heading out the other end, in the form of poop. In fact, up to 60 percent of the dry weight of your poop is composed of bacteria. You were an excellent host.

Looking Back on the Journey

That brings us to the end of our voyage. On this gastronomic cruise, we visited all the dark corners of your GI tract. We saw villi growing upon villi, and realized how ridiculously thin and tender your gut lining is, especially considering that it is under continuous assault by a menagerie of microbes. We encountered probiotic and psychobiotic microbes that turned out to be important companions, protecting that flimsy gut lining, day and night. We saw more mucus than we ever wanted to.

Perhaps you learned something about the gut part of this gut-brain puzzle, which turns out to be critical for your happiness. Whether you feel sick to your stomach or just have the butterflies that accompany anxiety, you can point to your gut and know that it is valiantly trying to fend off the worst pathogens nature can throw at it, even as we sabotage it by eating pathogen favorites such as doughnuts and ice cream.

In the following chapter, we'll look closer at the very intimate connections between your gut and your brain. If you think things are full of intrigue here in your gut, you'll be amazed to see how this all fits in with your brain.

CHAPTER 5

THE GUT-BRAIN AXIS

"Nature is everywhere gothic, not classic. She forms a real jungle, where all things are provisional, half-fitted to each other, and untidy."

—William James

Now that you've met the leading microbial players in your gut, including both psychobiotics and pathogens, let's look at how they manage to converse with your brain. Taken together, these intricate and interconnected channels of communication make up the powerful gut-brain axis that is where the psychobiotic revolution takes place.

> *Accumulating data now indicate that the gut microbiota communicates with the central nervous system (CNS) through neural, immune, and endocrine pathways—and thereby influences brain function and behavior. Studies in germ-free animals and in animals exposed to pathogens, probiotics, or antibiotics suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition,*

and pain. Thus, the emerging concept of a microbiota-gut-brain axis suggests that modulation of the gut microbiota may be a winning strategy for developing novel therapies for complex CNS disorders.[1]

There are three main communication channels between your brain and your gut: your nervous system, your immune system, and your endocrine system. The circulatory and lymphatic systems also play supporting roles, but these first three are dominant. Each system is used differently by the microbes that affect your mood. Each has its own unique chemical language, but they also need to coordinate with one another, and so they have some signaling molecules in common as well. These systems interact with each other, making it difficult to discuss any of them in isolation. (William James was right—nature is untidy—but let's give it a try.)

To keep the conversation lively between your second and first brain, the three main systems of communication have the following primary tasks and chemicals they use to accomplish them:

- The *nervous system* relays information to and throughout your brain. It communicates using chemicals called neurotransmitters. Its communication style is fast and point to point, but short-acting.
- The *immune system* is at the ready to rally a defensive response against threats to healthy homeostasis. It uses the protein molecules called cytokines to signal distress. It can communicate quickly, but its urgent chemical effect can be harsh enough to cause tissue damage.
- The *endocrine system* monitors and manages growth and metabolism. Its component glands communicate by secreting *hormones* into your blood and thus sending signals throughout the body. Its operations are slower, more moderate and systemic, but longer-acting than those of the other two systems.

We're going to see all of these systems in action with a case study in which they each make an appearance. But before we can do that, we need a little more background. Here's a quick overview of each system separately.

THE NERVOUS SYSTEM

The nervous system has two major divisions: the central nervous system (CNS), composed of the brain and spine, and the peripheral nervous system, less well known but just as important. The peripheral nervous system divides into four parts: somatic, sympathetic, parasympathetic, and enteric. To achieve optimal gut-brain health, all four parts are operative, in balance, and in communication with one another and with the CNS.

You use the *somatic* nervous system whenever you voluntarily do anything: walk, talk, wave your arms, look up, look down—all the many things you decide to do (or not to do). In the context of psychobiotics, the somatic system matters because you maintain voluntary control over what you eat (or don't eat)—and thus, you exert some nervous system control over your microbiota.

The *sympathetic* nervous system is the part often nicknamed "fight or flight." When stresses cross a threshold and press your brain and body into action, this system takes over, whether or not you want it to. When that happens, the sympathetic system takes priority; when it's activated, in other words, all other systems get put on the back burner. The stresses that activate this system can be

