte hunched over to

inspect the vials, whose samples had been spun down in a centrifuge to a radiant, golden broth. Lyte, 60, spoke fast and emphatically. “You wouldn’t believe what we’re extracting out of poop,” he told me. “We found that the guys here in the gut make neurochemicals. We didn’t know that. Now, if they make this stuff here, does it have an influence there? Guess what? We make the same stuff. Maybe all this communication has an influence on our behavior.”

Since 2007, when scientists announced plans for a Human Microbiome Project to catalog the micro-organisms living in our body, the profound appreciation for the influence of such organisms has grown rapidly with each passing year. Bacteria in the gut produce vitamins and break down our food; their presence or absence has been linked to obesity, inflammatory bowel disease and the toxic side effects of prescription drugs. Biologists now believe that much of what makes us human depends on microbial activity. The two million unique bacterial genes found in each human microbiome can make the 23,000 genes in our cells seem paltry, almost negligible, by comparison. “It has enormous implications for the sense of self,” Tom Insel, the director of the National Institute of Mental Health, told me. “We are, at least from the standpoint of DNA, more microbial than human. That’s a phenomenal insight and one that we have to take seriously when we think about human development.”

Given the extent to which bacteria are now understood to influence human physiology, it is hardly surprising that scientists have turned their attention to how bacteria might affect the brain. Micro-organisms in our gut secrete a profound number of chemicals, and researchers like Lyte have found that among those chemicals are the same substances used by our neurons to communicate and regulate mood, like dopamine, serotonin and gamma-aminobutyric acid (GABA). These, in turn, appear to play a function in intestinal disorders, which coincide with high levels of major depression and anxiety. Last year, for example, a group in Norway examined feces from 55 people and found certain bacteria were more likely to be associated with depressive patients.

At the time of my visit to Lyte's lab, he was nearly six months into an experiment that he hoped would better establish how certain gut microbes influenced the brain, functioning, in effect, as psychiatric drugs. He was currently compiling a list of the psychoactive compounds found in the feces of infant monkeys. Once that was established, he planned to transfer the microbes found in one newborn monkey's feces into another's intestine, so that the recipient would end up with a completely new set of microbes — and, if all went as predicted, change their neurodevelopment. The experiment reflected an intriguing hypothesis. Anxiety, depression and several pediatric disorders, including autism and hyperactivity, have been linked with gastrointestinal abnormalities. Microbial transplants were not invasive brain surgery, and that was the point: Changing a patient's bacteria might be difficult but it still seemed more straightforward than altering his genes.

When Lyte began his work on the link between microbes and the brain three decades ago, it was dismissed as a curiosity. By contrast, last September, the National Institute of Mental Health awarded four grants worth up to \$1 million each to spur new research on the gut microbiome's role in mental disorders, affirming the legitimacy of a field that had long struggled to attract serious scientific credibility. Lyte and one of his longtime colleagues, Christopher Coe, at the Harlow primate lab, received one of the four. "What Mark proposed going back almost 25 years now has come to fruition," Coe told me. "Now what we're struggling to do is to figure out the logic of it." It seems plausible, if not yet proved, that we might one day use microbes to diagnose neurodevelopmental disorders, treat mental illnesses and perhaps even fix them in the brain.

In 2011, a team of researchers at University College Cork, in Ireland, and McMaster University, in Ontario, published a study in Proceedings of the National Academy of Science that has become one of the best-known experiments linking bacteria in the gut to the brain. Laboratory mice were dropped into tall, cylindrical columns of water in what is known as a forced-swim test, which measures over six minutes how long the mice swim before

they realize that they can neither touch the bottom nor climb out, and instead collapse into a forlorn float. Researchers use the amount of time a mouse floats as a way to measure what they call “behavioral despair.” (Antidepressant drugs, like Zoloft and Prozac, were initially tested using this forced-swim test.)