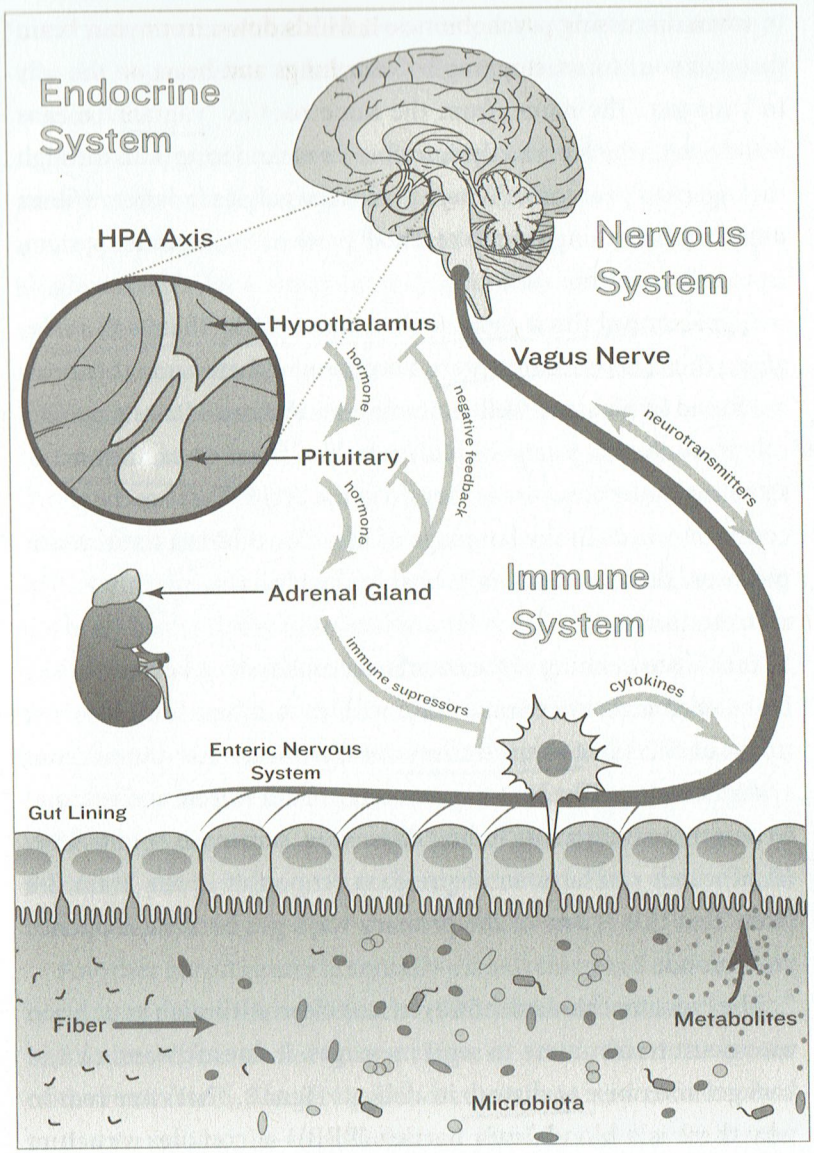
external—anything from a tiger attack to a frustrating traffic jam—or internal—tension held in muscles or, pertinent to psychobiotics, food habits that trigger continued inflammation in the gut.

The *parasympathetic* nervous system has a nickname, too: "feed and breed." This system is what life is really all about. Eat, drink, and be merry—and don't forget to have babies to keep the species going. When the parasympathetic nervous system is chugging along, you achieve a state of health, happiness, and balance we all strive for. The psychobiotic revolution—and the point of this book—promises that you can learn things and make decisions that will convert an abused sympathetic response into a happier parasympathetic response, where life is good.

The *enteric* nervous system is the one that operates in your gut, your second brain. It is intimately connected with the rest of the nervous system but operates with its own set of rules. This system, including your microbiota, holds the keys to dismantling any chronic stress responses you may be experiencing, and to returning your body to a healthy homeostasis. Tune in to the messages of your enteric nervous system, and you'll find the way to put yourself in a cheerier groove.

Becoming more aware of your enteric nervous systems may not be easy. Sympathetic, parasympathetic, and enteric—all three of these systems operate on autopilot, so typically you don't even think about them. Your gut is remarkably independent, and it doesn't really need your brain to tell it what to do. Peristalsis and other gut movements are under local control, so much so that you can cut all the gut's nerves to the brain and it will still pulse with purpose.

Your gut is wired to your brain through your spine and through your vagus nerve, but the vagus is the primary two-way communication channel for mood, so it's the one we pay the most attention



Gut-brain communication occurs through multiple channels, including the nervous system (using neurotransmitters via the vagus nerve), immune system (using cytokines via the blood system), and endocrine system (using hormones such as cortisol via the blood system).

to when discussing psychobiotics. It winds down from your brain through your torso, stopping by your lungs and heart on the way to your gut. The name, from the same root as "vagrant," means wandering, which perfectly describes its meandering path through the organs of your torso. Where it joins the gut, it sends nerve fibers out like a branching vine to reach all parts of the digestive system, from top to bottom.

Signals travel throughout the nervous system thanks to molecules we call neurotransmitters. Surprisingly, these same chemicals are found in plants as well as animals and bacteria, thus playing a role in all the kingdoms of life. In each of these cases, they act as signaling molecules, just as they do in the brain. They are the short, common words in the language of life. Considering their multiple uses, these molecules probably deserve a name other than neurotransmitter.

Inside the webbing of the enteric nervous system, bacteria busily make chemicals to communicate with each other—and they use many of the same neurotransmitter chemicals that the nervous system employs. The bacteria in your gut both secrete and respond to neurotransmitters including ***dopamine***, ***serotonin,*** and ***GABA,*** all of which can have antidepressant properties in the brain. It's likely that this is one of the primary ways gut bacteria influence your mood.

The exact mechanism, however, isn't clear. Although your brain uses neurotransmitters to send messages, it doesn't want a lot of background noise to disturb its delicate signals. That's one reason why there is a blood-brain barrier (BBB)—a complex structure protecting the precious organ from all that's around it. The BBB blocks most neurotransmitters from your gut—and the rest of your body as well. For the same reason, there is a barrier between your blood and your gut-brain as well. Still, research shows that

these neurotransmitters *do* have an impact on the brain and usually the vagus nerve is involved. But the details are still being worked out.

Why do bacteria churn out so many neurotransmitters? One theory is that these bacteria want to control your cravings. This makes perfect sense, really: If you feed *Streptococcus* (just to take a single example of a sugar-hungry microbe) with doughnuts, it chows down and then produces dopamine. It doesn't take long for you to connect those doughnuts to your happiness, and a new craving is established. A species of bacteria has used its own neurotransmitters to coerce you into delivering special foods to it.

Three Mood Centers

Where your spinal cord enters your brain, there is a swelling called the brain stem. There, in several special centers, neurotransmitters that control your mood are produced. One mood center is called the locus ceruleus (LC)—a fancy Latin name that means "blue spot." The LC produces noradrenalin (norepinephrine), which causes you to wake up and pay attention. In response to stress, the LC alerts your amygdala, which processes fear. If the stress continues or increases, you will move from being alert to feeling anxious and even panicked.

Another mood center is actually a small cluster of nodes in the brain stem called the raphe nuclei (RN). *Raphe* is Latin for "seam," and indeed these nuclei form a ridge, or seam, down the center of the brain stem. The RN produces serotonin and distributes it to the amygdala, the hypothalamus, the LC, and the forebrain, affecting wakefulness, cognition, and mood. When this mood center isn't functioning properly, it can cause sleep disruptions and changes in your perception of hunger and pain. It can also cause depression.

A third mood center is the ventral tegmental area (VTA), which produces dopamine. This neurotransmitter is involved with the brain's reward system. When you win the lottery, a rush of dopamine floods your brain, and you feel happy. Dopamine is involved with emotion, motivation, and addiction. Problems with your VTA can lead to anxiety and depression.

Many other centers around the brain stem all interact with each other, sending complex messages throughout the brain, sometimes lifting and sometimes crushing your mood. It's all interconnected, and many of these connections are still under study in research labs around the world. The basics are known without question, though: Neurotransmitters like serotonin and dopamine can make you happy, and their lack can make you depressed or anxious. And microbes make them.

YOUR IMMUNE SYSTEM

Your immune system includes nodes and lymph vessels that extend throughout your body. When you get a cut, immune cells rush to the rescue, and their activity produces the familiar heat, redness, and swelling of inflammation. It's a battle you need to win locally before it becomes systemic.

The immune reaction starts at the site of an infection and can grow from there. Cruising immune cells discover foreign bacteria, using antibodies to tag them. Antibodies are the main tools of the immune system, attaching themselves to specific molecules called antigens that exist on the surface of a pathogen. Once tagged, they can be rounded up or simply destroyed. The system uses cytokines to spread the alarm and coordinate the response of other immune cells. Cytokines are small proteins, so

they are mobile and therefore good for sending signals from one cell to another. Whenever a pathogen is detected, cytokines are produced by the heavy-hitter immune cells. But the cells lining the gut can also produce cytokines—which means that virtually every cell of the GI tract can trigger an immune response. Immune factors like fatty acids and cytokines activate ***microglia,*** the immune cells in the brain, which will fight pathogens but may also lead to anxiety or depression.

Microbes can also produce cytokines. Some of these microbes can talk directly to your immune system, which can be bad news or good news. The bad news is that pathogenic microbes can encourage inflammation. The good news is that psychobiotic microbes will lower inflammation, either directly or indirectly, by helping to heal the gut lining that became inflamed.

Acetylcholine plays a role in this healing. It is a neurotransmitter used throughout your entire nervous system, including your enteric system. Acetylcholine commands marauding immune cells to stop overreacting to microbes. Stimulating the vagus nerve causes acetylcholine to be produced, which, along with cortisol, suppresses the immune system.[2] Many bacteria, including *Lacto* species, can also produce acetylcholine, and they may thereby gain access to the powerful levers of the immune machine. They effectively inject themselves into your homeostatic system, and that is a major aspect of their psychobiotic effect.