For several weeks, the team, led by John Cryan, the neuroscientist who designed the study, fed a small group of healthy rodents a broth infused with *Lactobacillus rhamnosus*, a common bacterium that is found in humans and also used to ferment milk into probiotic yogurt. Lactobacilli are one of the dominant organisms babies ingest as they pass through the birth canal. Recent studies have shown that mice stressed during pregnancy pass on lowered levels of the bacterium to their pups. This type of bacteria is known to release immense quantities of GABA; as an inhibitory neurotransmitter, GABA calms nervous activity, which explains why the most common anti-anxiety drugs, like Valium and Xanax, work by targeting GABA receptors.

Cryan found that the mice that had been fed the bacteria-laden broth kept swimming longer and spent less time in a state of immobilized woe. “They behaved as if they were on Prozac,” he said. “They were more chilled out and more relaxed.” The results suggested that the bacteria were somehow altering the neural chemistry of mice.

Until he joined his colleagues at Cork 10 years ago, Cryan thought about microbiology in terms of pathology: the neurological damage created by diseases like syphilis or H.I.V. “There are certain fields that just don’t seem to interact well,” he said. “Microbiology and neuroscience, as whole disciplines, don’t tend to have had much interaction, largely because the brain is somewhat protected.” He was referring to the fact that the brain is anatomically isolated, guarded by a blood-brain barrier that allows nutrients in but keeps out pathogens and inflammation, the immune system’s typical response to germs. Cryan’s study added to the growing evidence that signals from beneficial bacteria nonetheless find a way through the barrier. Somehow — though his 2011 paper could not pinpoint exactly how — micro-organisms in the gut tickle

a sensory nerve ending in the fingerlike protrusion lining the intestine and carry that electrical impulse up the vagus nerve and into the deep-brain structures thought to be responsible for elemental emotions like anxiety. Soon after that, Cryan and a co-author, Ted Dinan, published a theory paper in *Biological Psychiatry* calling these potentially mind-altering microbes “psychobiotics.”

It has long been known that much of our supply of neurochemicals — an estimated 50 percent of the dopamine, for example, and a vast majority of the serotonin — originate in the intestine, where these chemical signals regulate appetite, feelings of fullness and digestion. But only in recent years has mainstream psychiatric research given serious consideration to the role microbes might play in creating those chemicals. Lyte’s own interest in the question dates back to his time as a postdoctoral fellow at the University of Pittsburgh in 1985, when he found himself immersed in an emerging field with an unwieldy name: psychoneuroimmunology, or PNI, for short. The central theory, quite controversial at the time, suggested that stress worsened disease by suppressing our immune system.

By 1990, at a lab in Mankato, Minn., Lyte distilled the theory into three words, which he wrote on a chalkboard in his office: Stress->Immune->Disease. In the course of several experiments, he homed in on a paradox. When he dropped an intruder mouse in the cage of an animal that lived alone, the intruder ramped up its immune system — a boost, he suspected, intended to fight off germ-ridden bites or scratches. Surprisingly, though, this did not stop infections. It instead had the opposite effect: Stressed animals got sick. Lyte walked up to the board and scratched a line through the word “Immune.” Stress, he suspected, directly affected the bacterial bugs that caused infections.

To test how micro-organisms reacted to stress, he filled petri plates with a bovine-serum-based medium and laced the dishes with a strain of bacterium. In some, he dropped norepinephrine, a neurochemical that mammals produce when stressed. The next day, he snapped a Polaroid. The results were visible

and obvious: The control plates were nearly barren, but those with the norepinephrine bloomed with bacteria that filigreed in frostlike patterns. Bacteria clearly responded to stress.

Then, to see if bacteria could induce stress, Lyte fed white mice a liquid solution of *Campylobacter jejuni*, a bacterium that can cause food poisoning in humans but generally doesn't prompt an immune response in mice. To the trained eye, his treated mice were as healthy as the controls. But when he ran them through a plexiglass maze raised several feet above the lab floor, the bacteria-fed mice were less likely to venture out on the high, unprotected ledges of the maze. In human terms, they seemed anxious. Without the bacteria, they walked the narrow, elevated planks.