Because so many cell types secrete cytokines and so many cell types receive them, it is a fantastically complex system. Some cytokines are inflammatory and others are anti-inflammatory. If the scales tilt chronically toward the former, depression and anxiety can set in over time. In fact, research has shown that just injecting certain cytokines can induce depression.[3] Immune cells produce cytokines when pathogens show up. These signals quickly reach

nerve cells in your gut and are then conveyed to the brain through the vagus nerve, providing information about the type and severity of the inflammation.

Your immune system thus serves as a key channel for microbe-brain communications, conveying information about microbial action going on in the gut to several parts of the nervous system at once and thereby meeting the microbial challenge head-on. It's faster and more direct than an endocrine response. The end result, if the pathogen is deemed nasty enough, is a purge, including vomiting and diarrhea. It's an unsubtle way to deal with pathogens, but it works.

This is the balancing act that your immune system maintains: It must be ready to kill invaders or infected cells at a moment's notice, and at the same time it must give similar-looking healthy cells a pass. And when it determines that the infection has been routed, your immune system then needs to calm down and morph back into a watchful state.

Unfortunately, it doesn't always work that way. The inflammation experienced as the immune system responds to pathogens may give rise to psychological problems. And it can also go the other way: Stress can change the effectiveness of your immune system responses as well.[4] Your immune system has been using antibodies as if they were "Wanted" posters identifying foreign microbes. But under stress, the antibody traffic slows down—one of your immune system's ways to conserve energy for the most essential tasks. That lowers the level of scrutiny, allowing pathogens to sneak through and gain a foothold. Once there, they can cause infection or make your gut develop leaks.

In short, your body hobbles your immune system while it deals with stress. For the short term, that may be a wise choice. If you are running from a tiger, your ulcer will have to wait. But if the stress

persists and the stress reaction goes on too long, that resulting leaky gut may itself cause further inflammation, initiating a deadly positive feedback loop. The sicker you get, the sicker you will get, raising depression to a new level.

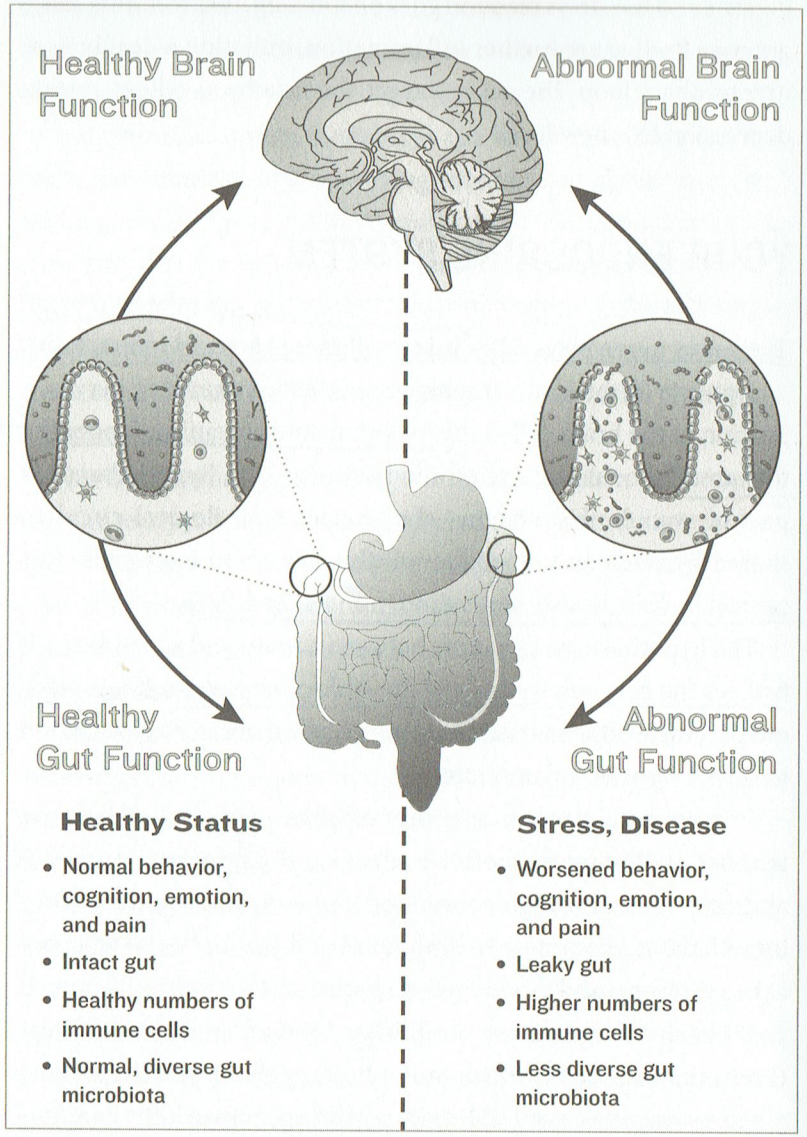
YOUR ENDOCRINE SYSTEM

The vagus nerve plays a key role in all these bacterial interactions. It connects to the brain through a specialized chunk of nerves, a portion of the brain called the hypothalamus, meaning "under the thalamus." About the size of a kidney bean, the hypothalamus is part of your limbic system—the ancient neurological circuitry shared by birds and crocodiles all the way up to mammals. It is central to your mood, motivation, hunger, and sleep.

The hypothalamus is a cross between a brain and a gland, and it bridges the nervous system and the endocrine system. It can reach out past the BBB with specialized nerve cells that sample your blood to detect signs of inflammation.

In your gut, immune cells snip off identifying bits of bacteria that act as ID tags for both beneficial and pathogenic microbes and carry them through your blood and lymphatic systems. Your hypothalamus responds to both good and bad bacterial tags, but it has a strong and prolonged response to the pathogen tags. It conveys alarm signals to your pituitary and adrenal glands. These three organs—the hypothalamus, pituitary gland, and the adrenal gland—constitute the ***HPA axis,*** a primary network for communication between the gut and the brain. When inflammation is detected, the HPA axis releases cortisol, among other hormones, to respond to the stress. This response is instrumental in mood regulation, and many people with depression or anxiety have a

HPA axis



A healthy gut (left) maintains homeostasis; a dysbiotic gut (right) lets pathogens through, sparking an inflammation in the brain as well as the gut.

problematic HPA axis. Fixing problems with this axis, we now understand, can be a way to relieve depression and anxiety.

THE QUEST FOR HOMEOSTASIS

The nervous, the immune, and the endocrine systems all have one thing in common: They are in a rut, and they like it that way. Or, to put it more scientifically, they all seek a state of ***homeostasis***. This aspect of living systems was first established by Claude Bernard, a French physiologist in the 1800s who realized that an animal adjusts its biology to its environment, compensating for external changes by using tools including heart rate, hormones, blood pressure, and immune responses, as well as dozens of other biological systems.

The biological imperative to stabilize the internal environment is called homeostasis, and it's fundamental to all living creatures—including bacteria. Homeostasis controls every aspect of your biological life. Your heart rate and breathing rate, for instance, are your body's ways to guarantee that your oxygen levels stay within a healthy range, no matter where you are or what you are doing. You may think it's boring to be in a rut, but when it comes to breathing and pumping blood, you don't want drama.

A classic homeostatic system is temperature regulation. It works like your home thermostat: When the room gets a couple of degrees lower than the set point, the thermostat turns on the heat. If the room gets a couple of degrees hotter than the set point, it turns on the air conditioner. Similarly, your body temperature wants to stay between about 97°F and 100°F. Too cold, and you shiver, generating heat. Too hot, and you sweat, dissipating heat. This is how homeostasis maintains equilibrium and keeps you—and your associated microbiota—alive.

Homeostasis is life pushing back, but it's a moment-by-moment adjustment not designed for long-term engagements. The ultimate goal is to return to an optimal set point, which is done with negative feedback: When a signal is detected, the feedback quickly dampens it. Mother Nature has evolved several different methods of negative feedback. One of the easiest is this: Make the end product turn off the starting switch. This is like the "useless machine" that you may have seen at novelty stores: When you click the switch on the box, a door opens and a hand comes out to turn the switch off. It's a goofy toy, but a great illustration of simple negative feedback. All organic systems include negative feedback of one form or another so that reactions will extinguish themselves, bringing everything back to a homeostatic ideal.

Most of the time, your body maintains homeostasis with ease. But at times things fall out of balance and there are no automatic ways to maintain homeostasis. When that happens, your brain is alerted. It may be a nudge or it may be a Klaxon call, depending on the problem. Sometimes these signals come from your gut, desperately trying to get your attention, but unfortunately, microbes mumble, and all you get is a vague sense of anxiety. If this process goes on for a long time, it can manifest as depression. And when you don't know what the problem is, it's hard to fix it.

Your microbiota is also trying to maintain homeostasis. It works hard to preserve a steady core group of microbes, and it's hard to change when it gets into a groove. Depending on what you eat, you encourage blooms of different bacterial species, but between meals your core microbiota will reassert itself. You have to do a lot of damage to upset this balance, but it can happen over time with a poor diet—or at a much faster pace with a course of antibiotics.

Negative feedback loops in living systems prevent runaway reactions that can be lethal. In the endocrine system, for example, a gland

produces a hormone that has a built-in side effect that stops production at a certain point, so only a small spurt is allowed before the loop automatically throttles back. In a stress-free environment, these hormonal systems oscillate during the day, following circadian rhythms and sleep patterns. But a stress-free life is not the norm, and circumstances inside and out can disrupt the cycle. The more effectively you can find ways to help your brain, gut, and body maintain homeostasis, the longer, healthier, and happier your life will be.