Each of these results was fascinating, but Lyte had a difficult time finding microbiology journals that would publish either. "It was so anathema to them," he told me. When the mouse study finally appeared in the journal *Physiology & Behavior* in 1998, it garnered little attention. And yet as Stephen Collins, a gastroenterologist at McMaster University, told me, those first papers contained the seeds of an entire new field of research. "Mark showed, quite clearly, in elegant studies that are not often cited, that introducing a pathological bacterium into the gut will cause a change in behavior."

Lyte went on to show how stressful conditions for newborn cattle worsened deadly *E. coli* infections. In another experiment, he fed mice lean ground hamburger that appeared to improve memory and learning — a conceptual proof that by changing diet, he could change gut microbes and change behavior. After accumulating nearly a decade's worth of evidence, in July 2008, he flew to Washington to present his research. He was a finalist for the National Institutes of Health's Pioneer Award, a \$2.5 million grant for so-called blue-sky biomedical research. Finally, it seemed, his time had come. When he got up to speak, Lyte described a dialogue between the bacterial organ and our central nervous system. At the two-minute mark, a prominent scientist in the audience did a spit take.

“Dr. Lyte,” he later asked at a question-and-answer session, “if what you’re saying is right, then why is it when we give antibiotics to patients to kill bacteria, they are not running around crazy on the wards?”

Lyte knew it was a dismissive question. And when he lost out on the grant, it confirmed to him that the scientific community was still unwilling to imagine that any part of our neural circuitry could be influenced by single-celled organisms. Lyte published his theory in *Medical Hypotheses*, a low-ranking journal that served as a forum for unconventional ideas. The response, predictably, was underwhelming. “I had people call me crazy,” he said.

But by 2011 — when he published a second theory paper in *Bioessays*, proposing that probiotic bacteria could be tailored to treat specific psychological diseases — the scientific community had become much more receptive to the idea. A Canadian team, led by Stephen Collins, had demonstrated that antibiotics could be linked to less cautious behavior in mice, and only a few months before Lyte, Sven Pettersson, a microbiologist at the Karolinska Institute in Stockholm, published a landmark paper in *Proceedings of the National Academy of Science* that showed that mice raised without microbes spent far more time running around outside than healthy mice in a control group; without the microbes, the mice showed less apparent anxiety and were more daring. In Ireland, Cryan published his forced-swim-test study on psychobiotics. There was now a groundswell of new research. In short order, an implausible idea had become a hypothesis in need of serious validation.

Late last year, Sarkis Mazmanian, a microbiologist at the California Institute of Technology, gave a presentation at the Society for Neuroscience, “Gut Microbes and the Brain: Paradigm Shift in Neuroscience.” Someone had inadvertently dropped a question mark from the end, so the speculation appeared to be a definitive statement of fact. But if anyone has a chance of delivering on that promise, it’s Mazmanian, whose research has moved beyond the basic neurochemicals to focus on a broader class of molecules called

metabolites: small, equally druglike chemicals that are produced by microorganisms. Using high-powered computational tools, he also hopes to move beyond the suggestive correlations that have typified psychobiotic research to date, and instead make decisive discoveries about the mechanisms by which microbes affect brain function.

Two years ago, Mazmanian published a study in the journal *Cell* with Elaine Hsiao, then a graduate student and now a neuroscientist at Caltech, and others, that made a provocative link between a single molecule and behavior. Their research found that mice exhibiting abnormal communication and repetitive behaviors, like obsessively burying marbles, were mollified when they were given one of two strains of the bacterium *Bacteroides fragilis*.