A CASE STUDY

To appreciate how all these gut-brain systems coordinate with each other, let's go back to the example of Walkerton, Ontario, the town mentioned earlier (page 43), where an infection struck the entire population of 5,000 people. Many suffered severely and remain affected to this day. It's a dramatic example, but it's not unusual. Infections like this lead to IBS and depression in more than 10 million Americans each year. It was a watershed case in the field of psychobiotics, providing clear evidence of how long-term exposure to pathogens can induce depression and anxiety. It can help us track the operations and interconnections of the three main communication channels in the gut-brain axis: the nervous, immune, and endocrine systems.

When the flood hit Walkerton in 2000, bacteria-ridden farm effluent contaminated the town's water supply with *Campylobacter jejuni*, a well-known pathogen that we will shorten to simply *Campy*. Thousands fell sick with bacterial gastroenteritis, and many of those people later came down with chronic depression and anxiety. Something like this, or a milder version of it, may be a part of your story, too. To really appreciate what these people

went through, let's imagine you are living in Walkerton as this catastrophe occurs.

It all starts innocently enough with a sip of water. *Campy* is sensitive to stomach acids, so when you drink the tap water containing it, some will be quickly killed. (If you happen to take antacids regularly, though, more *Campy* will make it through. And if you're on proton pump inhibitors, you double your risk of getting really sick.[5]) Although their numbers will be diminished on the way down, many of these pathogens will still make it to your small intestine and colon. These bacteria have recently come from inside a cow or a chicken, so they are pretty much at home in that environment. For most cows and chickens, *Campy* is a commensal. Not for humans! Why it goes berserk in the human gut is unknown, but *Campy* is potent: It is the number one cause of diarrhea in the United States, ahead of *Salmonella* and *E. coli*.[6]

1 Your Nervous System Is Notified

Within hours after your first drink of tainted water, you may feel a little queasy and anxious. This is a nervous system reaction—the first system of the gut-brain axis to be triggered by the pathogen. In response to the *Campy*, special cells lining your intestines secrete serotonin, which acts as a warning signal. The vagus nerve collects these complaints from your gut and relays them to your brain within seconds.

You may be about to become very sick, but for now what you feel is vague and hard to pin down. *Campy* and the gut commensals that rally to fight it can cause anxiety even without a full-blown infection. At this point your nervous system alone is detecting the pathogen. So far, your immune and endocrine systems are none the wiser, but your microbiota recognizes the threat and mounts a serious battle against the *Campy*, knocking its numbers down considerably. You

may start to feel a little anxious and antisocial, but with no real clue of what is about to occur. This is an early shot over the bow, but your brain now knows something is up down below.

Ironically, if by chance you have taken antibiotics recently for some other reason, you will not have your front line of defense and you will be harder hit by the *Campy*. Some heroic microbes—including *Bifido* and *Lacto* species, both psychobiotics—may emerge from your microbiota to face down the *Campy*.[7] If you're healthy, at this point they can probably outcompete and crowd out the *Campy*, preventing them from sticking to your cell walls. However, if you keep drinking the contaminated water, you will soon overwhelm your microbial defenses, and the pathogens will start to colonize your gut.

Campy can "taste" mucus and when it does, it moves toward it. Once there, it eats through your mucus lining, leaving your gut cells exposed. It attaches to cells and makes a toxin that stops your gut cells from dividing. Without division, your cells cannot renew themselves and instead they die. With an impaired lining, your gut starts leaking. By 24 hours after your first drink of infected water, *Campy* has seeped through your gut lining and is starting to move into the tissues surrounding your gut. Surprisingly, *Campy* has so far escaped the scrutiny of your immune system. Many pathogens have the ability to appear innocent to your immune system, but *Campy* is a master of the technique. Pathogen-induced leaky gut underlies dozens of diseases that are strongly associated with depression and anxiety. The worst is yet to come.

2 Your Immune System Wakes Up

After 48 hours you begin to sense real trouble. You start to get serious cramping and diarrhea. Your immune system has finally taken notice, and it becomes the second system of the gut-brain

connection to go on alert. More serotonin is released, causing strong pulses of peristalsis. Your immune system gets busy releasing cytokines, which act like sirens alerting the local immune community and summoning help. More immune cells are recruited, more cytokines are released, and the effect starts to cascade.

The immune system lacks subtlety and when it gets triggered, it can go crazy. In its zeal to track down and kill the *Campy*, your immune system sends out killer cells that may lay waste to your own gut lining, increasing inflammation and leakiness. Now headaches and fever may go along with your diarrhea as the cytokines make their way up to your hypothalamus via the bloodstream.

Your HPA Axis Is Turned On

Your hypothalamus is always alert to stress signals coming either from the outside or the inside environment. Cytokines trigger your HPA axis. Your hypothalamus responds to the cytokines that it senses in your blood by sending a message to your adrenal glands via the pituitary to secrete hormones designed to keep your infection from burning you up. The end product is the stress hormone cortisol. Now your endocrine system has entered the fray, the third channel of the gut-brain connection.

Cortisol can cause you to become anxious, but its main job here is to temper your immune reaction, which right now is continuing to heat up.[8] During an infection, your HPA axis acts as a pathogen monitor: The more pathogens, the more cortisol manufactured, and the greater your anxiety. Cortisol also exerts negative feedback on itself, dampening the whole HPA cascade—at least until cytokines are detected again, whereupon it again produces stress hormones.

Thus, chronic inflammation produces stress hormones indefinitely, leading to a surprising number of mental issues, including

bipolar disorder, post-traumatic stress disorder, attention deficit disorder, depression, and anxiety. Our story here is about *Campy*, but a similar process is initiated by hundreds of other infectious agents. A simple contagion can lead to long-term dysbiosis and consequent mental distress. Antidepressants are often prescribed for these maladies, but if your own psychobiotic microbes can reduce the inflammation, your HPA axis can return to homeostatic normalcy and you may be able to treat some of these conditions without drugs.

If you stop drinking the water, 30 days later you will start to feel better. Your commensal microbes have done their job and returned your microbiota to the homeostasis it craves. You have a low pathogen count, and you're feeling okay. But that's not going to be the case for everyone.

The Aftermath

Three to six months later, one in five of the people in Walkerton who was infected with *Campy* had come down with IBS and was still experiencing its psychological fellow travelers, depression and anxiety.[9] This delay is why many people don't make the connection, but the Walkerton example made it clear that inflammation lies behind many psychiatric issues. Thank goodness, most of the citizens of Walkerton are now fully recovered. The people who came down with IBS and depression have been treated with antidepressants and cognitive behavioral therapy. Some of them are using psychobiotics.

The Walkerton case is extreme, but this scenario represents a fairly typical course of inflammation. First the nervous system is alerted and your gut signals your brain through the vagus nerve. Then your immune system kicks in, battling the pathogens, but not without collateral damage. Finally your endocrine system is

called upon to moderate your raging immune system. These three systems represent fast, medium, and slow rates of communication, respectively—and each is capable of inducing anxiety and depression.

It's not known exactly how many cases of depression are related to infections like this one with *Campy*. But postinfectious dysbiosis is not uncommon. If you are depressed, think back. Have you suffered from a gastric insult? Bacterial gastroenteritis is very common: About 180 million cases occur each year in the United States. That's about half of us, each and every year. And gastroenteritis often does bring with it depression and anxiety, both acute and chronic. Learn to defend against this sort of bacterial dysbiosis, and you can improve your mood. A healthy microbiota is your first defense, and keeping it in working order is therefore the key to a good mood.

OTHER GUT-BRAIN CONNECTIONS

Gut microbes can talk to your brain in other ways, each one presenting an opportunity to intercede on behalf of a good mood. Every psychobiotic has its own habits and proclivities, and the more we know about them, the better we can treat them when they are unbalanced. Here are some of those other back channels.

Circulatory Systems

An important route from the gut to the brain is the circulatory system. Your blood regularly ferries microbes and their secretions throughout your body, including to the thousands of miles of capillaries in your brain. Generally speaking, microbes should stay in your gut, not your blood, where they can infect other bodily

systems. The job of the blood-brain barrier is to keep invading microbes (and other things) outside the brain, but you can do your part by keeping your gut lining healthy and intact to prevent systemic infections spread by your circulatory system.

Your lymphatic system transports lymph fluid throughout your body. It bathes and cleanses the tissues as it goes. It loads up with bacteria, both alive and dead, that need to be removed from your body. The brain was long thought to lack a lymphatic system, but we now know that it does indeed have one, and it may prove to play an important role in the gut-brain axis. There is no equivalent of a heart to pump the lymph. The circulation of lymph is entirely driven by body motion, so exercise is essential to lymphatic health.

Bacteria to the Rescue

Sometimes your gut bacteria get into the action and set up defenses against pathogens. *Lactobacillus reuteri,* for example, can directly excite sensory neurons in the gut and influence peristalsis, typically to slow it down. *L. reuteri* can also dampen pain, with signals to the brain through the vagus that things are okay in the gut.

Sometimes we can capitalize on long-standing family feuds between bacteria in your gut. Nurturing the proper microbes can subdue pathogens with very little collateral damage, so this is an important new research direction. The probiotic Nissle 1917, for instance, chases down and rids the body of closely related pathogenic *E. coli*. Once pathogens are selectively banished, an all-clear signal is sent to the brain, helping to allay depression and anxiety. This example stands as a possible direction for probiotics in the future. Because they can kill pathogens while leaving commensals alone, probiotics like this might replace antibiotics in some cases, all the more important as bacteria are becoming increasingly resistant to our best antibiotics.