The study added to a working hypothesis in the field that microbes don't just affect the permeability of the barrier around the brain but also influence the intestinal lining, which normally prevents certain bacteria from leaking out and others from getting in. When the intestinal barrier was compromised in his model, normally "beneficial" bacteria and the toxins they produce seeped into the bloodstream and raised the possibility they could slip past the blood-brain barrier. As one of his colleagues, Michael Fischbach, a microbiologist at the University of California, San Francisco, said: "The scientific community has a way of remaining skeptical until every last arrow has been drawn, until the entire picture is colored in. Other scientists drew the pencil outlines, and Sarkis is filling in a lot of the color."

Mazmanian knew the results offered only a provisional explanation for why restrictive diets and antibacterial treatments seemed to help some children with autism: Altering the microbial composition might be changing the permeability of the intestine. "The larger concept is, and this is pure speculation: Is a disease like autism really a disease of the brain or maybe a disease of the gut or some other aspect of physiology?" Mazmanian said. For any disease in which such a link could be proved, he saw a future in drugs derived from these small molecules found inside microbes. (A company he co-

founded, Symbiotix Biotherapies, is developing a complex sugar called PSA, which is associated with *Bacteroides fragilis*, into treatments for intestinal disease and multiple sclerosis.) In his view, the prescriptive solutions probably involve more than increasing our exposure to environmental microbes in soil, dogs or even fermented foods; he believed there were wholesale failures in the way we shared our microbes and inoculated children with these bacteria. So far, though, the only conclusion he could draw was that disorders once thought to be conditions of the brain might be symptoms of microbial disruptions, and it was the careful defining of these disruptions that promised to be helpful in the coming decades.

The list of potential treatments incubating in labs around the world is startling. Several international groups have found that psychobiotics had subtle yet perceptible effects in healthy volunteers in a battery of brain-scanning and psychological tests. Another team in Arizona recently finished an open trial on fecal transplants in children with autism. (Simultaneously, at least two offshore clinics, in Australia and England, began offering fecal microbiota treatments to treat neurological disorders, like multiple sclerosis.) Mazmanian, however, cautions that this research is still in its infancy. “We’ve reached the stage where there’s a lot of, you know, ‘The microbiome is the cure for everything,’” he said. “I have a vested interest if it does. But I’d be shocked if it did.”

Lyte issues the same caveat. “People are obviously desperate for solutions,” Lyte said when I visited him in Abilene. (He has since moved to Iowa State’s College of Veterinary Medicine.) “My main fear is the hype is running ahead of the science.” He knew that parents emailing him for answers meant they had exhausted every option offered by modern medicine. “It’s the Wild West out there,” he said. “You can go online and buy any amount of probiotics for any number of conditions now, and my paper is one of those cited. I never said go out and take probiotics.” He added, “We really need a lot more research done before we actually have people trying therapies out.”

If the idea of psychobiotics had now, in some ways, eclipsed him, it was nevertheless a curious kind of affirmation, even redemption: an old-school microbiologist thrust into the midst of one of the most promising aspects of neuroscience. At the moment, he had a rough map in his head and a freezer full of monkey fecals that might translate, somehow, into telling differences between gregarious or shy monkeys later in life. I asked him if what amounted to a personality transplant still sounded a bit far-fetched. He seemed no closer to unlocking exactly what brain functions could be traced to the same organ that produced feces. “If you transfer the microbiota from one animal to another, you can transfer the behavior,” Lyte said. “What we’re trying to understand are the mechanisms by which the microbiota can influence the brain and development. If you believe that, are you now out on the precipice? The answer is yes. Do I think it’s the future? I think it’s a long way away.”

Correction: June 25, 2015

An earlier version of this article described incorrectly the affiliation of Elaine Hsiao, an author of a study published in the journal Cell that linked bacteria to behavioral changes. At the time, she was a graduate student in the lab of Paul Patterson, another author of the study, not in the lab of Sarkis Mazmanian.

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