Short-Chain Fatty Acids

Your microbes can also communicate with your brain through small molecules called ***short-chain fatty acids*** (SCFAs), which some bacteria produce as they consume fiber. SCFAs can essentially melt through cell membranes. They are directly detected by your second brain, which has receptors for them all along the gut that are connected through the vagus nerve to your brain.

Not all SCFAs have the same impact on your gut health and mood, however. Some have been shown to reduce depression and sadness. In one study, people showed an improved mood within minutes of receiving a dose of lauric acid, a fatty acid component of coconut oil.[10] Butyrate is another SCFA with a lot of benefits. It's the preferred energy source for the cells lining your gut. It can also enter the brain, where it encourages brain growth factors and acts as an antidepressant.

> *Butyrate, along with other fermentation-derived SCFAs, shows promising effects in various diseases including obesity, diabetes, and inflammatory diseases as well as neurological disorders. Indeed, it is clear that host energy metabolism and immune functions critically depend on butyrate as a potent regulator, highlighting butyrate as a key mediator of host-microbe crosstalk. We hypothesize that butyrate and other volatile SCFAs produced by microbes may be involved in regulating the impact of the microbiota on behavior, including social communication.*

In higher doses, some SCFAs are detrimental. Propionic acid, another bacterial secretion, has been shown to induce autistic-like behavior in rats.[11] Propionic and acetic acids are also associated with elevated anxiety in patients with IBS.[12] Depleting bacteria that produce these SCFAs is important for balancing your microbiota.

Fatty acids, as the name implies, are energy rich, and too many of them may lead to weight gain, so this approach to psychobiotic therapy might need to be modified for people who are overweight. Nevertheless, SCFAs play an important role in psychobiotics. Later in the book we will come back to them, showing how to increase the butyrate-producing bacteria in your gut to improve your health and mood.[13]

THE GUT EFFECTS OF STRESS

The nervous system uses neurotransmitters to communicate while the endocrine system uses hormones. They have different names, but in reality these two classes of molecules are close relatives, and in fact some hormones can act as neurotransmitters and vice versa.[14] Some double-duty neurotransmitter/hormones, including norepinephrine and dopamine, have a curious effect on gut pathogens such as *Salmonella* and *E. coli*: They cause them to bloom, dramatically increasing their numbers.[15] Different species of bacteria each have a preference for specific hormones, but norepinephrine is a clear favorite of many.

These molecules are stress hormones, called upon as part of the fight-or-flight response. Their job is to make you anxious and alert. They act throughout your body as stimulants, increasing your heart rate and blood pressure. Fight-or-flight reaction takes precedence over all other bodily functions. It subdues the gut and the immune system, which lowers your guard throughout your entire GI tract, potentially allowing pathogens to thrive.

When you combine reduced gut scrutiny with hormones that encourage the growth of pathogens, you have a perfect storm. That means that when you're stressed and your defenses are down, the

odds become better for pathogens to attack.[16] People who are stressed become more susceptible to infection and inflammation. That in turn can lead to greater stress, a vicious spiral that can leave people deeply anxious and depressed.

Stress can cause other physical and chemical changes in your gut. It can alter the levels of acids, mucus, and other intestinal secretions, disturbing the cozy environment your microbes have grown accustomed to. These responses to stress can, perversely, favor increased levels of pathogens such as *Clostridia*, further aggravating your stress. One study compared fecal samples donated by students at the beginning of classes to samples donated during finals. The end-of-semester stress significantly lowered their levels of healthy *Lactobacilli*.[17] Stress hormones and neurohormones reduce your good microbes at the same time that they increase your pathogen load. Strategies to dampen these vicious cycles are central to psychobiotic therapies under development.

The evidence is clear: Microbes play a big role in managing your mood. Rather than a simple wad of bacteria, your microbiota acts much more like a bona fide organ, a bulwark against a world of ever-evolving predators. And in the process, it exerts a remarkable amount of control over your frame of mind. We've actually known about this state of affairs for centuries, but that knowledge has gone in and out of fashion repeatedly. In the next chapter, we'll take a closer look at that mottled history.

CHAPTER 6

DISCOVERING PSYCHOBIOTICS

"So, early as Hippocrates, the abdominal viscera were regarded as the principal seats of disease in mania and melancholia. This doctrine has been, at various times, forgotten and revived from that period to the present moment, according as circumstances have occurred to influence the minds of the medical practitioners and as the opinions of the metaphysical or physical pathologists have prevailed."

—David Uwins, M.D., physician to the City of London Dispensary, 1818

HAVE YOU HEARD? THERE IS AN EPIDEMIC OF DEPRESSION! We hear that pithy declaration a lot these days, but is it correct? How would we know? If you want to know the history of heart attacks, you've got data going back centuries. We even know about the arteries of a 3,000-year-old mummy, because we've examined them. Depression, however, doesn't leave marks. It is invisible to archaeology.